RECENT ADVANCES IN CHEMISTRY IN RELATION TO MEDICAL PRACTICE

W. McKIM MARRIOTT, B.S., M.D.

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Lectures of the San Diego Academy of Medicine
Series of 1927

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BY

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ILLUSTRATED

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PREFACE

The Lecture Courses of the San Diego Academy of Medicine were established in 1926 for the purpose of acquainting medical practitioners with some of the more recent advances in the fundamental medical sciences.

The present series of lectures deals with chemistry, a field in which rapid strides have been made in recent years. New conceptions have been formulated and new applications of established principles have been discovered. So rapidly has the science advanced that much of the recent chemical literature is likely to be unintelligible to the medical graduate of a few years ago. Yet so important are the applications of chemistry to clinical medicine that a knowledge of recent chemical advances is almost essential to modern practice.

It is the purpose of these lectures to summarize present knowledge concerning certain important phases of chemistry and to point out, in so far as possible, the clinical applications of chemical principles. The lectures do not deal solely with a consideration of those phases of chemistry which are of immediate clinical application. Fundamental chemical conceptions are discussed at length, for it is only with a full understanding of the nature of chemical processes that intelligent applications may be made. There is no sharp dividing line between "pure" and "applied" science. The pure science of today becomes the applied science of tomorrow. Throughout the lectures general principles rather than details are discussed, for a knowledge of details may readily be acquired once one's interest in the subject has been sufficiently aroused.

The author takes pleasure in acknowledging his indebtedness to Drs. Philip A. Shaffer and Alexis F. Hartmann, who have rendered invaluable aid and advice in the preparation of this series of lectures.

W. McK. M.

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LECTURE I

FUNDAMENTAL CHEMICAL CONSIDERATIONS

Atoms, Molecules, Ions, The Mass Law, Surface Tension, Osmotic Pressure, Colloids

Life, in its ultimate analysis, consists of a series of finely balanced chemical reactions occurring in the main within organized units known as cells. As the result of such chemical reactions, physical forces are brought into play which determine the size and shape of cells and bring about such phenomena as growth, reproduction, secretion, muscular contraction, and nervous impulses. An alteration in the chemical processes mentioned or interference with the action of the physical forces produced, results in disease or a complete incoordination of activities known as death.

We, as physicians, are concerned with the ways and means by which the chemical reactions and physical forces occurring within the body may be controlled, so as to bring about a continuance of normal function. The means at our disposal for accomplishing these ends are chemical and physical. Among the chemical means are included the food which supplies materials for the chemical reactions occurring within the cells, drugs or hormones which influence the character of the reactions, antiseptics and antibodies which prevent the activities of foreign cells and render inert chemical substances capable of disturbing the normal chemical reactions. Among the physical means, we have at our disposal radiant energy—classified as heat, visible light, ultra-violet light and the x-ray, all of which are capable of altering profoundly chemical processes; lastly, we have the gross physical methods of surgery with their obvious applications.

Certain valuable facts concerning the treatment of disease have been discovered through a process of pure empiricism, but such discoveries have been few in number as compared with those which have been made and are being made as the result of a detailed knowledge concerning the nature of the chemical and physical processes occurring within the body.

Progress in medicine today is very largely dependent upon additions to our knowledge of the chemical transformations occurring within body cells. Successful application of many of the newer contributions to medical science are also dependent upon such knowledge, and it is with this aspect of the subject that the practitioner of medicine is concerned. It is the purpose of this lecture to summarize some of the more important facts concerning the nature of matter in general and of body cells in particular which have become known as the result of recent investigations. In subsequent lectures the application of certain of these facts to the diagnosis and treatment of disease will be considered.

The Nature of Atoms

No very sharp distinction between living and dead and between organic and inorganic matter is possible. All matter is composed of aggregates of molecules which are, in turn, composed of atoms. The atoms themselves we now know to be very live and fairly complicated structures. The older atomic theory, familiar to most of us, recently has undergone extensive modification as the result of the establishment of new facts. The individual atom, as we now see it, is a miniature solar system, composed of a central "sun" or *nucleus* carrying positive electric charges and surrounded by a number of satellites or *electrons,* each of which carries a negative charge and each of which travels in a definite orbit about the central nucleus. The electrons of all atoms seem to be identical and indivisible. The nuclei, on the other hand, vary in size and in the amount of positive electrical charges. The nuclei of at least some atoms may be broken up into smaller particles under certain conditions, or may spontaneously disintegrate, as in the case of the atom of radium and of the other radioactive elements. The number of positive electrical charges on the nucleus determines how many electrons may be attracted and held within its sphere of influence and this number differs with each individual element. The nucleus of the hydrogen atom, for example, the smallest and simplest known, has only enough positive charge to attract one negative electron, whereas the nucleus of uranium, the most highly charged, has sufficient positive electrical charge to hold ninety-two electrons. In between these extremes we have the whole group of elements, the atoms of which differ only in the number of electrons associated with the central nucleus; thus, the carbon atom has six electrons, oxygen eight electrons, chlorine seventeen, calcium twenty, and so on.

Elements differ, therefore, from each other only in the number of electrons existing in association with the nucleus in the atom. The electrons arrange themselves about the nucleus and circulate in orbits in such a way as to establish a state of equilibrium. There are a number of factors which determine this equilibrium, or the gross geometrical structure of the atom. We have to deal, not only with the attractions between the positively charged nucleus and negatively charged electrons, but also with strong repulsions between the negatively charged electrons themselves, and the energy of movement or kinetic energy of the electrons.

With certain numbers of electrons, a stable equilibrium is readily attained, and we have a symmetrical and well-balanced arrangement within the atom. The atoms of the so-called "noble" gases, helium, argon, and krypton, are examples of such a stable arrangement. So stable are these atoms that it is impossible to disturb the balance, and these elements, therefore, do not unite or react with other elements. They are what have been termed the "unsociable" atoms. The balance within the atoms of certain other elements is not so perfect, and one or more electrons may move in wider orbits. These electrons may be likened to "comets."

The orbits in which the electrons move vary as the result of a number of factors. When an electron is revolving in a wide orbit, it possesses the greatest amount of potential energy. This energy is lost when it returns to a narrower orbit. The energy thus liberated is capable of bringing about a great variety of chemical and physical changes. An atom possessed of electrons circulating in a wide orbit is very active in a chemical sense. It becomes inert when the electrons have settled down to what may be considered their normal orbits. Many of the processes of metabolism are the result of alternate activity and quiescence of atoms. The absorption of light energy by living tissues results in a transfer of energy to electrons which swing away from the nuclei into larger orbits and thus become capable of producing such chemical changes as oxidation.

Molecules

In other atomic structures a more perfect balance can be attained by the addition of one or more electrons, that is, the geometric figure can be completed and made symmetrical. In such instances there is a strong tendency to come to a state of equilibrium by capturing one or more "comet" electrons from such other atoms as may be present. These electrons cannot be appropriated, without at the same time, attracting the atom associated with the electrons in question, so that two atoms are brought together and held in a state of more or less stable equilibrium. For example, the sodium atom has one "comet" electron, the other ten having a stable arrangement about the nucleus. The chlorine atom, on the other hand, with its seventeen electrons, requires one more to make a well-balanced system. When a chlorine and a sodium atom are brought into proximity, the extra electron from sodium is appropriated by the chlorine atom. This draws together the chlorine and sodium atoms to form a stable molecule of sodium chloride, or common salt.

When the salt is dissolved in water, the atoms tend to separate once more, due to the attraction of the water molecules, but when this separation occurs, the chlorine holds fast to the electron it has captured from the sodium. As a result the modified chlorine atom now contains an extra negatively charged electron, and therefore has an excess of negative charge, since the positive charge in the nucleus is only sufficient to balance the negative charge of the normal number of electrons. The sodium atom, on the other hand, having lost one negative electron with its charge, now has an excess of one positive charge. Such altered atoms in solution are known as *ions* and are designated as follows: $\overset{+}{Na}$ and $\overset{-}{Cl}$ or $\dot{Na}$ and Cl.′ When more than one electron is involved, the ions are said to be polyvalent and are indicated as Ca·· O″ Bi··· Whole groups of atoms joined together may, so far as fixed and separable electrons are concerned, act as single atoms or ions, for example, $\overset{+}{NH_4}$ or $\overset{\equiv}{PO_4}$.

When a chemical molecule in solution separates into charged ions, it is said to be dissociated. If an electric current is passed through such a solution, the positively charged ions are attracted to the negative pole or cathode and for that reason are designated as *cations.* The negatively charged ions go to the positive pole, or anode, and are designated as *anions.*

In general, molecules dissociate into ions more readily when dissolved in water than in other solvents, but not all molecules dissociate to the same degree, even in water. Sodium chloride, for example, is very completely dissociated, but sugar in solution is not. Inorganic acids, alkalies, and salts in general are well dissociated as compared with the compounds of carbon or "organic" substances. The physiologic action of dissociated ions is usually infinitely greater than that of undissociated molecules. For example, hydrogen, as it exists in molecular form, in hydrogen gas is not ionized and therefore exerts only a slight physiologic action.

The Unique Properties of the Hydrogen Ion

In the blood, under normal conditions, there exists about 1/20,000,000 of a gram of hydrogen ions per liter. If the amount of ionized hydrogen is increased to as much as 1/10,000,000 of a gram per liter, the maintenance of life in the body is no longer possible. Much smaller changes than this in the concentrations of hydrogen ions are capable of stimulating the respiratory center, of activating or inactivating enzymes, and of altering profoundly the character of the protoplasm of body cells and cell permeability and nutrition. The hydrogen ion has a more marked physiologic action, weight for weight, than almost any other known substance. Chemically, as well as physiologically, it is unique. As previously mentioned, the hydrogen atom consists of a nucleus with a single electron. When this electron is lost, all that is left is a nucleus with a single positive charge, the smallest known particle of matter.

Very few hydrogen ions exist in pure water, as water itself is only very slightly dissociated into $\overset{+}{H}$ and $O\overset{-}{H}$ ions, the amount of dissociated hydrogen ions being 1/10,000,000 gram per liter. So small are the ions, however, that there are approximately 6×10^{16} or 60,000,000,000,000,000 hydrogen ions in 1/10,000,000 gram. If a trace of any acid is added to the water, even such a small amount of carbonic acid as would be dissolved from contact with outdoor air, a considerable increase in the number of hydrogen ions occurs. In fact, an acid may be defined as a substance which in solution dissociates so as to liberate hydrogen ions. Some acids, for example, hydrochloric, dissociate much more completely than others, such as phosphoric or acetic. As the activity of acids is entirely dependent upon the number of free hydrogen ions liberated, the more completely dissociated acids are considered "strong" and the less dissociated "weak."

Ions in solution behave in an interesting way when additional ions of the same kind are introduced—they tend to associate again to form molecules. For example, a solution of hydrochloric acid is largely ionized into $\overset{+}{H}$ and $\overset{-}{Cl}$ ions, there being some undissociated molecules of HCl, the amount of undissociated HCl being determined by the number of contacts occurring in a unit of time between the free $\overset{+}{H}$ and $\overset{-}{Cl}$ ions. The whole state of affairs may be expressed in a simple chemical equation,

$$(HCl) \rightleftharpoons (\overset{+}{H}) \quad (\overset{-}{Cl})$$

which indicates that HCl is being constantly associated and dissociated. There is a certain point of equilibrium, however, at which as much HCl is formed as is broken up. Now, suppose we add to the solution some sodium chloride; this also dissociates into ions.

$$(NaCl) \leftrightarrows (\overset{+}{Na}) \quad (\overset{-}{Cl})$$

The increase in the number of Cl ions now present results in more contacts between $\overset{+}{H}$ and $\overset{-}{Cl}$ ions than before since the $\overset{+}{H}$ ions have just so much more chance of meeting and combining with $\overset{+}{Cl}$ ions the greater the number of the latter present. The point of equilibrium is therefore changed and the whole reaction shifts to the left.

$$\underleftarrow{(HCl) \leftrightharpoons (\overset{+}{H}) \quad (\overset{-}{Cl})} \quad (\overset{-}{Cl})$$

This means that the number of $\overset{+}{H}$ ions existing in solution has been decreased.

This phenomenon is an illustration of a principle known as the "mass law." The operation of this principle is of considerable importance in regulating the hydrogen ion concentrations occurring within the body. For example, carbon dioxide or carbonic acid is produced as one of the products of oxidation of all foodstuffs. This is poured into the blood and transported to the lungs where it is removed in the expired air. If carbonic acid gas were brought in contact with pure water at the same concentration of tension at which it exists in the body or in the air in the pulmonary alveoli, it would dissolve in the water and dissociate according to the following formula:

$$H_2CO_3 \rightleftharpoons (\overset{+}{H}) \quad (H\overset{-}{C}O_3)$$

The amount of ionized H present would be sufficient to exert a marked or even fatal physiologic action. If, however, there were added to the water a small amount of sodium bicarbonate, this latter salt would dissociate as follows:

$$(NaHCO_3) \rightleftharpoons (\overset{+}{Na}) \quad (H\overset{-}{C}O_3)$$

The $H\bar{C}O_3$ ions present will cause the $H\bar{C}O_3$ ions from the carbonic acid to unite with more hydrogen ions, or in other words, to shift the reaction towards the left. This is exactly what happens in the blood serum which may be considered a dilute solution of sodium bicarbonate (0.25%). Were it not for the bicarbonate (and other substances acting in a similar manner) the carbonic acid formed during metabolism would give rise to a sufficient number of hydrogen ions to poison the entire body. This is what happens when the blood bicarbonate is reduced in the clinical condition known as acidosis. (See Lecture II.)

Before leaving the subject of hydrogen ions, attention should be drawn to other means by which these ions may be removed from solution and thus rendered innocuous to the body. Of course, the simplest method of all is to neutralize the $\overset{+}{H}$ ions by means of $\bar{O}H$ ions, or in other words to add an alkali which may be defined as a substance giving rise to $(\bar{O}H)$ ions in solution. If we add to a solution of HCl some NaOH we will have the constituents for the following ions in solution:

$$(\overset{+}{H}) \quad (\bar{C}l) \quad (\overset{+}{N}a) \quad (\bar{O}H)$$

But practically all of the $\overset{+}{H}$ and $\bar{O}H$ ions will immediately unite to form undissociated water molecules and the solution will contain only $\overset{+}{N}a$ and $\bar{C}l$ ions, there being no more hydrogen ions present than in pure water.

Another very similar means of removal of hydrogen ions is by means of poorly dissociated salts or "buffers." For example, a solution of sodium phosphate Na_2HPO_4 is very slightly dissociated into $(\overset{+}{N}a)$ $(NaH\bar{P}O_4)$ and if to this is added HCl we have in solution the following ions ($\overset{+}{H}$) ($\overset{-}{Cl}$) ($\overset{+}{Na}$) ($\overset{-}{NaHPO_4}$). The ($\overset{-}{NaHPO_4}$) ion not being readily dissociated, will hold to both ($\overset{+}{H}$) and ($\overset{+}{Na}$) depending upon the relative amounts of each present. The ($\overset{+}{H}$) ions will therefore be in part bound or will cease to be ions, so that the number of hydrogen ions remaining in solution is much smaller than in the case of HCl dissolved in water. Or, putting it in another way Na_2HPO_4 in solution is a very weak base, NaH_2PO_4 a very weak acid. When HCl is added to Na_2HPO_4 it is changed to NaH_2PO_4 according to the following equation: $Na_2HPO_4 + HCl = NaCl + NaH_2PO_4$, but this causes only a very slight change in acidity because the weak acid NaH_2PO_4 has taken the place of the stronger acid HCl. It is interesting to note that dilution of buffered solutions, even with large volumes of water, does not change very greatly the hydrogen ion concentration. Proteins which, under certain conditions behave as weakly dissociated acids, have a similar effect in removing hydrogen ions from solutions. Such buffer substances are present in all fluids and tissues of the body and may be considered as the natural protectors against the toxic hydrogen ion.

It must not be assumed that the hydrogen ion is the only one which is capable of exerting a physiologic action. Many other ions, both anions and the cations, are capable of exerting marked effects on body cells. The hydroxyl ion $\overset{-}{OH}$ is about as important as the $\overset{+}{H}$ ion in this respect. An increase in $\overset{+}{H}$ ions is necessarily associated with a decrease in $\overset{-}{OH}$ ions and for most physiologic processes a certain balance between the two is essential, a slight predominance of the hydroxyl ions being the rule in body tissues and fluids.

The ions of potassium, calcium, magnesium, sodium and iodine play a very important rôle in the body. For example, potassium ions when present in the circulating blood, in very minute amounts, cause a relaxation of the heart muscle. Calcium ions, on the other hand, lead to increased tone of the same muscle. A balance between the two is essential for normal cardiac action. Calcium ions are necessary for the coagulation of the blood and the curdling of milk and when removed by specific buffers or by precipitation, these coagulation phenomena do not occur. When there is a decrease in the number of calcium ions in the blood serum in comparison to sodium and hydroxyl ions, an increased irritability of the nerves and muscles occurs which is manifested clinically as tetany. Some of the conditions just mentioned will be discussed more fully in subsequent lectures.

The ionization occurring in watery solutions is of great physiologic importance, but there are still further properties of aqueous solutions which are equally important.

Surface Tension

The molecules composing water are held together by a force of unknown nature termed, for want of a better name, "molecular attraction." This force is tremendous and quite comparable to that holding together the molecules in a bar of iron. Water can be made to change its shape readily, but can hardly be pulled apart any easier than it can be compressed.

At the surface of water we have a unique physical condition. The molecules there are acted upon by the forces of molecular attraction exerted only in certain directions, that is, downwards and sidewise, but not upward. This may be appreciated from the diagram in which lines of attraction are represented by the dotted lines. (Fig. 1.)

There exists therefore a surface film one molecule thick which differs in its properties from the remainder of the water. This film in fact acts like a thin stretched elastic membrane. Its action can be demonstrated by a

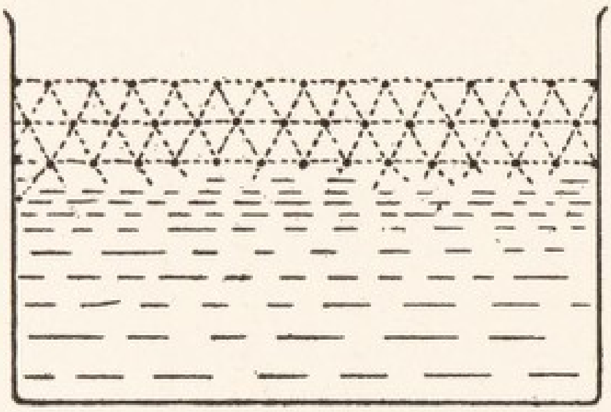


Fig. 1.—Illustrating molecular attractions in solution. The dotted lines represent hypothetical lines of attractive force. Note that a single layer of molecules at the surface has attractions exerted only to the side and downward.

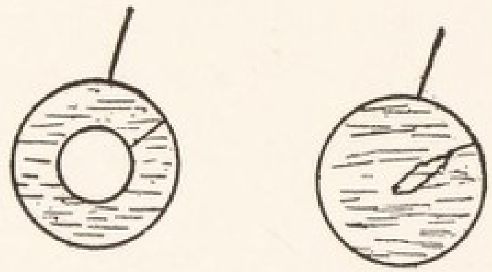


Fig. 2.—Illustrating the force of surface tension. A loop of silk thread is suspended inside a wire loop filled with a soap film. When the film is punctured inside the thread loop, the loop is held open by the surface tension of the surrounding film.

simple model. (Fig. 2.) A loop of silk thread is fastened within a wire loop and the whole filled with a soap-water film. The film is punctured inside the thread loop. Immediately the loop is pulled out in the form of a perfect circle being held open by the tension exerted by the surface film. The strength of this potential membrane may be readily measured in terms of units of force or *dynes* necessary to pull it apart. This force is known as the "surface tension."

Two methods of measurement are in general use. One of these (the Du Noüy method) consists in suspending at the surface of the liquid a circle of platinum wire and measuring the force necessary to pull the wire away from the surface. The second method depends upon the principle that the size of a drop of liquid falling from a pipette is influenced by the surface tension. When the surface tension is low, the drop falls off quickly and

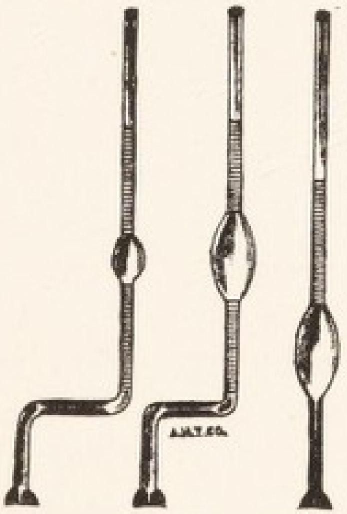


Fig. 3.—Traube's stalagmometer. The surface tension is proportional to the number of drops formed in a given time. The right-angled tubes are for thin liquids, and the straight one for blood and other viscous fluids. (Macleod.)

is small; when high, the drop is larger. A special pipette for measuring the number of drops in a given amount of liquid is known as a *stalagmometer* and provides a quick and simple means of determining the surface tension. (Fig. 3.)

Pure water has a high surface tension as compared with most other liquids, but when certain substances such as soap or bile salts are dissolved in the water, the surface tension is distinctly lowered. It has been found that molecules of the substances which lower surface tension concentrate at the surface in accordance with a certain well-known law of physics. This concentration of molecules occurs at every surface whether between air and water or between water and glass or at the surface of any substances suspended in the water. If a sufficiently large surface of solid material is exposed practically all of the dissolved substance may accumulate at the surface and thus be removed from the bulk of the solution. For example, if a solution of potassium permanganate is poured through a tube containing glass wool with its large exposed surface, the liquid running out at the end of the tube will be practically colorless, all of the salt having collected at the surface between water and glass. This phenomenon of concentration of dissolved substances at surfaces is known as *ad*sorption and plays a very important rôle in biological processes.

As we shall see later, the structure of protoplasm is such that enormous areas of surface are exposed. Adsorption at the surface of body cells seems to be necessary in order to bring about certain biological reactions, such as the interchange of fluids and salts between the inside and outside of cells. Adsorption of molecules at the surface of small suspended particles often accelerates chemical action and some enzymes are believed to act by adsorbing reacting substances at the surface of small particles existing in suspension. The union of diphtheria toxin with antitoxin seems to be an adsorption phenomenon rather than a true chemical union. The action of the so-called opsonins in rendering bacteria more easily engulfed by leucocytes has been supposed to be due to changes in surface tension. The action of the urinary antiseptic hexylresorcinol is assumed to be largely that of altering surface tension of the media in which bacteria are present. In the fertilization of eggs, and fission of cells, as well as in the migration of plasma cells and leucocytes in the body, changes of surface tension occur which seem to initiate the activity.

The lowering of surface tension of the blood by the production of certain bacteria growing in the body results in an injury to body cells evidenced clinically by edema and albuminuria. This is seen in the familiar acute parenchymatous nephritis or nephrosis. Other substances which raise the surface tension of the blood tend to alter adsorption phenomena at the surface of body cells and membranes in such a way that water and salts pass out of the tissues and into the blood. The use of theobromin sodio-salicylate (diuretin), is a clinical application of this fact. This substance, when administered, tends to oppose a decrease in the surface tension of the blood; when this is administered, fluids and salts pass into the blood from the tissues and edema is decreased. Fluid and salts from the cerebrospinal system also tend to pass into the blood. This phenomenon has been utilized in the treatment of hydrocephalus by diuretin.

Osmotic Pressure

One more important property of solutions from the biological standpoint remains to be considered, namely the so-called "osmotic pressure." It has already been mentioned that molecules of water have strong attractions for each other. It should also be noted that there is an attraction between molecules of water and those of dissolved substances. The intensity of this attraction can readily be demonstrated and measured. We are all familiar with the fact that water containing salt boils at a temperature higher than pure water. This is apparently due to the fact that the nonvolatile salt molecules exert an attraction on the water molecules and prevent them from leaving the solution, until by the extra energy of motion imparted to them by heat they are able to break away. Likewise the freezing point of salt water is lower than that of pure water because the attraction of salt for the water molecules does not allow them as great freedom to form into aggregates as ice. A still better demonstration is based on the fact that membranes can be prepared with holes of such size that water molecules can pass through but the molecules of dissolved substances cannot.

Suppose we put pure water in a cylinder, one end of which is closed with such a semipermeable membrane and immerse the cylinder in water. The levels of fluid inside and outside would quickly become the same, as water would pass through freely in each direction.

If we place salt solution instead of water inside the cylinder, water from the outside would still be able to pass in freely, but the water inside could not pass out as readily, on account of being held by the molecular attraction of the salt. As a result, the amount of water inside would increase and the level of the fluid would rise until the pressure within the cylinder became sufficient to counteract the molecular attraction and force as much water out as is drawn in. This pressure could easily be measured by attaching a narrow manometer tube to the top of the cylinder and noting the height reached by the column of water. (See Fig. 4-*A*.)

As the height to which the water would rise would be many feet in the case of even dilute salt solutions, a mercury manometer is usually used and the pressure expressed in terms of the number of centimeters height to which the mercury rises (Fig. 4-*B*). This pressure is known as "osmotic pressure." Substances which dissociate, such as salt, have a distinctly higher osmotic pressure in solution than substances, such as sugar, which do not dissociate. This is apparently due to the fact that individual ions each exert an attraction for water comparable to that of intact molecules. As osmotic pressure is dependent upon molecular attraction, it is proportionate to the number of molecules present. Therefore, the larger the molecule and the higher the molecular weight, the greater must be the amount of dissolved substances in order to produce a given osmotic pressure. A solution of sodium chloride with its small molecules would have, therefore, a far greater osmotic pressure than a solution of protein of the same concentration but with larger and consequently fewer molecules.

Some idea of the magnitude of osmotic pressure may be gained from the fact that the salts dissolved in the

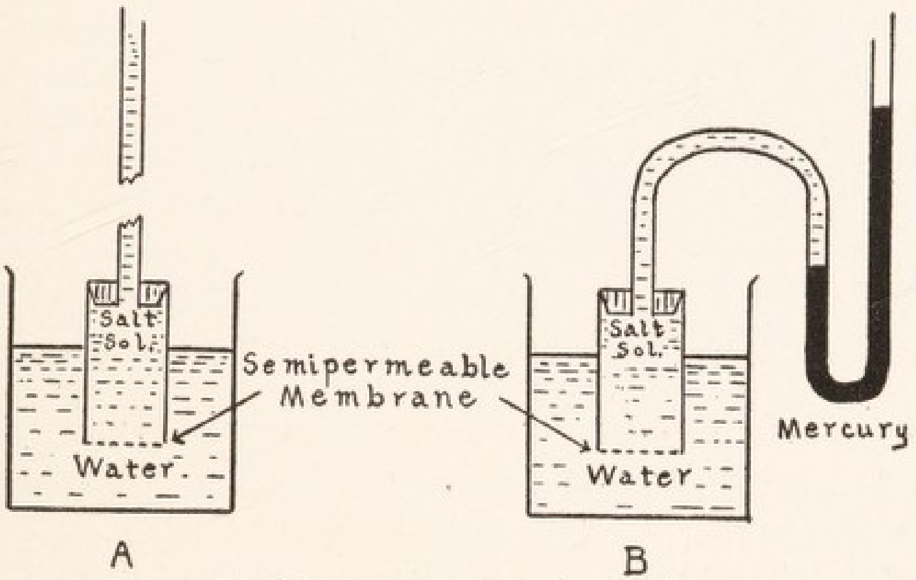


Fig. 4.—The direct measurement of osmotic pressure.

blood plasma give it an osmotic pressure of about 7 atmospheres, which is equivalent to about 100 pounds to the square inch. This represents the pressure which theoretically would be exerted within a red blood cell, and other body cells, if placed in distilled water. Under such circumstances, the increasing pressure would cause first swelling and then bursting of the cell long before the maximum pressure was attained. A solution having the same osmotic pressure as the blood is designated as *isosmotic,* or *isotonic,* a solution with a higher osmotic pressure as *hypertonic* and one with lower as *hypotonic.*

From the foregoing it is evident why hypotonic solutions lead to swelling of body cells and hypertonic solutions lead to a shrinkage of cells and a passage of intercellular fluid out into the more concentrated solution. The use of concentrated salt solutions intravenously to relieve intracranial pressure and of strong solutions of glucose for nasal irrigations are practical applications of these facts. In this connection it should be mentioned that an isotonic solution of sodium chloride has a strength of 0.9%, of glucose 5.0%.

Osmotic pressure plays an important rôle in physiology, since semipermeable membranes occur throughout the body. These membranes differ greatly in structure and in permeability. Most of them are of such character as to allow the free passage of water, salts and small organic molecules, but not the larger molecules of protein. During the process of digestion in the intestinal tract small molecules broken off pass into the blood; the larger molecules remain until they in turn are broken down into smaller particles. Individual body cells retain their protein, while small molecules of food materials pass in and waste products pass out through the cell walls. Certain cells have a peculiar selective permeability as yet not completely explained. Thus red blood corpuscles allow oxygen, carbon dioxide, water, glucose, chlorine and ammonium ions to pass through freely but are almost impermeable to sodium and potassium ions. Some cells are permeable to sodium but not to calcium, and others which are permeable to either potassium or calcium become impermeable to both when they are present together in the surrounding fluid. The walls of capillaries are practically impermeable to proteins when they are contracted, but are freely permeable when dilated.

The membranes of many of the body cells seem to be associated with fat-like substances or lipoids, the best known of which are lecithin and cholesterol. Both of these substances lower surface tension and hence by adsorption tend to accumulate at cell surfaces. They undoubtedly have an effect in altering cell permeability. Most anesthetics are soluble in these lipoids and possibly influence the cells in this way.

The addition of substances which lower the surface tension more than those already present in solution tends to displace the substances from the surface and thus alter cell permeability. This apparently occurs in tubular nephritis.

In certain skin diseases, such as eczema, there seems to be a change in permeability of cells which results in a pouring out of exudate, a lowering of the surface tension of the blood has been demonstrated in certain cases of eczema, and it is interesting to note that one of the effective local remedies for the condition, namely, coal tar, is a substance having a marked influence on surface tension. It would not be surprising if a good many of the problems of dermatology should be solved by application of some of the principles just mentioned.

Colloids

Mention has been made of the fact that proteins do not pass through most of the semipermeable membranes, for example, hemoglobin does not pass through a collodion or parchment membrane, or through the walls of red blood cells. This inability of protein to pass through membranes has been explained on the basis of the large size of the molecule. Other substances besides proteins have this same characteristic. As a group, these substances are known as colloids because of their resemblance to glue (Greek *Κoλλα* glue).

Substances which permeate readily have been termed crystalloids because many of them may be crystallized.

The distinction is really one only of degree. Proteins which make up the bulk of the body tissues are all composed of very large molecules, some of them so large in fact that they can be discerned by means of the ultra-microscope. The molecular particles themselves cannot

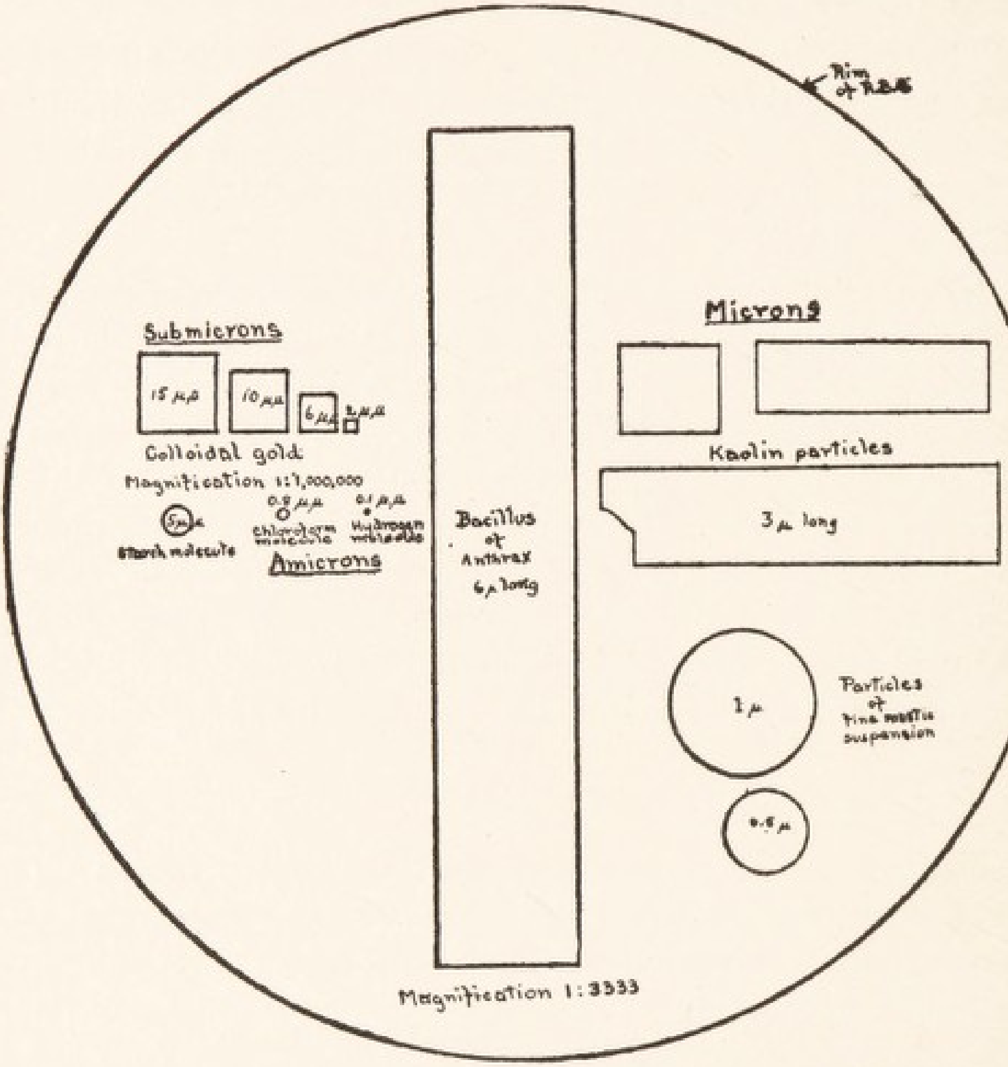


Fig. 5.—Diagram from W. Ostwald showing the relative size of various particles and colloidal dispersoids compared with a red blood corpuscle and an anthrax bacillus. (Macleod: Physiology and Biochemistry in Modern Medicine.)

be seen in the same sense that ordinary objects are seen, but in the way that dust in the atmosphere is made visible by an indirect beam of sunlight, a visible halo being thrown around each particle. The large molecules of protein act more like suspended particles in a liquid rather than as true solutes. They expose a large surface and therefore favor adsorption phenomena.

Proteins in solution have other interesting properties. They are slightly ionized and give rise to either hydrogen or hydroxyl ions, that is, they act either as acids or alkalies. In a solution slightly alkaline they act as acids, dissociating so as to liberate hydrogen ions. This

Fig. 6.—Dissociation of protein molecules in alkaline solution.

Fig. 7.—Dissociation of protein molecules in acid solution.

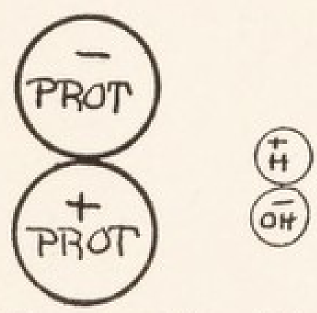


Fig. 8.—Dissociation of protein at "isoelectric" point.

may be pictured as in Fig. 6, the large protein molecule separating a small hydrogen ion. This leaves the remainder of the molecule with a negative charge. In acid solutions, on the other hand, the proteins dissociate as shown in Fig. 7, the large protein remnant now having a positive charge. At a certain degree of acidity or alkalinity of the solution, which is different for each protein, the dissociation into H and OH ions is equal and the remnants of the molecule are partly negatively and partly positively charged and tend to unite in large aggregates to form semisolid masses (Fig. 8). The particular point at which this occurs is known as the isoelectric point. At this degree of acidity or alkalinity proteins may readily be precipitated. This principle is applied in the precipitation of the active portion of pancreatic extracts containing insulin so as to separate the insulin from contaminating substances.

The property of proteins of acting as either acids or bases enables them to neutralize considerable amounts of either acid or alkali. They are excellent buffers, for example, excessive acid in the stomach is rendered largely inactive by the feeding of protein, and a fair number of hydrogen ions in the blood are cared for by the hemoglobin of the corpuscles.

Colloids, other than proteins, also consist of electrically charged particles in a state intermediate between suspension and solution. Examples of such colloids are the gums of acacia and mastic and the "colloidal solutions" of the heavy metals, gold, platinum and iron, and such finely divided material as kaolin.

When a solution containing positively charged colloid particles is mixed with one containing negatively charged particles, these two types of particles are attracted to each other as always occurs in the case of bodies with opposite charges, and under these circumstances precipitation is likely to occur. This is the principle upon which the colloidal gold and mastic tests on spinal fluids are based. It is stated that bacteria are, in general, negatively charged, that is to say, they wander to the anode when an electric current is passed through a suspension of bacteria in water. When agglutinins are added, the negative charge is neutralized and the bacteria do not wander to either pole. It is also claimed that toxins and antitoxins carry electrical charges and that this accounts for some of the phenomena of immunity reactions.

Protein molecules in solution have an attraction for water, which is an important factor in maintaining a normal water content of the blood and tissues, since the protein is held back in vessels and cells, and holds with it an amount of water corresponding to its osmotic pressure. When the volume of the blood is diminished, as in shock, and following hemorrhage, the intravenous administration of such a colloid as acacia, which acts in a similar manner to protein, serves to restore temporarily the blood volume.

We have considered, so far, a few of the more important facts concerning the nature of the materials which go to make up the body and the manner in which these materials react with each other, and thus give rise to the phenomena of life. In describing the mechanism of these processes certain terms have been used which, until recent years, have been unfamiliar to most persons outside of the laboratories of physiologic chemistry. During the next few years we, who are practitioners, will hear more frequently of these terms and the mechanisms which they imply. Phenomena of disease which are now obscure will become clearer and with a more complete understanding of the forces acting within the body will come a greater ability to direct those forces in such a manner as to lead to the maintenance of normal bodily functions.

LECTURE II

ACIDOSIS AND ALKALOSIS

Very considerable amounts of acid are constantly being produced in the body during the processes of normal metabolism. These acids, like all others, owe their activity to the hydrogen ions liberated in solution and, as we have seen in the preceding lecture, the hydrogen ion is capable of bringing about marked physiologic changes, or even death. Fortunately, the body possesses very effective mechanisms for rendering the hydrogen ions ineffective. So efficient are the mechanisms that under all ordinary conditions of life the chemical reaction, that is, the hydrogen ion concentration of the blood and of the fluids bathing the body cells, remains practically constant. Some idea of the delicacy of the regulation may be obtained from a consideration of the fact that a reaction of the blood as acid as distilled water, on the one hand, or as alkaline as ordinary tap water, on the other, is incompatable with life.

The degree of acidity or alkalinity within the various cells of the body differs slightly from that of the blood, but the blood reflects the reaction throughout the body.

Before considering the means of defense of the body against acid, we should become familiar with certain terms and methods of expression.

Hydrogen Ion Concentration

We are all familiar with the fact that acids turn litmus paper red and alkalies turn it blue. We also know that the amount of acid in an ordinary solution in the chemical laboratory can be determined by adding a little litmus or other "indicator" and then, drop by drop, a standard solution of alkali until the color changes, such methods, however, are not nearly delicate enough for the estimation of the degree of acidity or alkalinity of body fluids, for the addition of a single drop of tenth normal acid to a quart of water would change the reaction to a greater degree than any changes occurring in the blood during life. We must, therefore, seek for a new means of expression. The most logical means of expressing the degree of acidity of a solution is in terms of the number of hydrogen ions present, since it is the hydrogen ions which give to solutions of acids their characteristic chemical and physiologic properties.

In one liter of a solution of "normal" hydrochloric acid there is approximately 1 gram of free hydrogen ions. A tenth normal solution, the strength usually used in chemical work, contains one-tenth of this amount, or 0.1 gm. ionized hydrogen per liter. Pure water, which is slightly dissociated into ($\overset{+}{H}$) and ($O\overset{-}{H}$) ions, contains only 0.000,000,1 gm. of ionized hydrogen per liter. There are, of course, as many ($O\overset{-}{H}$) ions as ($\overset{+}{H}$) ions. Water is chemically neutral, inasmuch as there is a predominance of neither hydrogen nor hydroxyl ions, the one giving the solution acid qualities and the other alkaline. A "neutral" solution may, therefore, be defined as one containing exactly 0.000,000,1 gm. of hydrogen ions per liter. An acid solution will contain a larger amount and an alkaline solution a smaller amount than this. In order to avoid the use of cumbersome decimals, a simplified method of expression is adopted. The figure 0.000,000,1 or 1/10,000,000 is the same as $1/10^7$ or 10^{-7} the negative exponent 7 simply meaning that the 10 is divided by itself 7 times. This is expressed still more simply by omitting the minus sign of the exponent and using the term pH 7 to indicate that the solution contains 0.000,000,1 gm. of ionized hydrogen per liter. This is the expression for a neutral solution. A solution of pH 6 would have 0.000,001 or ten times as many H ions and only 1/10 as many OH ions, that is, there would be an excess of the H ions, so the solution

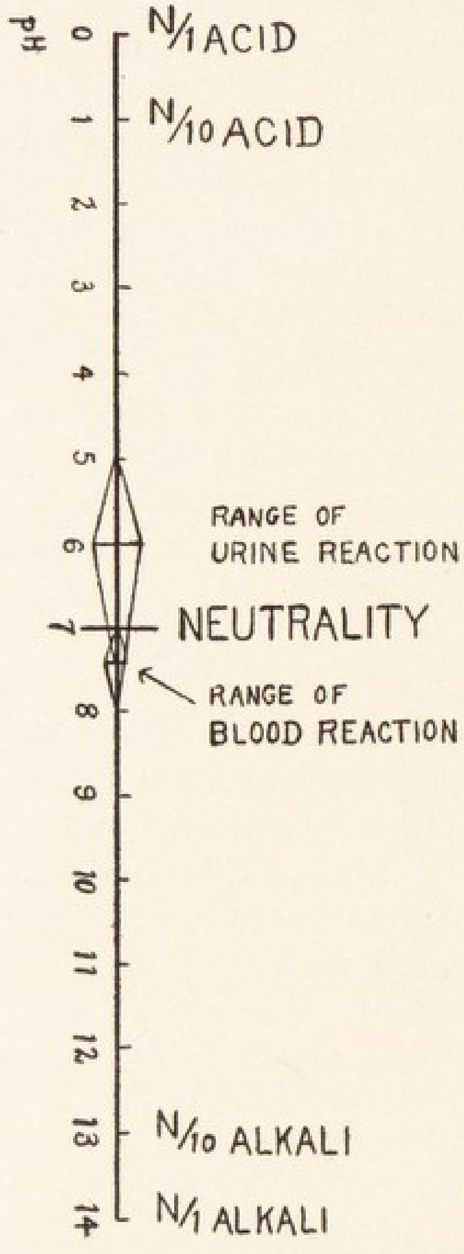


Fig. 9.—Chart illustrating the meaning of the term pH or hydrogen ion concentration, and ranges of chemical reactions of blood and of urine.

would be acid. A solution having a pH of 5 would, in turn, be 10 times as acid as one having a pH of 6, etc. It is to be noted that the *lower* the pH figure the *greater* the acidity. A pH greater than 7 would indicate that the solution had fewer hydrogen ions than water and therefore a relative preponderance of OH ions, which is the same as saying that the solution is alkaline. In the chart (Fig. 9) these relations are expressed graphically.

The Reaction of the Blood

To return to the blood, the reaction under normal conditions is in the neighborhood of pH 7.4. It is, therefore, slightly alkaline. During health the variation is probably not greater than from pH 7.3 to pH 7.5. In fatal cases of acidosis the reaction may vary as far as pH 7.0 or pH 6.9 to the acid side. On the other hand, a variation as far as pH 7.8 to the alkaline side would be manifested by the clinical symptoms of alkalosis, a condition quite as serious as acidosis.

Let us now consider the means by which the blood retains its reaction with such constancy. The blood plasma may be considered as a solution of sodium bicarbonate of a strength of 0.25 per cent, that is 2.5 grams of bicarbonate to a liter of water. This is a bicarbonate concentration equal to that of two soda mint tablets dissolved in a tumbler full of water. Besides bicarbonate other inorganic salts and protein are also present, but these need not concern us for the time being.

When carbonic acid is added to a weak solution such as sodium bicarbonate, the reaction changes from the alkaline toward the acid side. This can well be illustrated by adding to the solution a drop of an indicator such as phenol red, which is red in alkaline solutions, yellow in acid, and which undergoes a series of intermediate color changes between pH 7 and pH 8. The greater the amount of carbonic acid present in proportion to the amount of bicarbonate, the more acid will be the solution, that is, the reaction will be determined by the proportion $\frac{H_2CO_3}{NaHCO_3}$. When this as approximately 1/20 the reaction will be pH 7.4. The reaction of a solution of sodium bicarbonate will not change nearly as much to the acid side on the addition of carbonic acid as will pure water, because of the effect of the HCO_3 ion of the $NaHCO_3$ in preventing the dissociation of carbonic acid, as explained in the first lecture; that is, the bicarbonate acts as a "buffer solution." A slight change in reaction, however, will occur.

The change occurring in blood plasma on the addition of CO_2 is somewhat less than in the case of a pure solution of sodium bicarbonate, because of the fact that the protein of plasma also acts, to some extent, as a "buffer" substance. Whole blood, with its corpuscles as well as plasma, changes its reaction still less on addition of considerable amounts of carbonic acid. This is explained by the fact that the red cells also take up carbonic acid, but in addition, due to their peculiar permeability, allow hydrogen and chlorine ions to pass through into the cells, but not sodium or potassium ions. As the plasma contains also some sodium chloride, this, reacting with carbonic acid, according to the following equation:

$$NaCl + H_2\,CO_3 \rightleftharpoons HCl + NaHCO_3$$

gives rise to sodium bicarbonate and a very small amount of hydrochloric acid, which is constantly removed by entrance into the red cells. This leaves behind some extra sodium bicarbonate to further neutralize the carbonic acid. The corpuscles can, in this way, care for considerable acid. In severe anemia, the blood can care for less acid because of the reduction in the number of red cells.

Chemical Regulation of the Respiration

The reactions described are exactly those which occur when the blood passes through the tissues. Here it comes in contact with carbonic acid produced from the combustion of foods. Blood leaving the tissues, that is to say, venous blood, contains considerable amounts of carbonic acid, but has only a slightly different pH from the arterial blood reaching the tissues. This venous blood goes to the lungs and is there aerated on passing through the thin walled capillaries surrounding the pulmonary alveoli on the opposite side of which is air containing relatively little carbonic acid. The capillaries being freely permeable to carbonic acid, allow this gas to escape until the concentration or tension is the same outside as inside the capillaries. In this way carbonic acid is again removed from the blood and the reaction shifts again slightly towards the alkaline side. This change may readily be demonstrated in the test tube by blowing a little pure air through a weak bicarbonate solution containing an indicator and into which carbonic acid has previously been passed.

Of course all of the carbonic acid is not removed from the blood as it passes through the lungs, for the air in the pulmonary alveoli will never be pure air but will always contain a certain amount of carbonic acid. An equivalent amount will remain in the blood. This amount remaining in arterial blood is sufficient when the blood now passes through the respiratory center in the brain to stimulate this center with resulting respiratory movement. The more carbon dioxide that remains, the greater will be the stimulus and the deeper the inspirations. This will, in turn, have the effect of reducing the carbonic acid content. When this has fallen to normal limits, the respiratory stimulation will then be normal and the respirations of normal depth. If one takes a number of voluntary forced respirations, so much carbonic acid may be removed from the blood that an insufficient amount remains to stimulate the respiratory center, and for a period of time there may be no spontaneous respiratory movements. This fact, as we shall see later, explains some of the irregular respiratory movements observed in certain clinical conditions.

When carbon dioxide is removed from the blood in the lungs, the blood is then ready to return to the tissues for another "load" of this waste product. But this is not the sole function of the blood. Not only must carbonic acid be removed, but oxygen must be carried to the tissues. In the lungs, oxygen enters the blood, but as it does not combine with any constituent of the plasma and is only slightly soluble in water, a relatively small amount is retained in the plasma. It quickly diffuses through into the red blood cells where it combines with hemoglobin to form oxyhemoglobin. Hemoglobin itself is a protein which, at the reaction of the blood, acts as a very weak acid. Oxyhemoblobin is a considerably stronger acid. The passage of oxygen into the red blood cells, therefore, results in the liberation of additional hydrogen ions inside the red blood cells and these in turn unite with such base as may be available and displace a part of the bound carbonic acid which then escapes out through the cells into the plasma and finally into the pulmonary alveoli. Conditions in the lungs are therefore very favorable for the removal of carbonic acid from the blood. When the blood again circulates through the tissues it reaches locations where very little oxygen is present, on account of having been utilized. Oxygen of the blood, being at a higher concentration, tends to diffuse out into the tissues where the concentration is low. As the oxygen leaves the hemoglobin, the inside of the red cell becomes more alkaline and therefore capable of taking up more carbonic acid and so the cycle continues.

When excessive amounts of carbonic acid are produced in the tissues, as after severe muscular exercise, the amount of carbonic acid poured into the blood may be more than can be removed by normal respiratory movements, an excess of carbonic acid remains in the arterial blood leaving the lungs and when this blood reaches the respiratory center, the respiratory movements are stimulated, hence the increased breathing following exercise. It is thus seen that the activity of the respiratory system is an important factor in keeping the hydrogen ion concentration of the blood within normal limits, any increase in hydrogen ion concentration resulting in a stimulation of the respiratory center which stimulus continues until an approximately normal reaction of the blood is attained by the blowing out of carbonic acid.

The respiratory center may be damaged by disease or injury so that it fails to respond to a normal stimulus and in that case there may be prolonged periods of apnea. The obvious treatment in such cases is to apply a greater stimulus to the respiratory center, and this can be done most readily by increasing the carbonic acid content of the blood, acid in general, and carbonic acid in particular, being the normal respiratory stimulant. The amount of carbonic acid in the blood may be greatly increased by having the patient breathe a mixture of oxygen and carbon dioxide, using artificial respiration at the start, if necessary. A mixture of 5 per cent carbonic acid in oxygen (which can be obtained in tanks) is a suitable mixture to use continuously. A larger amount of carbonic acid, up to 30 per cent, or even a few whiffs of carbon dioxide from a tank or generator may be used at the start to supply a strong stimulus to the respiratory center. This is a valuable means of treatment of infants who, as the result of intracranial birth injuries, suffer from periods of apnea and become cyanotic. In such instances oxygen inhalation alone is not successful on account of the suppressed breathing. A mixture of carbon dioxide and oxygen provides a method for administering more oxygen than would otherwise be possible.

In the case of newly born infants who do not begin to breathe promptly, the oxygen of the blood is used up and must be replenished. A 5 per cent mixture of carbon dioxide in oxygen serves as a stimulus to the respiration and leads to an increased intake of oxygen. Respirations must, however, be initiated by the usual means such as skin stimulation or artificial respiration. The inhalation of carbon dioxide mixtures is a safe and more effective and more rational procedure than the administration of alpha lobelin.

Carbonic acid inhalation is also of value in the case of apnea occurring as the result of anesthesia. Stimulation of the respiratory center by inhalation of carbonic acid is also an effective means of increasing the respiration in order to remove carbon monoxide from the body in cases of poisoning from illuminating gas or from the exhaust gases of automobiles. Stimulation of the respiration by this means also results in removal of alcohol and other volatile poisons from the body by way of the lungs. It is a good means of reviving those completely anesthetized by overdoses of alcohol.

We have seen that carbonic acid is readily cared for by the body, being volatile and readily expired by the lungs. All acids cannot be disposed of in quite so simple a manner. Under certain conditions, which will be referred to later, large amounts of nonvolatile acids such as acetoacetic, betaoxybutyric and lactic are produced in the body, and mineral acids, such as hydrochloric, sulphuric, and phosphoric are introduced with the food or are produced during the processes of metabolism.

Let us consider what happens to the blood when such acids are added. Consider first the simple bicarbonate solution which represents the plasma. If we add an acid to a bicarbonate solution, the following reaction occurs:

$$Na\,HCO_3 + HCl = NaCl + H_2CO_3.$$

The amount of bicarbonate is decreased and the amount of carbonic acid increased. The solution, therefore, becomes more acid. The carbonic acid formed could be blown out of this solution, or in the case of the blood, removed by the lungs, but the amount which would have to be removed would be different than under normal conditions if the reaction of the solution were to remain constant. With the bicarbonate reduced to one-half, the carbonic acid would likewise have to be reduced to one-half in order to maintain the normal hydrogen ion concentration, since it is the ratio $\frac{H_2CO_3}{NaHCO_3}$ which determines the pH. In the body, however, the production of carbonic acid as the result of activity would continue at a normal rate and this amount thrown into the blood would be relatively in excess of the amount of bicarbonate present. The hydrogen ion concentration would therefore, increase and the respiratory center would be stimulated to a greater degree than normal. This would lead to increased pulmonary ventilation which would continue indefinitely unless the bicarbonate of the blood were in some way replenished. With these deeper respirations the concentration of carbonic acid in the pulmonary alveoli would be lessened, the air in the alveoli would, in fact, be in equilibrium with that in the plasma and if the carbonic acid of the plasma were reduced to one-half the concentration or tension of this substance in the lungs would be proportionately reduced. It is for this reason that the concentration, or tension, of carbonic acid in the alveolar air is a measure of the degree of acidosis, and hyperpnea, or increased pulmonary ventilation, is the clinical evidence of the condition.

When the bicarbonate is seriously depleted, increased ventilation almost, but never quite, brings the hydrogen ion concentration of the blood back to normal. The reaction of the blood shifts ever so slightly towards the acid side changing from the normal pH 7.4 to 7.3 or 7.2, or in extreme cases to 7.0 or even 6.9. This shift in reaction brings about certain changes in the body cells and eventually damage so great that life is no longer possible.

Removal of Acid by the Kidneys

Unless there were means of replenishing the depleted blood bicarbonate or means other than the respiration for the removal of foreign acids from the body, fatal acidosis would frequently occur. Fortunately, there is a mechanism for the replenishment of bicarbonate. The kidneys are able to secrete urine which is much more acid than the blood. This is accomplished by the excretion, chiefly of acid phosphate, which is formed from a more alkaline phosphate occurring in the blood plasma. The reaction taking place is as follows:

$$Na_2HPO_4 + H_2O + CO_2 = \underset{\text{excreted}}{NaH_2PO_4} + \underset{\text{remains in blood}}{NaHCO_3}$$

The amount of bicarbonate saved by this action of the kidneys may amount to a liter or more of tenth normal alkali in a day. This in itself allows the body to care for a great deal of foreign acid. In addition, the kidneys are capable of excreting considerable organic acid as such.

In the presence of acidosis the urine is usually more acid than normal. The urine is normally somewhat acid, having an average pH of about 6.0, although the reaction shifts from time to time during the day, depending upon the intake of food. When any significant degree of acidosis is present, the urine becomes regularly more acid than pH 6.0.

A valuable test for the presence of acidosis consists in adding to the urine the indicator brom cresol purple, which is purple beyond pH 6.0 and greenish yellow to the acid side of pH 6.0. Normal urine may change this indicator either color, but when acidosis is present the pH of the urine will be such almost invariably that the color with the indicator is greenish yellow. If the color is purple, it is presumptive evidence that acidosis is not present. A yellow color does not, however, necessarily indicate that acidosis is present. If a small amount of sodium bicarbonate (4 or 5 grams, or 1 dram) is taken by mouth this will suffice to raise the bicarbonate of the plasma to such an extent in a normal individual that the urine secreted within one-half hour's time will be definitely alkaline to brom cresol purple, that is to say, will give a purple color. In the presence of acidosis larger amounts of alkali will be necessary to accomplish the same result. It is not usually advisable, however, to administer larger doses of bicarbonate in order to render the urine alkaline, especially in cases of nephritis. This phase of the subject is considered further in the discussion of alkalosis.

Another mechanism for the neutralization and elimination of foreign acids consists in the production of ammonia from urea, a neutral substance. This ammonia seems to be formed chiefly in the kidneys and is used to neutralize foreign acids which can then be eliminated as neutral salts. An increase in the amount of combined ammonia in the urine, in proportion to the amount of urea present, is one of the indications of the presence of acidosis. The determination of this value, known as the "ammonia coefficient," is a somewhat difficult procedure and one rarely used at the present time in clinical work. Its significance is also somewhat questionable since in the acidosis of nephritis, there is no increase in the ammonia coefficient because the kidneys then fail to produce or excrete much ammonia.

Ketosis

Let us consider next some of the conditions in which acids accumulate in the body in sufficient amounts to cause a depletion of bicarbonate of the blood and an actual increase in the hydrogen ion concentration. One of the most common causes of acidosis is the overproduction of acids of the ketone group, namely, betaoxybutyric and acetoacetic acids, the condition being designed by the term "ketosis." The ketone acids are produced from fats used as fuel in the body. Under normal conditions fats are broken down by a series of steps, one of the last stages being the two acids mentioned. These two acids cannot be broken down further unless sugar is being utilized at the same time. A peculiar reaction occurs whereby apparently one molecule of sugar is united with two molecules of the acids in question, the product being readily broken down to form carbon dioxide and water. A sufficient amount of sugar for this purpose is not always present. In prolonged starvation, for example, the available sugar in the body is used up and the fuel needs are then supplied largely from stored fat and to a lesser extent from body protein. The amount of sugar available from protein under such circumstances is usually insufficient to unite with the fatty residues and betaoxybutyric and acetoacetic acids are not utilized but accumulate in the tissues and are poured out into the blood. A certain amount of these acids can be cared for by the normal mechanisms previously described, but when large amounts are formed a true acidosis may occur, although it is rarely of a degree sufficient to require treatment or to endanger life, when due simply to starvation.

In severe untreated diabetes, little or no sugar is utilized, although an abundant amount may be present. The fats used therefore go no further than the acetone acid stage and the amount of acid so produced may be sufficient to almost completely neutralize the blood bicarbonate and to lead to a distinct increase in the hydrogen ion concentration of the blood and tissues. The administration of insulin makes it possible for the body to utilize carbohydrate. The acetone acids are then quickly converted to the end-products. Further details as to the action of insulin will be discussed in a subsequent lecture.

In the presence of certain infections, especially some epidemic nose and throat infections and bacillary dysentery, there is an overproduction of the ketone acids. Just how this is brought about is not known. In some of the forms of vomiting in children known as "cyclic vomiting" there occurs a similar toxemia. The production of acetone bodies is also, in part, accounted for by the starvation incident to repeated vomiting. In cases of so-called cyclic vomiting the acidosis is rarely of a sufficient degree in itself to endanger life. There is a mistaken idea that the vomiting in these cases is the result of acidosis and that the administration of alkali will therefore stop the vomiting. Acidosis of a moderate degree does not lead to vomiting. Indeed, one often sees diabetic or nephritic patients with an extremely high degree of acidosis, much greater than that observed in cyclic vomiting, who do not vomit at all. In cyclic vomiting the acidosis and the vomiting are probably each due to the same underlying cause and not necessarily dependent upon each other.

Acidosis Due to Lactic Acid

The forms of acidosis so far considered are due to the ketone acids. There are, however, other forms of acidosis. A common type is that due to the increased production or accumulation of lactic acid. During muscular contraction and during the growth of cells, there is always a considerable amount of lactic acid produced from carbohydrate. This lactic acid plays a very important part in muscular contraction. It is produced from sugar, serves its purpose in bringing about muscular contraction, and is then in part broken down to carbon dioxide and water and in part reconverted back into carbohydrate. When excessive muscular contraction occurs, large amounts of lactic acid are produced which cannot be completely removed, unless sufficient oxygen is available. The necessary oxygen is not always supplied, especially if the circulation is impaired; and as a result, lactic acid accumulates in the body. Slight acidosis occurs after all muscular exercise and is one of the factors leading to the increased respirations. When the circulation fails as the result of cardiovascular disease, so that less blood is brought to the various parts of the body, or when pulmonary aeration of the blood is incomplete, due to pathologic conditions in the lungs, an insufficient amount of oxygen reaches the tissues and lactic acid accumulates.

One important factor leading to decreased circulation of the blood and consequent accumulation of lactic acid is the condition of *anhydremia,* or desiccation. This occurs as the result of excessive vomiting or diarrhea, or exposure to high temperatures or when the water intake is inadequate. When the blood becomes concentrated as the result of desiccation, the rate of circulation is lowered and lactic acid acidosis results. This also occurs when the blood volume is reduced following sudden hemorrhage, or when the blood corpuscles are so few in number that an insufficient amount of oxygen is carried. It is an interesting fact that acidosis due to the acetone bodies and that due to lactic acid rarely, if ever, occur at the same time in the same patient, even though conditions may be such that the combined form of acidosis would be expected to occur.

Acidosis of Nephritis

In nephritis of the glomerular or interstitial type, acidosis is of frequent occurrence. This acidosis is not due to an increased amount of acetone acids, or to any appreciable increase in lactic acid. It is caused, in part, by the failure of the kidney to excrete acid phosphate so that this substance accumulates in the blood, and in part to lack of formation of ammonia. As a result of the failure of these two important mechanisms, the normal acids produced in metabolism may not be completely neutralized and eliminated. A further cause for the acidosis of nephritis is retention of nonprotein nitrogen and in certain instances, sodium chloride. The retention of these two substances is often sufficient to raise the osmotic pressure of the blood, were it not for a compensatory elimination of bicarbonate so that the total osmotic pressure remains the same, nonprotein nitrogenous constituents and chlorides having taken the place of bicarbonate. The reduction in bicarbonate so produced gives rise to a condition of acidosis.

Miscellaneous Types of Acidosis

Following anesthesia, acidosis of a different type develops. This is due, only in part, to an excess of lactic acid or the acetone acids. Other acids of an unknown nature are occasionally present, and there is some damage to the regulating mechanism. In certain cases of pneumonia there is a considerable amount of an unidentified acid in the urine and this acid may be produced in such large amounts that actual acidosis occurs. This, however, is rare.

Following severe burns of the skin acidosis has been observed. This acidosis is due, in part, to lactic acid accumulating as the result of concentration and resulting diminished flow of the blood. It is also due, in part, to other acids, presumably derived from the incomplete breakdown of proteins.

In the presence of severe diarrhea there is sometimes a considerable loss of alkali by way of the bowel, and it has been claimed that the loss may be great enough to lead to actual depletion of the blood bicarbonate. In the presence of severe diarrhea anhydremia occurs and leads to acidosis in the manner just mentioned. There is also present, in some instances, an unidentified acid apparently related to oxyproteic acid, a product of protein destruction.

Signs of Acidosis

Whatever the form of acidosis, certain characteristic symptoms will be present and there will be changes occurring in the body which may be detected by laboratory means. In all forms of acidosis *hyperpnea,* or deep breathing, occurs. The reason for this has already been explained. The breathing differs from that of pneumonia in that it is deep, not shallow, and is not accompanied by cyanosis except in the case of cardiorespiratory involvement. It is pauseless and regular, differing in this way from the respirations of the Cheyne-Stokes or Biot types.

Hyperpnea is the most striking clinical sign of acidosis, but may, at times, be deceptive as it may not be observed in the chronic acidosis of nephritis, but, on the other hand, may be observed in emotional states and following brain injuries.

There are a number of laboratory tests which may be applied to confirm the diagnosis. The determination of the actual hydrogen ion concentration of the blood serves to indicate the presence of an acidosis which has been uncompensated by pulmonary activity in removing CO_2 or by the action of the various other mechanisms for caring for excess acid. The determination of the hydrogen ion concentration of the blood is not difficult. The simplest method and one readily adapted to clinical use depends upon the addition of an indicator (phenol red) to the diluted blood plasma or to the dialysate from blood. The color shown is compared with that of solutions of known hydrogen ion concentration. This method is not sufficiently delicate to detect slight degrees of acidosis, but is very useful in determining the degree of compensation.

A more accurate method applied to the blood consists in a determination of the total content of carbonic acid, both free and combined. This is most readily determined by means of the Van Slyke apparatus in which carbon dioxide is removed in a partial vacuum following the addition of acid. The volume of carbon dioxide evolved is measured. Normally the carbon dioxide content of the plasma is from 60 to 70 volumes per cent in the case of adults, and 50 to 60 volumes per cent in the case of young children. A carbon dioxide content of below 40 volumes per cent is indicative of definite acidosis. Coma usually results when the carbon dioxide falls as low as 15 volumes per cent, and recovery is rare with acidosis of any greater degree.

One of the earlier methods used clinically for the detection of acidosis was the determination of the carbon dioxide content of the alveolar air. This method is applicable only to patients with normally functioning respiratory centers. The method is not as accurate as the determination of blood carbon dioxide but is sufficiently accurate for most clinical purposes. Better results are obtained in the case of patients who can cooperate, but fairly satisfactory results may be obtained even in the case of comatose patients or of infants. No complicated apparatus is required and it is not necessary to remove blood from the patient.

The simplest clinical method of all is the determination of the hydrogen ion concentration of the urine by the use of brom cresol purple as described in the early part of this lecture.

The clinical symptoms and tests which have been mentioned apply to any form of acidosis. There are certain tests, however, which are applicable only to certain types of acidosis. The acetone bodies, betaoxybutyric acid, acetoacetic acid and acetone, are present in excess in only one type of acidosis. These substances are then present in the urine and a small amount of acetone may be present in the expired air sufficient to give it a characteristic fruity odor. The presence of acetone in the expired air may be confirmed and the amount roughly estimated by bubbling some of the patient's breath through Scott-Wilson reagent, an alkaline mercury solution. When acetone is present, a distinct cloud forms in the solution, the density of the cloud being proportionate to the amount of acetone present.

In the presence of acetone body acidosis, all three of the acetone bodies are excreted in the urine. When one is present, the others may be assumed to be present also. Acetoacetic acid is the one which can be most readily detected. The Rothera test with sodium nitroprusside is so delicate (1:400,000) as to detect slight traces of acetoacetic acid which have but little clinical significance. It is often stated, incorrectly, that this is a test for acetone and that ferric chloride is used for the detection of acetoacetic acid. As a matter of fact, ferric chloride is only a less delicate reagent for the detection of acetoacetic acid (1:8,000). Unless there are large enough amounts of the acetone bodies in the urine to give a positive ferric chloride test, they may be disregarded. The ferric chloride test is carried out simply by adding to the urine a 10 per cent solution of ferric chloride until no more precipitate forms and the color becomes no darker. This may require a considerable amount of ferric chloride, as no color will develop until all the substances in the urine, which may be precipitated by the ferric chloride, have been thrown out. In the presence of acetone bodies, ferric chloride gives a deep reddish brown color. This test cannot be applied to the urines of patients who have been receiving salicylates, as salicylate derivatives present in the urine give a deep purple color with ferric chloride which obscures the reaction. When the ferric chloride test is strongly positive, it indicates that considerable amounts of acetone bodies are being produced. It does not, however, prove that actual acidosis is present. The acetone bodies may be completely cared for by the regulatory mechanism of the body so that the carbon dioxide content of the blood and the hydrogen ion concentration remain entirely normal. The urine may even be alkaline in reaction and the blood have an excess of bicarbonate present. When considerable amounts of acetone bodies are present one should look for other signs of acidosis. A small amount of acetone bodies in the urine does no harm, but does indicate a derangement of the metabolism, the cause of which should be ascertained.

There are no simple clinical tests for the presence of an excess of lactic acid, although there are laboratory procedures by which the amount of lactic acid in the blood may be accurately estimated. The method of Clausen is the best of these. The amount of lactic acid present normally in the blood ranges from 18 to 25 mg. per 100 c.c. of blood. In acidosis due to lactic acid, the amount may increase to as much as 100 or 150 mg.

The Treatment of Acidosis

The treatment of acidosis depends upon the type present and consists in the treatment of the underlying cause rather than in an effort to neutralize the acids present. In the acetone body type the essential indication is to give carbohydrate in such form that it may be utilized. Carbohydrate should be given by mouth in the form of sugar or starches, or intravenously in the form of glucose solutions. A five per cent glucose solution is isotonic, but stronger solutions up to 10 or 20 per cent may be given with safety, provided the injection is made slowly. The amount of such solution given should not usually exceed 20 c.c. per kilo (1 oz. for each 3 pounds) of body weight. The addition of insulin to the injected glucose in the proportion one unit of insulin to each 2 or 3 grams of glucose insures the prompt utilization of the sugar.

In diabetes larger amounts of sugar than normal are present in the blood and tissues, but this sugar can not be burned. The object of treatment is to bring about the combustion of sugar and in this way the simultaneous combustion of the acetone acids with the liberation of the base bound to these acids. In diabetic acidosis the amount of sugar accumulated in the body may be four or five times the normal amount. When the blood sugar is as high as 500 mg. per 100 c.c. (0.5 per cent), it may be assumed that a similar concentration of sugar is present in the other fluids of the body and that there are consequently 5 grams of sugar per kilo of body fluid. The body is composed of approximately 60 per cent fluid, so that there will be in the whole body 3 gm. of sugar per kilogram. In the case of a 70 kilogram man, this will be 210 grams of sugar. The amount of sugar which should normally be present in such an individual is only 42 grams, based on a normal blood sugar content of 100 mg. per 100 c.c. (0.1 per cent). There is, therefore, an excess of approximately 160 gm. of glucose. In order to bring about the combustion of this amount of sugar from 80 to 100 units of insulin would be necessary, on the assumption that 1 unit of insulin is able to bring about the combustion of from 1.5 to 2.0 grams of glucose. It is not altogether safe to inject the total amount of insulin necessary at one time. Usually not more than one-half or two-thirds of the calculated dosage is given intravenously as an initial dose. In the case in question this would be about 50 units. The remainder of the insulin dose is given subcutaneously after an interval of four or five hours. At this stage, enough glucose will have been oxidized to have caused the simultaneous oxidation of considerable amounts of the acetone bodies, and as a direct consequence, the base released by these acids will have been sufficient to have raised materially the sodium bicarbonate content of the blood and tissues. Clinical evidence of these changes is seen in the respiration which becomes less deep, slower and altogether more normal. At about this time, also, the bicarbonate begins to be excreted through the urine, and the reaction shifts towards alkalinity. Treatment from this point on is more or less empirical and consists in the administration of insulin at intervals of about 6 hours until the blood sugar and bicarbonate have returned to normal values and acetoacetic acid is no longer detectable in the urine and the reaction of the urine is alkaline to brom cresol purple.

Following a return to normal conditions, the diet and insulin dosage should be regulated according to the method to be described in a subsequent lecture. The general plan outlined above is that carried out when it is possible to make estimations of the blood sugar. Where this is not possible, the insulin dosage is necessarily empirical and depends upon the degree of acidosis, as judged by the clinical symptoms. In such instances the principal object is the relief of the acidosis, rather than a lowering of the blood sugar. It is usually advisable to inject glucose simultaneously with the insulin in order to guard against possible insulin reactions. The amount of glucose given under these circumstances will be approximately 1 gram per unit of insulin. This is given in 10 per cent solution. To an adult patient, in coma, the amount of insulin given with glucose will ordinarily be about 50 units for the initial dose. With milder degrees of acidosis the insulin dosage will be correspondingly less. With the disappearance of the symptoms of acidosis the further dosage of insulin will be based upon the appearance or disappearance of sugar from the urine.

In all forms of acidosis, and especially in that of diabetic coma, there is a tendency to anhydremia, or desiccation of the body. Water, in large amounts, is indicated in order to make up for previous loss of fluid and to favor the elimination of the neutralized acids. Fluids should, therefore, be forced and, if necessary, given intraperitoneally and intravenously in the form of normal salt solution. One might suppose that the administration of sodium bicarbonate would be indicated in severe diabetic acidosis, but this is rarely the case, because of the fact that when the acetone bodies are burned the base with which they have been bound is left free to form bicarbonate. The administration of bicarbonate intravenously to a patient in diabetic coma disturbs the osmotic equilibrium of the blood and often leads to the forcing out of sodium chloride into the tissues and the urine. Later, when the acetone bodies are destroyed, a condition of alkalosis may supervene, which is as serious as the acidosis. There is some evidence that the administration of alkali leads to an increased production of acetone bodies. The use of fruit juices by mouth has been recommended. These supply a certain amount of carbohydrate and, although they are acid as taken, the acidity is due to organic acids which are destroyed, leaving behind bases. Fruit juices supply alkali in small amounts, but as this alkali is slowly liberated, no harmful results are seen and the small amount may be advantageous in replenishing the blood bicarbonate.

In acetone body acidosis resulting from starvation no treatment other than the administration of carbohydrate food is indicated. In the types seen in cyclic vomiting, in grippal infections and dysentery and following anesthesia the degree of acidosis may be insignificant and require no especial treatment. The obvious indication, however, is to give carbohydrate in available form and an abundance of water.

In lactic acid acidosis due to severe anhydremia or desiccation of the body, such as occurs following vomiting or severe diarrhea, the one effective treatment is the administration of large amounts of fluid by mouth, intravenously or intraperitoneally. When the acidosis is the result of failure of the circulation, due to cardiac insufficiency, phlebotomy may occasionally be used to advantage. Alkali should never be administered in this form of acidosis.

The acidosis of nephritis is but one of the manifestations of renal insufficiency. It does not in itself require special treatment other than that directed toward the underlying nephritis. The administration of fairly large amounts of calcium acetate or lactate by mouth results in an increased excretion of retained phosphoric acid by way of the bowel, and this is advantageous. In the types of nephritis associated with acidosis large amounts of fluid are generally advisable. Alkalies are very definitely contraindicated as they may cause convulsions. This is due to the fact that in the acidosis of chronic nephritis the calcium of the blood is usually lowered and, as we shall see later, one of the conditions in the blood which brings about the manifestations of tetany is a lowered calcium ion content and a high sodium or hydroxyl ion content. The administration of sodium bicarbonate to nephritics with acidosis is frequently followed by the development of edema. In general, the acidosis of nephritis, in itself, seems to produce very little harm and if of a mild degree, it may be present over longer periods of time without causing any especially serious symptoms. The respiratory center accommodates itself so that there may be little or no obvious dyspnea.

Alkalosis

Alkalosis as a clinical condition has received relatively less attention than acidosis, yet it is probably of as frequent occurrence and may be quite as serious in its effects upon the body.

Alkalosis occurs when there is an excessive loss of acid from the body or an abnormally large intake of alkali. Alkalosis is frequently produced as the result of an excessive removal of carbonic acid by way of the lungs. Voluntary forced breathing, or hyperventilation, as the result of organic brain lesions involving the respiratory center, or psychic disturbances may lead to the removal of so much carbonic acid that distinct alkalosis occurs. In infants and young children excessive crying may be sufficient to bring about alkalosis. In the presence of fever, the respirations are increased in rapidity, rather than in depth, so that the total pulmonary ventilation is only slightly increased. At times, however, the ventilation is excessive and a disproportionately large amount of carbonic acid is removed.

The body may also lose considerable acid in the form of hydrochloric acid as the result of vomiting from any cause. A large amount of acid is normally secreted into the stomach and this, under normal conditions, is reabsorbed in the intestinal tract so that there is no change in the acid-base equilibrium of the body. When vomiting occurs, however, the acid is actually lost, and there remains in the body, unless eliminated, an excess of alkali, chiefly sodium bicarbonate. Not only is acid lost when vomiting occurs, but also a certain amount of sodium chloride. The blood is thus left with a deficiency of chlorides and an excess of bicarbonate. It might be expected that the excess of bicarbonate would be excreted by the kidney so that the blood bicarbonate concentration would fall to a normal level. This, however, cannot readily occur, as it would lead to a lowering of the osmotic pressure of the blood, and under such circumstances salts are not readily excreted by way of the urine. Consequently we have, in the blood, a decrease in sodium chloride and a corresponding increase in sodium bicarbonate.

We have seen already that the reaction of the blood is dependent upon the ratio $\frac{H_2CO_3}{NaHCO_3}$; a relative increase in the bicarbonate leading to alkalosis and an increase in carbonic acid to acidity. Under normal conditions, the ratio is approximately 1/20. With an increase in bicarbonate, therefore, a normal reaction can be maintained only if the carbonic acid is proportionately increased. This is exactly what happens. With the more alkaline blood, the respiratory center receives less than its normal acid stimulus, the respirations become more shallow and less carbonic acid is removed from the blood. Finally sufficient carbonic acid accumulates to render the proportions between carbonic acid and bicarbonate approximately normal. The maintenance of such an increased amount of carbonic acid in the blood is only possible if the respirations remain depressed so that the concentration of carbonic acid in the pulmonary alveoli is higher than normal. For this reason, depressed and irregular respirations are one of the characteristic symptoms of alkalosis. Cyanosis may, at times, supervene as the result of a correspondingly decreased oxygen intake. Should such a patient take a few deep breaths or even breathe as deep as a normal person, an excess of carbonic acid is removed and the blood becomes distinctly more alkaline than normal. Definite symptoms of alkalosis then become manifest.

Although the blood in these cases contains an excess of bicarbonate, this is not excreted in the urine, but is retained so that the urine remains acid. *It is important to realize the fact that a strongly acid urine may be compatible with the condition of alkalosis.* If sodium chloride is administered, however, so as to supply the lacking chlorides of the blood and restore a normal osmotic pressure, the excess of bicarbonate is eliminated by way of the urine, and the urine becomes strongly alkaline. The administration of hydrochloric acid to a patient with alkalosis due to vomiting would result in the conversion of a certain amount of the sodium bicarbonate of the blood into sodium chloride. The alkalosis would thus be overcome without the occurrence of any particular change in the osmotic pressure of the blood or in the character of the urine.

Alkalosis may be caused by an excessive intake of alkali. Under normal conditions the body can protect against an excess of alkali through elimination by way of the urine and, to a lesser extent, by way of the intestinal tract. When the kidneys are damaged, however, or when large amounts of alkali are administered, complete elimination may be impossible. In the presence of pyelitis and of nephritis, alkali elimination is poor and retention therefore likely to occur. In pyelitis, vomiting is often a complicating factor and this in itself tends to lead to alkalosis and retention of administered bicarbonate. Alkalies, in the form of sodium bicarbonate or other salts, are often given in large amounts for the treatment of acidosis. When the acidosis is due to the acetone acids, or to lactic acid, and simultaneous measures are adopted which lead to the oxidative destruction of these acids, a very large excess of base remains temporarily in the body. Acidosis is thus superceded by alkalosis.

The practice of giving alkali in the treatment of various forms of vomiting based on the false assumption that such vomiting is due to acidosis is one likely to bring about a serious degree of alkalosis. Alkalosis is frequently observed in patients with nephritis, toxemia of pregnancy, pneumonia or gastric ulcer who have been treated by the administration of alkalies. Symptoms of alkalosis are especially likely to develop in the case of patients with fever because of the effect of the increased respirations in removing carbonic acid.

Signs of Alkalosis

When alkalosis occurs, there is a tendency for the hydrogen ion concentration of the blood to become less and the hydroxyl ion content to increase; in other words, the reaction shifts towards the alkaline side. This causes a change in the ionization of other constituents of the blood, notably the calcium salts. As we shall see later, the decrease in the amount of ionized calcium in the blood results in an alteration in neuromuscular irritability throughout the body, manifesting itself clinically as *tetany*. The characteristic symptoms of alkalosis are, therefore, irregular depressed respirations and tetany. The respirations of alkalosis are slow, shallow, and associated with longer or shorter periods of apnea. They are the exact counterpart of the respirations of acidosis which are increased in rate, and depth and are pauseless. In alkalosis the depressed respirations result in a deficient oxygenation of the blood and, for this reason, cyanosis not infrequently occurs, especially during the apneic pauses. Tetany may manifest itself by muscle cramps, tingling in the fingers and slight mental disturbance, or there may be marked carpopedal spasm and general convulsions. A positive Chvostek sign (contraction of the facial muscles upon mechanical stimulation of a branch of the VII nerve) and the Trousseau sign (carpal spasm induced by constricting the veins of the upper arm) or characteristic electrical reactions of the peripheral nerves may be present (Erb's sign).

The diagnosis of alkalosis may be confirmed by laboratory tests. The bicarbonate content of the blood is increased, except in the alkalosis due to hyperventilation. The total CO_2 content rises, often to as much as 100 or more volumes per cent, as determined by the Van Slyke method. There is a change in the hydrogen ion concentration or pH of the blood, the reaction varying from the normal pH of 7.4 up to as high as 7.8 or above. The carbon dioxide tension of the alveolar air is increased above the normal level.

Treatment of Alkalosis

The treatment of alkalosis, once it has developed, consists in measures designed to bring about the elimination of alkali and the neutralization of such excess of alkali as is present. Alkali cannot be burned up in the body as can organic acids, and being nonvolatile, cannot be removed as is the carbonic acid by way of the lungs. It may, to a slight extent, be neutralized by the production of organic acids. This latter effect is observed when, as the result of convulsions in tetany, a sufficient amount of lactic acid and carbonic acid accumulates to neutralize the alkali.

Elimination of alkali is favored by the administration of large amounts of fluid, which should be given in every way possible, by mouth, proctoclysis, subcutaneously and intraperitoneally. In the alkalosis resulting from vomiting, such as is seen in pyloric stenosis, high intestinal obstruction, or other causes, the administration of sodium chloride by restoring the normal chloride content of the blood, favors elimination of alkali by way of the urine. Salt, as well as water, is therefore indicated in these cases. The subcutaneous or intraperitoneal injection of normal saline by supplying both water and sodium chloride is the ideal method of treatment.

In the presence of severe manifestations of alkalosis, such as depressed breathing and tetany, the inhalation of carbonic acid in the form of a CO_2-O_2 mixture, is theoretically indicated and is of practical value. There is no advantage in the administration of most organic acids by mouth, or otherwise, as these are promptly burned and exert no acid effect. Inorganic acids, such as hydrochloric, may be given added to the food, but only a relatively small amount of acid can be taken in this way. The most palatable means of administering hydrochloric acid is in the form of milk, hydrochloric acid being added until the milk has a distinctly sour taste. It has been found that when ammonium or calcium chlorides are given, the effect is essentially that of giving hydrochloric acid itself. When ammonium chloride is administered, the ammonia is converted into urea, leaving the hydrochloric acid. In the case of calcium chloride, the calcium is excreted by the bowel and the hydrochloric acid is left in the body. Ammonium chloride may be given by mouth in a dosage of from 75 to 150 grains (5 to 10 grams) daily. Calcium chloride may be given in the same dosage, but has a bitter, unpleasant taste. As an emergency measure, in the presence of severe alkalosis, calcium chloride may be given intravenously. The dosage is 25 mg. per kg. of body weight, or 0.5 c.c. of a 5 per cent solution per kilogram of body weight. Calcium chloride cannot be given subcutaneously as it causes sloughing. The administration of calcium chloride not only neutralizes base but leads to an increase of calcium ions in the blood, for the time being at least.

In conclusion it should be emphasized that neither acidosis nor alkalosis are primary diseases, both are secondary manifestations of some underlying condition and can be treated successfully only if the primary cause receives adequate attention.

LECTURE III

THE CHEMISTRY OF THE BLOOD

Oxygen, Inorganic Salts, Organic Constituents

In the discussion of acidosis, the transport of carbon dioxide from the tissues to the lungs, by way of the blood, was described. An approximately equal volume of oxygen is carried in the opposite direction. Carbon dioxide is carried largely by the plasma, oxygen almost entirely by the corpuscles in which it exists in combination with hemoglobin. Normal adult blood contains an average of about 14 grams of hemoglobin per 100 c.c., and this amount of hemoglobin is capable of combining with approximately 18.5 c.c. of oxygen. The amount of oxygen taken up by hemoglobin is dependent, within certain limits, upon the concentration or "tension" of oxygen in the medium with which the blood is brought in contact. Ordinary atmospheric air contains approximately 20 per cent of oxygen, and since the total atmospheric pressure is equivalent to approximately 760 mm. of mercury, the partial pressure or *tension* of oxygen in the atmosphere is 20 per cent of 760 or 152 mm. The air in the pulmonary alveoli does not contain as high a proportion of oxygen because of the fact that a portion of the oxygen has been absorbed by the blood and further the air is diluted with water vapor and carbon dioxide. The amount of oxygen in the alveolar air is not likely to be over 14 or 15 per cent, corresponding to about 100 mm. tension. The blood when exposed to this tension of oxygen is capable of taking up almost as much oxygen as when exposed to atmospheric air having an oxygen tension of 152 mm. or to pure oxygen at a tension of 760 mm. On the other hand, when the tension of oxygen is reduced below 100 mm. the amount of oxygen combining with hemoglobin is distinctly less. The amounts of oxygen with which whole blood combines at various tensions of oxygen is shown in Fig. 10. The "dissociation curve" plotted is that of human blood which has been exposed to various oxygen tensions and simultaneously to a carbon dioxide tension of 40 mm.,

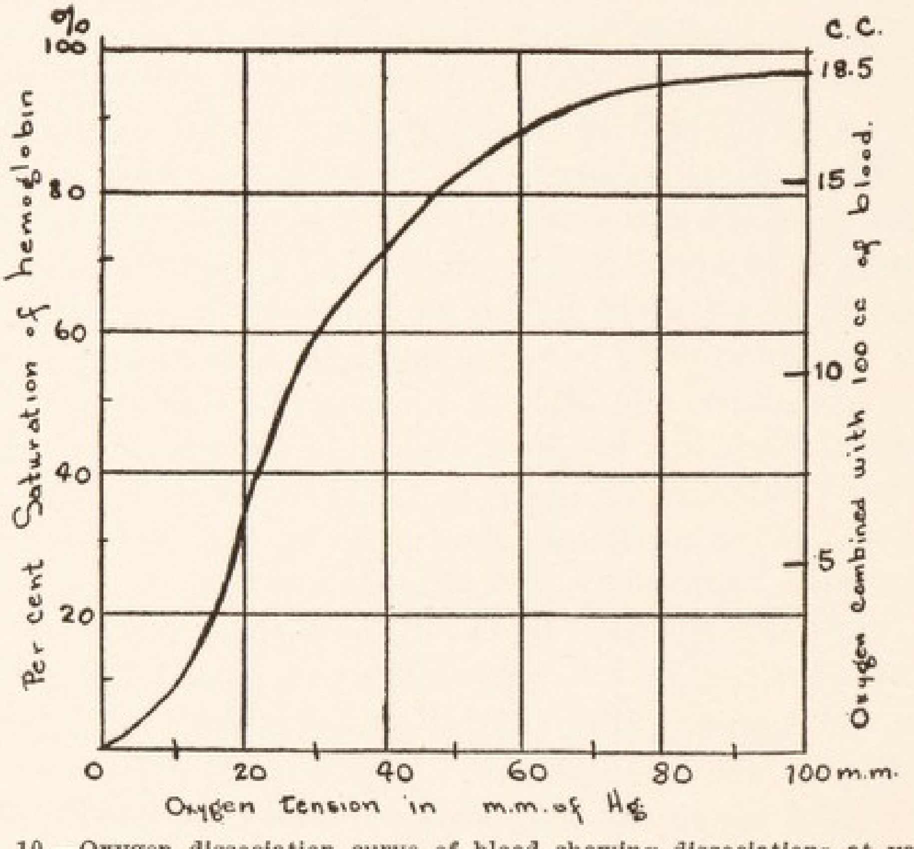


Fig. 10.—Oxygen dissociation curve of blood showing dissociations at various tensions of oxygen and at 40 mm. tension of carbon dioxide.

this being the average CO_2 tension existing in the pulmonary alveoli.

From the curve, it is seen that, when the oxygen tension falls below 60 mm., there is a very rapid decrease in the amount of oxygen combined with the blood.

In the body the blood is normally almost saturated with oxygen, as it leaves the lungs. On reaching the tissues the blood comes in contact with areas in which the oxygen tension is very low because of the fact that the tissues have used up oxygen. Consequently oxygen diffuses out from the hemoglobin until an equilibrium is attained. For example, at an oxygen tension of 30 mm. about one-third of the combined oxygen is liberated; at a tension of 20 mm. two-thirds of the combined oxygen is given off. At the same time carbon dioxide, produced in the tissues, is taken up by the blood and makes it slightly more acid, which still further decreases the capacity of hemoglobin for combination with oxygen and this aids further the liberation of oxygen to the tissues. The blood then returns to the lungs where the carbon dioxide is eliminated and the hemoglobin becomes once more saturated with oxygen.

Cyanosis

Under normal conditions the circulation and respiratory activity are so regulated that blood leaving the lungs, that is to say, arterial blood, is almost completely saturated with oxygen and circulates at such a rate as to meet the oxygen needs of the tissues. During exercise the increased oxygen demand is met by an increased rate of the circulation, an increased respiratory exchange, and an increased removal of oxygen from the blood by the tissues. Under certain pathologic conditions, which will presently be discussed, the hemoglobin of arterial blood is incompletely saturated with oxygen. When this is the case blood, instead of being bright red, assumes a more or less blue color, depending upon the degree of unsaturation.

Oxyhemoglobin, that is, hemoglobin combined with a full amount of oxygen, is red. Reduced hemoglobin, or hemoglobin combined with no oxygen, is distinctly blue. It has been shown by Lundsgaard that when the amount of reduced hemoglobin in the arterial blood is as much as 5 gm. per 100 c.c. the color of the blood is sufficiently blue to lead to the appearance of cyanosis. This means that, given a normal hemoglobin content of the blood, approximately one-third must be in the form of reduced or unoxygenated hemoglobin before cyanosis will appear. In the case of polycythemia, with an abnormally large amount of hemoglobin present in the blood, cyanosis is especially likely to appear because even with a moderate degree of oxygen unsaturation, there may be as much as a total of 5 grams per 100 c.c. of reduced hemoglobin. It is the total amount of reduced hemoglobin present and not the relative amount which determines cyanosis. In anemia, on the other hand, cyanosis does not readily occur. Where the hemoglobin of the blood is as low as one-third of the normal amount, that is in the neighborhood of 5 gm. per 100 c.c. of blood, the entire amount would have to be in the form of reduced hemoglobin before cyanosis would be detectable.

Anoxemia

Cyanosis is usually, but not always, evidence of a deficient oxygen supply to the tissues or *anoxemia*. As already mentioned, cyanosis may accompany polycythemia, and yet there may be no true anoxemia. On the other hand, anoxemia of a severe degree may exist in an anemic patient, and there may be no cyanosis. Cyanosis, in a patient with a normal hemoglobin content of the blood is, however, presumptive evidence of anoxemia. Oxygen deficit or anoxemia may give rise to other manifestations than cyanosis. When long continued, there occurs fatty degeneration of the various organs. In all cases of anoxemia there is a tendency to the accumulation of lactic acid in the blood and tissues. An increased irritability of the respiratory center usually occurs in anoxemia and this leads to rapid respiration.

There are, at times, psychic disturbances, usually of a mild degree. Anoxemia occurs as the result of a variety of causes.

In pneumonia, the respirations, though rapid, are shallow and at times of insufficient depth to allow for normal ventilation of the pulmonary alveoli. The air in the alveoli, therefore, may contain a lower tension of oxygen than under normal conditions and, as a result, the blood circulating in the capillaries surrounding the alveoli becomes incompletely saturated with oxygen. It is also likely that there is, especially in cases of bronchopneumonia, interference with the diffusion of oxygen through the alveolar walls, which interferes with the complete oxygenation of the blood. During the stage of gray hepatization in lobar pneumonia, the affected lobes are relatively bloodless and because of this fact cyanosis is less likely to occur than when the blood is circulating freely through an area of the lungs in which ventilation is deficient, as in the case of bronchopneumonia. With the circulation completely closed off from an affected lung area, no admixture of venous with arterial blood occurs, and if the remaining lung areas are well expanded, there may be no variation from the normal in oxygen content of the blood. In pneumonia, there is in addition at times the factor of cardiac failure resulting in a decreased circulation.

In the treatment of the anoxemia of pneumonia, inhalation of oxygen is theoretically indicated and is of practical value. The inhalation of air with a higher tension of oxygen leads to a proportionately higher tension of oxygen in all parts of the lungs, including the pulmonary alveoli. When the tension of oxygen in the alveoli is raised by this means, to a normal value, the symptoms of anoxemia may be improved. When pathologic conditions of the walls of the alveoli are present, an oxygen tension higher than normal favors more rapid diffusion and consequently more complete saturation of the blood.

Administration of oxygen by the common method of holding a funnel near the face is ineffective and wasteful of oxygen. A more efficient method is to insert a narrow rubber tube or catheter into one nostril, the oxygen being first bubbled through water in a bottle. This method is more effective if the opposite nostril is closed at the beginning of each inspiration. Various types of face masks have been devised for the administration of oxygen, but the most satisfactory method of all is the oxygen chamber. This latter method is now coming into fairly general use for patients who show the symptoms of anoxemia, especially those suffering from pneumonia.

When compression of a lung, or portion of a lung, occurs as a result of pneumothorax or fluid, to such an extent that no aeration occurs, but the circulation continues, venous blood circulating through the pulmonary vessels returns to the left side of the heart without becoming oxygenated. Under such circumstances anoxemia and cyanosis may result. In this case inhalation of oxygen is only effective if there is some expansion of the affected lung, otherwise neither air nor oxygen can enter the alveoli. On the other hand, if the lung is compressed or fibrosed to such an extent that the circulation as well as ventilation is cut off, neither cyanosis nor anoxemia may occur, because there is then no admixture of venous with arterial blood. Oxygen therapy is then not indicated.

In obstruction occurring in various parts of the respiratory tract, portions of the lung may be incompletely aerated and the blood passing through these portions of the lung may be incompletely oxygenated. In partial obstruction, oxygen inhalation is of value in raising the oxygen tension in the poorly ventilated alveoli, but when complete obstruction of a bronchus occurs, oxygen inhalation cannot be expected to be effective.

When the respiratory center is injured by disease, so that it fails to respond to a normal stimulus, the respirations may be slow and infrequent. In such instances, the oxygen tension in the pulmonary alveoli falls because of insufficient aeration, and anoxemia results. Stimulation of the respiratory center by inhalation of carbon dioxide and oxygen mixtures is the treatment indicated. In alkalosis the normal stimulus to the respiratory center is lacking, and therapy consists in the administration of acid or the inhalation of carbon dioxide.

Exposure to cold, by bringing about capillary stasis and increased desaturation of hemoglobin, leads, at times, to cyanosis.

At high altitudes, on account of the diminished atmospheric pressure, the tension of oxygen falls correspondingly and may become so low that the tension in the pulmonary alveoli is considerably below the level necessary for oxygen saturation of the blood. In such instances all the symptoms of anoxemia, including cyanosis, occur. The symptoms may be relieved by the inhalation of oxygen.

In certain types of cardiac disease, especially those associated with mitral lesions, cyanosis may be observed. The cyanosis in these cases seems to be the result, chiefly, of decreased oxygenation of the blood passing through the pulmonary circulation, this in turn being due to the back pressure induced in the pulmonary system. Inhalation of oxygen benefits the majority of these patients. Cyanosis in uncomplicated aortic disease rarely occurs.

In congenital heart disease there occurs usually a shunting, or short circuiting, of a portion of the blood between the right and left sides of the heart. A passage of blood from left to right does not lead to cyanosis, but a passage of blood in the opposite direction results in an admixture of venous with the circulating arterial blood. A shunting of at least one-third of the total blood passing through the heart is necessary in order to produce cyanosis. In these cases inhalation of oxygen cannot cause any greater oxygenation of the blood which passes through the lungs, and can obviously have no effect upon the venous blood which is shunted from the right to the left side of the heart. Oxygen therapy is, therefore, ineffective in the usual types of congenital heart disease.

We have, so far, considered the mechanisms whereby oxygen is brought to the tissues and carbon dioxide removed; mention has been made incidentally of certain other substances existing in the blood. Let us turn now to a somehat more detailed consideration of some of the more important blood constituents.

Calcium and Magnesium

There have been, in recent years, a number of studies of the calcium content of the blood, as related to a variety of conditions, especially tetany, rickets, and nephritis.

Practically all of the calcium of the blood is in the serum and is there combined with protein and with the various anions present. The total calcium content of the serum under normal conditions averages 11 mg. per 100 c.c. In tetany, occurring as the result of operative removal of the parathyroid glands, the serum calcium is much decreased and may be as low as 2 or 3 mg. per 100 c.c. In the idiopathic tetany of infants, accompanied by convulsions, a low serum calcium content is also found. In latent tetany, demonstrable only by altered electrical reactions and by the Chvostek sign, the serum calcium usually varies between 6 and 10 mg. When the calcium content falls below 5 or 6 mg., active manifestations with convulsions usually occur. An infant may, however, have a low blood calcium content and yet show very few symptoms, unless the respirations are increased by crying, or by fever, when active symptoms are likely to become manifest. This is due to the removal of carbonic acid causing temporary alkalosis. In rickets, in the absence of tetany, the blood calcium is only slightly lowered.

In advanced nephritis of the glomerular or interstitial type, the calcium of the serum often falls to a very low level, especially in those cases accompanied by uremic manifestations. The lowering of the blood calcium in these cases is apparently the result of excessive retention of phosphates in the blood. Under such circumstances, only very small amounts of calcium can be carried by the blood, at its normal reaction, because of the precipitation of calcium phosphate. This mechanism may be demonstrated in the test tube. A solution containing the same proportions of inorganic constituents as the blood remains practically clear under conditions approximating those in the body, but even a very slight excess of phosphate added results in a precipitation of some of the calcium.

Since it is only the ionized calcium which exerts a physiologic effect, any condition which decreases the ionization of this element brings about the same effect as an actual decrease in the total amount of calcium present. We have already seen that such an effect is observed in the case of alkalosis. When a decrease in the ionized calcium of the blood occurs, the symptoms of tetany appear. In parathyroid tetany and in the idiopathic tetany of infants, the calcium of the blood is actually lowered. In the tetany of alkalosis, the total amount of calcium is not necessarily low, although there may be a decrease in the ionization of calcium. The absolute amount of ionized calcium present is probably the most important factor in the pathogenesis of tetany, but the relation to other ions is also of moment. The balance between ions concerned in tetany may be expressed as follows:

$$\frac{Ca + Mg + H}{Na + K + OH}$$

An increase in any of the ions in the denominator tends to bring about the manifestations of tetany; an increase in the factors in the numerator tends to prevent the manifestations. Tetany may thus be brought about by the presence in the blood of an excess of alkaline salts of sodium or potassium and the symptoms may be relieved by administration of calcium or magnesium salts or of acid.

In the tetany associated with a low calcium content of the blood, treatment consists in the administration of soluble calcium salts by mouth or intravenously. Calcium chloride is, in this respect, far more effective than the organic calcium salts such as calcium lactate, both in increasing the calcium content of the serum and in producing an acid effect. The dose of calcium chloride for an infant may be as much as 15 grains (1 gram) four to six times a day. For intravenous administration a five per cent solution is used, the dosage being 0.5 c.c. of this solution per kilogram of body weight. Calcium chloride cannot be administered subcutaneously as it leads to sloughing of the tissues.

In advanced nephritis with phosphate retention in the blood and a correspondingly low calcium content there is a certain advantage in administering calcium lactate or acetate by mouth as this leads to an increased excretion of calcium phosphate by way of the bowel. A portion of the retained phosphate is in this way removed from the blood.

The fact that removal of the parathyroid glands results in a fall in blood calcium would point to the fact that some secretion of these glands must influence the calcium carrying power of the blood. Within recent years, Collip has isolated a substance from the parathyroid gland (parathormone) which, when injected subcutaneously, leads to a marked increase in the calcium content of the blood. This active principle is of very considerable value in the treatment of tetany associated with low blood calcium.

As is well known, ionized calcium is necessary for the coagulation of the blood. Blood from which the calcium has been precipitated by oxalate or rendered nonionizable by the addition of citrate does not clot. The addition of sufficient calcium salts, to such blood again brings about clotting. Only a very small amount of calcium is necessary for normal coagulation of the blood and rarely, if ever, does the calcium in the circulating blood drop to such a level as to affect the coagulation time. The blood of patients with tetany having less than 2 mg. of calcium per 100 c.c. clots well. Hemorrhagic conditions are often erroneously attributed to lack of calcium in the blood and are treated by the administration of calcium salts. Not infrequently the clotting time of the blood is determined before surgical operations and, if prolonged, calcium salts are administered. Such a procedure is entirely illogical, as the failure of coagulation is not due to diminished calcium and the administration of calcium salts will not increase the blood calcium above normal, nor would such an increase materially change the coagulation time, even should it occur. In obstructive jaundice the coagulation time and bleeding time is prolonged although the blood calcium is not lowered. It may be that the bile constituents unite with calcium salts in such a manner as to reduce the ionization. In this particular condition the administration of calcium salts is said to shorten coagulation time.

There is no lowering of the blood calcium in purpura, hemophilia, leucemia, or in the other common conditions associated with hemorrhage. These are not influenced by calcium administration.

Calcium has an interesting effect on the permeability of cells and of capillaries. Variations in the calcium content of the blood have been observed in such conditions as urticaria and exudative eczema and the course of these conditions, which are associated with changes in permeability is, at times, distinctly modified by the administration of calcium salts.

Magnesium occurs in the blood in small amounts and in many respects exerts an action similar to calcium, although in certain particulars, antagonistic. The administration of magnesium salts exerts a favorable influence on the course of tetany by reducing neuromuscular irritability. Magnesium salts are not absorbed from the intestinal tract, but may be administered subcutaneously without causing sloughing. For the control of the convulsions of tetany, magnesium sulphate is given in the form of a ten per cent solution of the anhydrous salt (20 per cent of the crystalline epsom salt) in a dosage of 2 c.c. per kilogram of body weight. The effect of this is especially marked in the case of the convulsions of tetany, but convulsions due to other causes are also influenced, to some extent. Magnesium salts depress the respiratory center, and must, therefore, be administered cautiously when there are any evidences of respiratory involvement.

Phosphates

The reciprocal relationship between calcium and phosphorus in the blood has been mentioned. Most of the phosphorus of the serum is in the form of inorganic phosphate which, expressed in terms of phosphorus, is present in amounts varying from 2 to 5 mg. per 100 c.c. In advanced glomerular or interstitial nephritis there occurs a retention of phosphate, the total phosphates going as high as 20 mg. or more per 100 c.c. Such retention of phosphorus is indicative of severe renal damage and is of bad prognostic omen. The phosphate of the blood serum, on the other hand, is distinctly lowered in the case of active rickets and when the phosphorus falls below a certain level proper calcification does not occur in the bones. It is interesting to note that administration of the antirachitic vitamine of cod liver oil or exposure to sunlight or artificial ultraviolet radiations result in a prompt increase in the phosphorus of the blood to a normal amount.

Sodium and Potassium

Sodium and potassium are the most abundant cations in the blood. Potassium occurs almost exclusively in the red blood cells and sodium in the plasma. Both sodium and potassium are combined partly with protein to form weakly ionized salts, but to a greater extent with chloride, bicarbonate, and phosphate.

Sodium chloride is the most abundant mineral constituent of the serum, the amount present under normal conditions being from 575 to 600 mg. per 100 c.c. When vomiting occurs, the amount falls, as has been previously indicated, and sodium bicarbonate takes the place of sodium chloride. In tubular nephritis with edema (nephrosis) due to a change in permeability of the cells and vessels, sodium chloride escapes from the serum and enters the tissues; the serum chloride is consequently reduced and often below the level necessary for renal excretion, so that the urine in these cases becomes practically free of chlorides. When salt is given to patients with nephrosis it promptly passes from the blood into the tissues, taking with it a certain amount of water. In interstitial nephritis, on the other hand, there may be a definite increase of sodium chloride in the blood.

Blood Proteins

Turning to a consideration of the organic constituents of the blood, the plasma contains considerable amounts of protein; the so-called serum albumin and serum globulin, together with a small amount of fibrinogen, the latter being the substance which forms the basis of the clot.

The total protein of the serum is fairly constant in normal individuals, but varies with age, being somewhat lower during infancy and early childhood than in adult life. The average protein content of the serum of adults is 7 or 8 per cent, of infants 6 per cent.

The total serum protein concentration is markedly increased in the condition of anhydremia or desiccation occurring as the result of a deficient water intake or excessive water loss due to diarrhea, vomiting, exposure to high temperatures or as a result of certain specific infections. Under these conditions the blood loses water and becomes concentrated so that the total protein may increase to as much as double the normal amount. Such high protein concentrations occur only when a rather sudden drying out of the body takes place. If water is not supplied, within a reasonably short time, destruction of the blood protein occurs and the amount present falls towards a normal level.

In tubular nephritis with edema there is a marked reduction in the serum protein, which may fall to as low as 3 or 4 per cent. Decrease in protein in these cases is not the result of dilution of the blood by retained water, as the total blood volume is actually lower than normal. It is due to a passage of protein out of the vessels and into the tissue spaces, and to a loss of protein by way of the urine. In glomerular or interstitial nephritis, the serum protein is not low, but either normal or slightly increased. In severe malnutrition, especially as seen in infants, the serum protein is decreased in amount and there is also a decrease in the total blood volume.

The determination of total serum protein may readily be carried out in the clinical laboratory by the micro-kjeldahl process. Serum proteins may also be determined with a fair degree of accuracy by the use of the refractometer. For this determination only a drop or two of serum is necessary, and the test requires but a few minutes time. Refractometric readings are somewhat inaccurate when there is nonprotein nitrogen retention or when the serum is colored by hemoglobin. The determination of the protein is of value in gauging the degree of desiccation. It also serves to differentiate the different types of nephritis.

Taking the blood as a whole, the proteins of the serum comprise only one-fourth of the total protein present. The hemoglobin of the corpuscles makes up most of the remainder of the protein.

Nonprotein Nitrogenous Constituents

Besides protein, the blood always contains considerable amounts of protein derivatives. These nitrogen-containing substances represent, for the most part, waste products produced in the tissues and carried, by way of the blood, to the kidneys and there excreted. These substances, as a class, are referred to as the nonprotein nitrogenous constituents, and the total amount present is expressed in terms of nitrogen. The total nonprotein nitrogen varies somewhat with the diet, being higher after a meal containing protein. For this reason determinations are usually made following a fast of several hours, blood generally being obtained before breakfast from individuals receiving no food during the night. Under normal conditions, the total amount of nonprotein nitrogen varies from 25 to 40 mg. per 100 c.c. Of the total nonprotein nitrogen, urea accounts for approximately one-half, under normal conditions, but when there is retention of waste products, as in nephritis, urea increases more proportionately than the other constituents, the nitrogen from this source often being three-fourths of the total.

The chief interest in the nonprotein nitrogen of the blood has been in connection with the retention occurring in cases of nephritis. Damage to the renal glomeruli results in a decreased capacity of the kidney to excrete. There is no retention of nonprotein nitrogen in cases of pure tubular nephritis (nephrosis).

It is important to realize that nephritis is only one of the conditions in which an increase in the nonprotein nitrogen of the blood occurs. Failure to realize this has often been responsible for an erroneous diagnosis of nephritis. When vomiting occurs as the result of intestinal obstruction or when vomiting is accompanied by severe diarrhea, not only is there a loss of chlorides from the gastric juice, but also a loss of alkaline intestinal secretion. When both chlorides and bicarbonate are thus lost from the blood, the osmotic pressure of the blood and tissues necessarily tends to fall. Under such circumstances the normal kidney holds back soluble substances until the accumulation of these substances is sufficient to restore a normal osmotic pressure. Urea and other nonprotein nitrogen constituents are, therefore, retained. In such cases the total nonprotein nitrogen may rise to 200 mg. or more per 100 c.c. of blood. When water and sodium chloride are given, the nonprotein nitrogen promptly falls to a normal level.

In severe anhydremia there is insufficient fluid in the blood to allow for adequate renal secretion and a functional incapacity of the kidney results with retention of nonprotein nitrogen. There is no real nephritis present in these cases. The nonprotein nitrogen promptly falls to normal following the administration of sufficient fluid.

Cholesterol

One more organic constituent of the blood deserves special mention. This is cholesterol. This substance, which is a higher alcohol, resembles, in its physical properties, the fats and is a constituent of all cells and tissues. It appears to be concentrated at the cell walls and, as mentioned in the first lecture, has an important effect in regulating the permeability of the cells. A small amount of cholesterol, partly free and partly combined as esters, occurs in the serum (0.15 to 0.18 per cent). In tubular nephritis with edema the amount of cholesterol present in the serum is much increased. In these cases cholesterol may also be detected in the urine and may, at autopsy, be demonstrated in excessive amounts in the renal tubule cells. Nephritis associated with cholesterol retention is sometimes referred to as "lipoid nephritis." The cause of this hypercholesterolemia is not altogether clear. It is possible that the cholesterol is displaced from the surfaces of the cells by the action of the surface tension lowering substance known to be present in the blood of these patients. Displacement of cholesterol from the surface of the cells would be expected to result in a marked change in permeability of the cells and such a change we know occurs in cases of tubular nephritis with edema.

An excess of cholesterol in the blood is seen also in advanced diabetes, in obstructive jaundice, and occasionally in arteriosclerosis. On the other hand, in pernicious anemia the amount of cholesterol in the blood serum is below the normal amount.

The sugar of the blood is discussed in Lecture IV.

There are numerous other constituents of the blood occurring in small amounts which have an important bearing upon physiologic processes. There are other constituents whose significance is unknown. Chemical studies on the blood which have been made possible by the development of micromethods of analysis have already given us a great deal of information regarding the nature and treatment of disease. Further developments may confidently be expected.

LECTURE IV

FOODS AND METABOLISM

Calories, Proteins, Carbohydrates, Fats, Mineral Salts

The human body, like a machine, requires fuel, materials for repairs and replacements and what might be referred to as "lubrication." In the young individual there is the additional requirement of materials for growth. These needs are met by the food, which must have a sufficient fuel value, that is, must supply enough calories; it must supply a certain minimum amount of protein, carbohydrate, mineral salts, water and vitamines. For practical purposes, the food should be composed partly of fat, although this is not an absolutely indispensable constituent. Besides having the proper composition, the food must be capable of digestion, free from irritating or toxic materials and from pathogenic bacteria.

Calories

No matter what the type of food, it must provide sufficient energy or fuel value to meet the needs of the individual. This value may be most conveniently expressed in terms of heat units, or *calories.* The calorie is merely a measure of energy expressed in terms of heat. To make the meaning of this clear, let us take a simple food, such as sugar. If this is burned, a certain amount of heat is liberated; at the same time oxygen is taken up and carbon dioxide and water are produced. The exact amount of heat given off by this combustion and the amount of oxygen consumed and carbon dioxide produced may conveniently be measured in an apparatus known as a calorimeter. In such an apparatus a known amount of sugar, say 1 gram, is placed in a small, water tight, metal "bomb" and oxygen under pressure is introduced so as to insure complete combustion. The bomb is immersed in a known amount of water and the sugar ignited by an electric spark. The increase in the temperature of the surrounding water, following the burning of the sugar, is noted and subsequently the oxygen and carbon dioxide contents of the gas in the bomb are analyzed. If one gram of sugar were used, and the volume of water surrounding the bomb were one liter, it would be found that the temperature was raised approximately 4° C. Since a large calorie is defined as the amount of heat necessary to raise the temperature of one liter of water 1° C., the gram of sugar in burning gave rise to four calories.

If we could imagine a small steam engine placed inside the bomb and the sugar burned under the boiler of this engine, so as to make it run, the heat of the burning sugar would be converted into mechanical energy which would, in turn, be converted back into heat, so that when the whole system once more came to rest, it would be found that the temperature of the outside water would be raised to exactly the same extent, as when the sugar burned directly, without first producing mechanical energy. A calorie, in terms of mechanical energy, is equivalent to approximately 3000 foot pounds, that is to say, the energy of one calorie is sufficient to raise a ton and a half to a height of one foot, or to raise one pound to a height of 3000 feet.

When sugar is "burned" in the body, it produces exactly the same amount of heat as when burned in the air, and exactly the same amount of oxygen is absorbed and carbon dioxide given off. The energy produced may be converted into such mechanical work as muscular contraction, but will ultimately appear as heat. If an individual is put into a large enough calorimeter chamber surrounded by water and the air entering and leaving this chamber is analyzed, the exact amount of sugar or other foods utilized in the body may be determined and from this the amount of heat which should be produced can be calculated. It has been found by actual experiment that the amount of heat so calculated is the same as that produced and measured by the rise in temperature of the surrounding water.

All foods do not have the same fuel value. One gram of fat has a fuel value of a little over 9 calories in the calorimeter, and in the body. Protein does not form the same end-products when burned in the air as in the body, but when due allowance is made for the fact that a portion of the protein in the body is converted only to the stage of urea, instead of being completely oxidized as in the calorimeter, it is found that the fuel value is the same in and out of the body, namely, 4 calories per gram. Individual sugars, fats, and proteins have slightly different fuel values. The figures given above are rough averages.

During life, the human body continuously gives off heat, the source of which is the combustion of protein, carbohydrate, and fat, together with small amounts of other foodstuffs such as alcohol and organic acids.

Even when no food is taken, the body continues to give off heat, which, in this instance, comes from the utilization of stored food material in the body, chiefly glycogen and fat and to a lesser extent protein of the body tissues. The amount of material consumed by the body, as measured by the oxygen intake and carbon dioxide output, or by the actual heat production, bears a definite relationship to the age, weight and size of the body. The average output of heat or "basal metabolism" of individuals fasting and at complete rest is in the neighborhood of 1 calorie per kilogram of body weight per hour; that is, an individual weighing 60 kilograms

(132 pounds) would consume food having an energy value of 60 calories per hour, or 1440 calories in twenty-four hours. As all of this energy is derived from utilization of food materials in the body, obviously the amount of food taken daily must have a caloric value at least this great or the body itself would be consumed as fuel.

If food having a caloric value just equal to the basal metabolism were given, it would be found somewhat insufficient because the utilization of food, in itself, leads to a certain increase in the heat output. On an average, the increase in heat production due to the taking of a mixed diet is approximately 10 per cent. Carbohydrate raises the rate of metabolism very little, fat somewhat more, and protein very appreciably. This effect of food in increasing the rate of metabolism, or heat output, is known as the "specific dynamic action." In order, therefore, to give enough food to meet the minimum energy requirements of the body, at least 10 per cent above that corresponding to the basal metabolism is necessary. The patient in question would, therefore, need an additional 144 calories, or a total of 1584 calories.

These calculations have all been based on the assumption that the patient remains at complete rest in bed. Any activity necessarily calls for a greater expenditure of energy; for example, merely sitting in a chair increases the metabolism by about 8 per cent. Any form of active exercise increases this still further. Walking, at a moderate rate on the level for one hour, requires the expenditure of from 150 to 200 additional calories. Walking up a moderate incline might increase the energy requirement by as much as 400 or 500 calories in 1 hour, while severe muscular exercise would cause considerably larger increases in fuel requirement, all of which must be supplied by the food.

In determining the total food requirement, one must also take into consideration the fact that all of the food taken by mouth is not digested or absorbed. A portion (5 to 10 per cent) is lost in the excreta. During the period of active growth a considerable portion of the food taken in is not utilized to produce energy but goes to form new body tissue and due allowance for this must be made in the case of growing individuals.

It has been found that smaller individuals, whether in the stage of growth or not, have a greater fuel requirement than larger individuals per unit of body weight; thus, the basal metabolism of a mouse is 450 calories per kilogram per day, while that of a horse is only 14.5. Smaller human beings, likewise, have a relatively higher energy requirement than larger ones. The average caloric requirement of an infant is 100 calories per kilogram per day, of an adult engaged in moderate activities 40 calories per kilogram per day.

Even though the variations in caloric requirement per kilogram of body weight are great, there is a very close correspondence between the energy metabolism and the surface area of the body. This is practically constant for normal individuals of varying size, and approximates 40 calories per square meter of body surface per hour, under resting conditions. It is obvious that the smaller the individual, the greater the surface area, in proportion to weight. A comparison may make this clear; if a ball of lead weighing one pound is converted into a pound of small shot, the total surfaces of the individual shot will, of course, be enormously greater than that of the original ball. There is a small variation for age, the energy output being greater in younger individuals.

Ingenious graphic charts have been worked out by DuBois and by Boothby, from which the surface area of the body may be directly read off, provided the weight and height are known (Fig. 11). From such information an approximation of the total caloric requirement of any individual may readily be determined. Taking into consideration all the factors mentioned, the total daily caloric requirement of an average sized adult, under varying conditions, is approximately as follows:

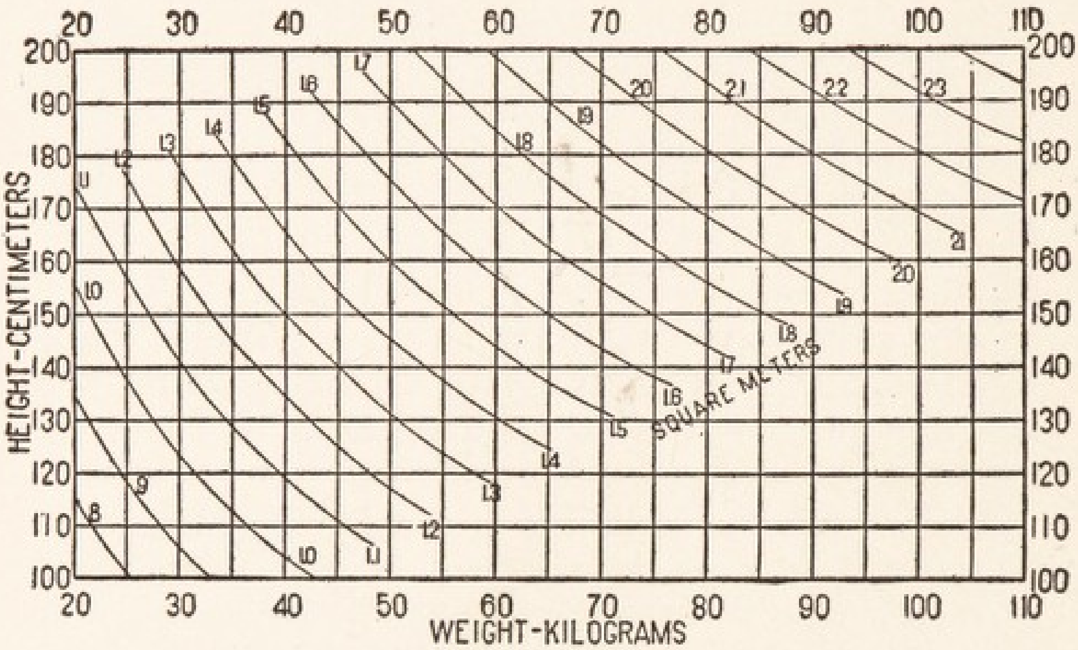


Fig. 11.—Chart for determining surface area of man in square meters from weight in kilograms (Wt.) and height in centimeters (Ht.) according to the formula: Area (Sq. Cm.) = Wt. 0.425 × Ht. 0.725 × 71.84. (From DuBois, Arch. Int. Med., 1917, vol. 17.) (Macleod: Physiology and Biochemistry in Modern Medicine.)

In bed 24 hours	1700 calories
In bed 8 hours, sedentary occupation remainder of time	2200 calories
In bed 8 hours, moderate exercise such as taken by a person with office employment	2500 calories
In bed 8 hours, moderately severe manual work 8 hours	3500 calories
In bed 8 hours, very heavy manual labor 8 to 10 hours	7000 calories or more

Adolescent individuals from the ages of thirteen to seventeen years have relatively high caloric needs, due largely to growth and activity. The food requirements of a boy of sixteen are distinctly greater than those of a man of twenty. These facts are well shown in the accompanying chart (Fig. 12).

One more factor which influences the caloric output should be mentioned, and that is the body temperature. In fever, the metabolism increases approximately 7 per

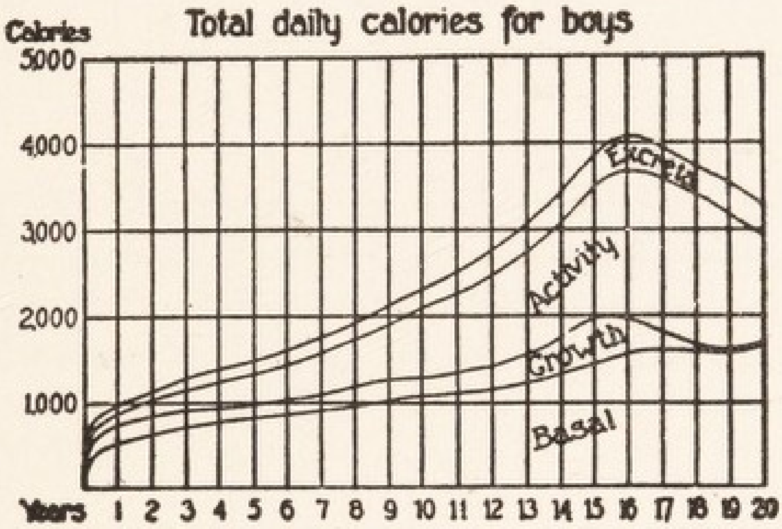


Fig. 12.—The distance between the base and the upper lines shows the allowance for total daily calories according to age from childhood to adult life. The spaces between the various lines from the base upward indicate the allowance for the different factors which make up the total, that is, for basal requirement, growth, activity, and loss in excreta. (Holt and Fales.)

cent for each degree Farenheit of temperature above the normal.

It is, of course, not possible to calculate exactly the caloric requirement of a given individual, but fairly close approximations may be made if the factors mentioned are taken into consideration. Unless a sufficient number of calories in assimilable form are supplied, proper nutrition becomes impossible. We hear a great deal of dietary fads and recommendations as to the type and quantity of food to be eaten. Any of these suggestions should first be considered in the light of actual calories supplied.

A proper number of calories are essential, but the form in which such calories are supplied is also of importance. If an individual receives the total caloric requirement in the form of pure carbohydrate, the maintenance of life and health over a prolonged period is not possible. Certain essential elements are necessary to supply the wear and tear of the body tissues, to build up new tissues, and to assure the proper utilization of the food. The diet must be correct in quality as well as in quantity.

Proteins

Protein is essential for the maintenance of life and for the repair and building up of body tissues. All body cells are composed partly of protein. During the processes of life, a certain amount of body tissue is necessarily broken down and sufficient protein must be supplied to replace this. If a normal adult receives a sufficient amount of carbohydrate and fat to cover all of his caloric requirements, but receives no protein, he will nevertheless eliminate constantly in the urine a certain amount of protein end products, the result of breakdown of body protein. The amount so eliminated in terms of nitrogen is in the neighborhood of 5 grams per day, which corresponds to about 30 grams or one ounce of protein. Unless at least this amount of protein is supplied, the individual will gradually waste away because of destruction of his own tissues. An average adult, given a free choice of food, usually takes something over 100 grams of protein per day, or about 1.5 gram per kilogram of body weight. Some individuals, living under unusual conditions, such as Eskimos, take considerably larger amounts; others, due to poverty, a smaller amount, but rarely less than 50 grams per day, or 0.75 grams per kilogram. An amount of protein less than 0.50 grams per kilogram per day is not sufficient for continued health and efficiency.

All proteins do not have the same composition or the same value in nutrition, although they are all composed of combinations of "*amino acids.*" These individual "building stones," as the amino acids have been called, exist in very different proportions in various proteins. When protein is fed, it is broken down in the intestinal trace into the individual amino acids, which, being small molecules, pass readily through the walls of the intestine and into the blood. These amino acids, being carried to the cells, are reconverted into body tissue. If the protein fed had exactly the same relative proportions of amino acids as body tissue, one gram of protein would supply material for the building up of one gram of body tissue. If, however, one of the essential amino acids were present in only one-half the proportion in the protein fed as in body cells, a gram of such protein would allow for the building up of only one-half of a gram of body protoplasm; that is, as much body protoplasm as corresponds to this particular amino acid. Any excess of the other amino acids could not be used for the formation of body tissue but would be converted into urea and excreted. If the protein fed were lacking entirely in one of the essential amino acids, no body tissue at all could be built up. Gelatin is a protein which is deficient in the amino acids, tyrosin, cystin and tryptophane. In an individual fed on gelatin as the sole source of protein, a nitrogen loss from the body occurs just the same as if no protein at all were fed, and no new body tissue is built up. If, on the other hand, the lacking amino acids in pure form are added to the gelatin diet, new body tissue may be formed.

Most vegetable proteins contain relatively small amounts of certain essential amino acids. One of the proteins of wheat, for example, contains no lysin. Gelatin, on the other hand, contains a large amount of lysin, so that when wheat protein and gelatin are fed at the same time, new tissue is formed and the combination of the two acts as a complete protein, whereas neither alone is of value as a protein food. When vegetable proteins form the sole source of protein in the diet, much larger amounts must be taken in than in the case of proteins of meat or milk. For example, it has been found that 30 grams, or one ounce of meat protein is the equivalent for the building up of body tissue of 54 grams of bean protein, 76 grams of bread protein or 102 grams of corn protein. This fact is of considerable importance in consideration of vegetarian diets. In the diet of nephritics showing nitrogen retention, the proteins of meat and milk, being complete, are preferable to the vegetable proteins as they may be used to build up body tissue with the production of less waste amino acids. As proteins, white or red meat have essentially the same nutritional value, they are equally digestible and one gives rise to no more harmful waste products than the other. Red meat, however, contains a larger amount of pigment, which is valuable in the building up of hemoglobin.

Of the various types of food, proteins, as a class, are the most completely digested and absorbed, even when the digestive function is impaired. Proteins are less likely to lead to diarrhea than are either carbohydrates or fats. Digestion of proteins begins in the stomach where they are broken down to smaller molecules, the albumoses and peptones, by the action of the pepsin and hydrochloric acid of the gastric juice. Gastric digestion, however, is not essential, as proteins which escape digestion in the stomach may be completely digested in the small intestine. This latter digestion is brought about first by the action of the trypsin of the pancreatic juice, which breaks the protein down into smaller molecules, albumoses, peptones and polypeptides and finally to the individual amino acids. Another enzyme "erepsin," produced in the intestinal mucosa, also acts upon the polypeptides to convert them into amino acids.

Under normal conditions, no absorption of any products of protein digestion other than the amino acids occurs. When the mucosa of the intestinal tract is injured, however, a small amount of unchanged protein or of partially digested protein remnants may be absorbed directly into the circulation. The absorption of any considerable amount of these latter substances is distinctly harmful to the body. Practically all of the protein fed is digested and absorbed in the small intestine. There are some protein remnants present in the large intestine and in the stools, but these represent largely the protein of bacterial bodies and protein secreted in small amounts by the intestinal glands.

After absorption from the intestinal tract, the amino acids are in part used for the building up of protein to repair destroyed tissues, and in the case of growing individuals for the production of new protoplasm. In the case of adults very little new protoplasm is formed. The remaining amino acids not needed for the formation of new tissue, are promptly utilized as fuel. The amino group (NH_2) is removed and converted into urea. Other portions of the molecules of certain amino acids are converted into creatin, creatinine, uric acid and small amounts of other substances. During the transformations involved, approximately 58 per cent of the total protein molecule is converted into substances behaving in the body in the same way as sugar—a fact of considerable importance in connection with the diet of diabetics.

All of the nitrogenous constituents, other than those used for the production of new tissue, are eliminated in the urine within a comparatively short time after the taking of a meal containing protein. Of the total output of nitrogenous material in the urine, under normal conditions, urea comprises about 85 or 90 per cent, ammonia and creatinine 3 to 5 per cent, uric acid about 1 per cent. In the presence of acidosis, other than that associated with nephritis, there is an increased excretion of ammonia salts in the urine, the ammonia being produced at the expense of urea.

Carbohydrates

Carbohydrate, in the average diet, supplies from one-half to three-fourths of the total calories. Carbohydrates are chemically simpler substances than proteins. They are composed only of carbon, hydrogen, and oxygen, the latter two elements being in approximately the same proportions as in water. The simplest carbohydrates are the monosaccharides, such as glucose, levulose, and galactose. Two molecules of any of these joined together form the disaccharides, examples of which are cane sugar, milk sugar, and malt sugar. Still larger molecules, composed of many monosaccharide molecules, also exist as, for example, starch which is composed of a very large number of molecules of glucose.

All carbohydrates are ultimately utilized by the body in the form of the monosaccharides or simple sugars. When starch is fed, it is acted upon to some extent by an enzyme in the saliva (ptyalin) which breaks it down to smaller molecules of dextrin. In the small intestine, starch is acted upon by the enzyme amylopsin, of the pancreatic juice, which is similar to ptyalin in its action. This enzyme breaks down the starch first to one of the dextrins and later to the disaccharide maltose. The term "dextrin" is applied to a whole group of partial decomposition products of starch having various sized molecules. The dextrins as a group are soluble in water, but the molecules are too large to pass through the intestinal wall into the blood. During further digestion the dextrins are converted into maltose, a disaccharide, and ultimately into glucose. Cane sugar and lactose are broken down by enzymes secreted by the intestinal mucosa so as to form the monosaccharides, glucose, levulose, and galactose, in which forms carbohydrate is finally absorbed. Only when the intestinal mucosa is injured, does any disaccharide pass into the circulation. Cane sugar or lactose entering the blood stream in this way or injected intravenously are not utilized but are excreted unchanged in the urine.

During the absorption of carbohydrate, there occurs a slight rise in the glucose content of the blood. During fasting, the sugar content of the blood averages about 0.1 per cent. At the height of digestion of a meal containing considerable carbohydrate the blood sugar level does not usually go higher than 0.15 per cent. With an increase to as high as 0.17 per cent, which rarely occurs, in the normal individual except when huge amounts of carbohydrate are given, some glucose passes out into the urine.

The level of the blood sugar is kept within narrow limits by an efficient regulatory mechanism. Glucose, which is needed for fuel, is promptly burned in the tissues and the remainder stored in the liver and muscles in the form of glycogen, or animal dextrin, or converted into fat and stored in the subcutaneous tissues. During starvation the stored glycogen is broken down to form glucose, which is poured out into the blood and utilized as food. When carbohydrate is fed in the form of starch, digestion and absorption take place more slowly than when given in the form of a simple sugar. The rate of absorption of sugar from starch is such that the blood sugar of the normal individual never rises above the point where sugar is excreted in the urine; that is to say, the normal individual has a practically unlimited metabolic "tolerance" for starch.

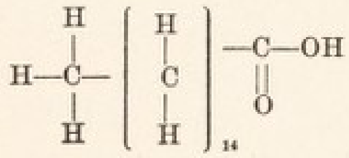
When, however, a simple sugar, such as glucose, is fed, absorption may occur more rapidly than the blood sugar can be oxidized or stored as glycogen and fat, and under such circumstances the blood sugar rises above 0.17 per cent and a small amount of sugar appears in the urine—the so-called "alimentary glycosuria." A normal individual can utilize as much as one gram of glucose per kilogram of body weight per hour, which means a total tolerance of from 1500 to 1700 grams (3 to 3½ pounds) per day in the case of an average sized individual. An adult can take as much as 100 grams (three and one-third ounces) of glucose at one time without showing an alimentary glycosuria. In diabetes, however, as we shall see later, the body is unable to utilize sugar at a normal rate, so that the blood sugar rises markedly and sugar consequently appears in the urine.

During the utilization of sugar for the production of energy, a portion is converted into lactic acid which, under normal conditions, is subsequently oxidized to carbon dioxide and water. When a sufficient supply of oxygen is not available, the lactic acid is not completely burned but accumulates in the blood and tissues.

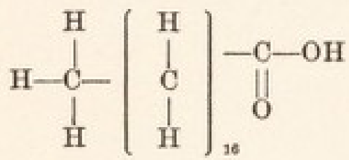
A certain amount of carbohydrate is necessary in the diet, for, as we shall see subsequently, fats and some of the products of protein metabolism cannot be completely utilized unless a certain definite amount of carbohydrate is being metabolized at the same time.

Fats

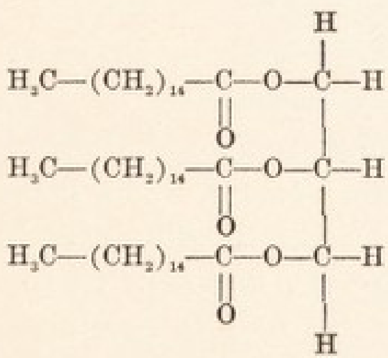
The fats, like carbohydrates, are composed of carbon, hydrogen and oxygen; the proportions, however, are quite different than in the case of carbohydrate, there being considerably less oxygen present. All fats consist of a combination of fatty acids with glycerin. The fatty acids are composed of long chains of carbon atoms united with hydrogen, each chain having at the end a group capable of breaking up in solution so as to liberate a hydrogen ion, this giving the fatty acids their acid character. The fats which are of chief interest in nutrition are those containing either 16 or 18 carbon atoms. These are united with glycerol, an alcohol containing three carbon atoms and two hydroxyl groups, as in the following formulas:



Palmitic acid.

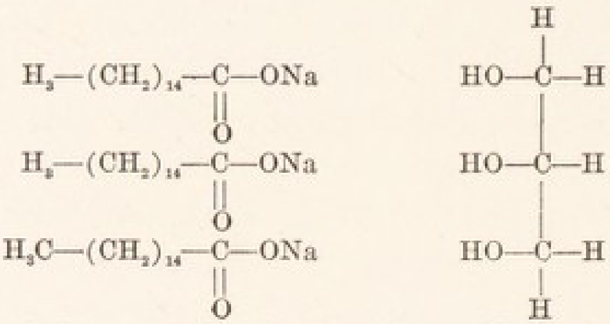


Stearic acid.



Tri-palmitin a fat.

When fats are subjected to the process of digestion, or heated with alkalies, the fatty acids are separated from the glycerin and unite with such alkalies as may be present to form the salts of these acids, the salts being known as *soaps*. The reaction occurring is as follows:



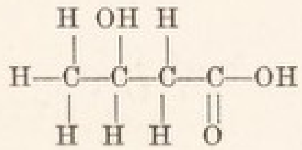
Sodium soap of palmitic acid Glycerol

Ingested fats undergo very little change in the stomach. In the small intestine, however, under the influence of the enzyme steapsin, secreted by the pancreas, the fats are broken down into fatty acids and glycerin. The fatty acids are largely converted into sodium soaps through combination with the alkali secreted by the bile and pancreatic juice. A small amount of calcium soaps are also formed by combination with the lime salts of the food. These latter are much less soluble in water than the sodium soaps and are, therefore, not as readily absorbed. Bile salts, however, have the property of rendering calcium soaps more soluble and consequently more readily absorbable.

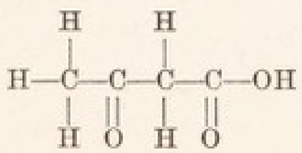
No matter what the form of fat given, it must be completely broken down to fatty acids or soaps and glycerol; in other words, it must be saponified, before any can be absorbed. Absorption takes place not through the blood, but through the lymphatic system. The fatty acids and soaps pass through the cells of the intestinal mucosa where they are reunited with glycerin to form fat once more. This fat, in the form of fine emulsion, is carried by the lymphatics into the thoracic duct and thence into the blood stream. Fats that are not saponified, and such substances as mineral oil, which is not a fat at all, cannot be absorbed by the intestinal tract.

The fat which enters the blood is, in part, carried to the subcutaneous tissues and deposited, in part to the liver, where it undergoes a chemical transformation, rendering it capable of being metabolized as fuel. When there is abundant carbohydrate and protein in the diet, relatively little fat is burned, the major part being stored. During starvation, however, a large portion of the energy requirement is met by the utilization of fat previously stored in the subcutaneous tissues and elsewhere.

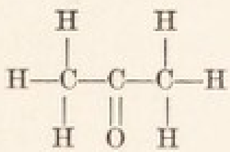
When fat is utilized the long chain of carbon atoms is broken down apparently two atoms at a time, until a short chain of 4 carbon atoms is left. When this stage is reached, further combustion cannot occur unless a certain amount of carbohydrate is present and is being burned simultaneously, or as aptly stated by Rosenfeld, "fats burn only in the fire of carbohydrates." One molecule of glucose is necessary for the complete combustion of two molecules of fatty acid remnants in the body. Unless glucose is present and being used at the same time, the four carbon atom chain is converted into betaoxybutyric acid:



and acetoacetic acid:



the latter is in part decomposed in the body to form acetone:



It is the two acids, betaoxybutyric and acetoacetic, known as the "ketone" acids, which are responsible for the acidosis of carbohydrate starvation and of diabetes.

Just how glucose brings about the complete combustion of the ketone acids is not known, but much information on the subject has been obtained especially by Shaffer, within recent years. It has been found, for example, that if acetoacetic acid and hydrogen peroxide are added together in a test tube, no oxidation of the acetoacetic acid occurs. If, however, glucose in alkaline solution is added, prompt oxidation of the acetoactic acid is brought about. One molecule of glucose is found sufficient to bring about the decomposition of two molecules of acetoacetic acid. It would seem at least probable that some such reaction occurs within the body.

It is known, from actual experience, that when, in the process of metabolism more than two molecules of fatty acid in proportion to one molecule of carbohydrate are being utilized, the acids which are the products of the incomplete combustion of fat appear in the tissues, blood and urine. In order to calculate a diet which will give a sufficient amount of carbohydrate to prevent *ketosis,* or the appearance of these acids, certain factors must be taken into consideration. These are: (1) the total metabolism, that is, total calories; (2) the amount of protein metabolized; (3) the amount of fat metabolized; (4) the amount of carbohydrate metabolized.

The total metabolism will depend upon the size and activity of the individual rather than the food intake, for, as already mentioned, the metabolism proceeds whether or not the individual receives food.

On an insufficient diet, body fat will be consumed, and conversely, if the diet contains a considerable amount of fat, together with an amount of carbohydrate sufficient in itself to cover the caloric needs, the fat of the diet will be largely converted into body fat and not burned. In other words, the total fat used does not correspond to the amount taken in the food.

The amount of protein used by the body, provided the minimum requirement of one-half gram per kilo of body weight is given, will, in the case of an adult, be the same as the amount of protein taken in the food, that is, the total nitrogen of the urine will be approximately the same as the nitrogen of the protein ingested. In the case of growing individuals, however, a portion of the protein will be stored in the body and not burned. A true measure of the amount of protein actually used may be obtained by determining the total nitrogen of the urine. This figure multiplied by 6.25 gives the amount of protein metabolized in the body.

When protein is broken down, some of the constituents form chains of 4 carbon atoms and are convertible into the ketone acids. Other remnants, breaking down into chains of 3 carbon atoms, are converted into glucose and aid in the combustion of the ketone acids. There is a considerable excess of the latter, so that protein as a whole tends to act antiketogenically rather than ketogenically. The amounts of fat and carbohydrate metabolized, that is, burned, in the body will depend upon how much total food is given and what proportion of this is composed of carbohydrate.

Shaffer has devised an ingenious formula which takes into consideration all of the factors mentioned and which provides a simple means for the calculation of a diet designed either to prevent or to cause ketosis. This formula is as follows:

Shaffer's Formula

$$\frac{\text{Total metabolism expressed as calories} - (\text{urine N} \times 100)}{50} = \text{minimum food carbohydrate}$$

The use of this formula is very simple. Suppose, for example, we have a patient whose total caloric output is calculated at approximately 2500 per day. If the patient weighs 70 kilograms and is given 1 gram of protein per kilogram of body weight, a reasonable allowance, such a patient should excrete in the urine practically all of the nitrogen of the protein taken in. As protein contains 16 per cent of nitrogen, this will be 70×16 or 11.2 gm. We then have $\frac{2500 - (100 \times 11.2)}{50} = 29+$ gm. This will mean that the patient should receive a minimum of 30 grams of carbohydrate in the daily food. Since it is not certain that this minimal amount of carbohydrate will be utilized just as needed, it is always advisable to double the minimum amount, in order to insure the prevention of ketosis. The patient should, therefore, be given at least 60 gm. of carbohydrate. The diet would then be composed of:

60 gm. carbohydrate, yielding	240	calories
70 gm. protein, yielding	280	calories
Total calories	520	

Since the total caloric requirement is 2500, the amount supplied by fat, whether from the body or from food given, will be approximately 2000 calories. As the fuel value of fat is 9 calories per gram, there will be required $\frac{2000}{9}$ grams of fat, or 222 grams. The formula is of great value in calculating a diet for diabetic patients. This phase of the subject will be referred to again in the following lecture.

There are certain conditions, for example, epilepsy, in which it is desired to give a diet which will produce ketosis. In calculating such a diet, Shaffer's formula is also used and only the minimum carbohydrate is given at the start. The amount of carbohydrate is then gradually reduced until ketosis occurs, as indicated by the appearance in the urine of a positive ferric chloride test. According to Peterman and Helmholz of the Mayo Clinic, diets producing ketosis are very effective in preventing epileptic seizures.

Occasionally diets designed to be ketogenic or antiketogenic are calculated on the basis of the ratio between fat and carbohydrate, it being stated that a ratio of 4 of fat to 1 of carbohydrate represents the minimum amount of carbohydrate to prevent ketosis. Such a formula, although simple, is not altogether correct, as it fails to take into account the total caloric intake and the fact that the fat of the food does not necessarily represent the amount of fat actually burned in the body.

It is only under such unusual conditions as diabetes and epilepsy that diets containing such high proportions of fat as that just calculated are indicated or desirable. Under ordinary conditions the amount of fat in the diet of an adult varies from 50 to 150 grams per day and supplies from 25 to 35 per cent of the total calories.

Fat and carbohydrate are more or less interchangeable as sources of energy provided the proportions are such that ketosis does not develop. Certain fats, however, have a special value in that they contain two of the essential vitamines. This phase of the matter will be discussed presently.

Mineral Salts

Proteins, fats, and carbohydrates supply the necessary fuel for the human engine. Protein supplies in addition materials for the construction of the body. But these three foodstuffs together fail to supply all of the materials necessary to support life. Mineral matter, as well as the three foods mentioned, is essential. All cells, tissues, and fluids of the body contain salts, which serve to maintain constant osmotic pressure, to supply the necessary balance of ions for the normal functioning of cells and aid in the digestion of food in the intestinal tract. Even on a diet free from mineral matter, there occurs a constant excretion of mineral salts, therefore, unless an equivalent amount of these salts is supplied in the diet, wasting of the body occurs.

Growth and life do not continue in animals fed on purified proteins, fats and carbohydrates. Fortunately many foods contain considerable amounts of mineral salts. Milk is especially rich in calcium and phosphates. Meat contains practically all of the essential salts in small amounts and a relatively large amount of potassium. Salt water fish contain appreciable amounts of iodine. Green vegetables contain sodium and potassium salts, iron and traces of iodine; fruits a good deal of potassium; whole grains most of the mineral constituents including iron, but purified grains such as white flour and polished rice contain very little mineral matter. With a free choice of food, most individuals obtain sufficient mineral salts, but those subsisting largely on starches, sugars, butter or oleomargarin, a minimal amount of meat, and little or no milk or green vegetables may suffer from a mineral deficit, especially of calcium.

In certain parts of the country the soil and the surface waters contain so little iodine that an individual drinking the water and eating vegetables raised on the soil in question may not receive enough iodine to meet the body's need for this element. Iodine is required for the normal activity of the thyroid gland. When deficient, colloid goiter occurs. The whole human thyroid contains only from 10 to 25 mg. of iodine, and it has been shown that the ingestion of as small an amount of iodine as 0.1 mg. daily for 15 or 20 days out of the year is usually sufficient to protect against colloid goiter.

When the drinking water contains as much as one part of iodine to the billion, the incidence of goiter is slight, but with amounts of iodine less than 0.1 parts per billion, the incidence of goiter is likely to be as much as two or three per cent of the population. The addition of iodine to the diet in minute amounts is indicated in the case of individuals living in goiterous regions, where the drinking water contains very small amounts of iodine.

Very little iron is necessary in the diet of an adult in normal health, but in the case of a growing child or in adults following loss of blood, considerable amounts of iron in the diet are necessary in order to provide for the building up of hemoglobin. The hemoglobin molecule is a complex one, composed of a protein united with hematin; the hematin in turn is composed of iron and a pigment substance known as hematoporphyrin. Hematoporphyrin is a complex compound composed in part of molecular groups arranged in a form known as pyrrol rings. Such complex groups probably cannot be synthesized in the body, but have to be taken in with the food. One of the amino acids of proteins (proline) contains these complex groups and supplies the materials from which hematin is made. There is not a large amount of this particular amino acid in most proteins, so that when anemia is marked, it is desirable to supply additional hematin-forming materials in the food. Chlorophyll, the green coloring matter of plants, contains the same complex molecular groups as hematin and it has been found experimentally that the feeding of green vegetables together with iron leads to a more rapid regeneration of the blood than when iron alone is administered.

In certain foods the mineral matter contains a preponderance of bases, in others a preponderance of acid elements. It is interesting to note that acid fruits, such as oranges and lemons, contain a preponderance of bases. When these fruits are ingested, the organic acids are completely consumed in the body, leaving behind the bases. Benzoic acid, however, which is present in certain fruits, such as prunes and cranberries, is not burned in the body, so that these fruits give rise to an acid residue. A patient, however, probably never develops acidosis as a result of taking foods with a preponderating acid ash, or alkalosis from those having a preponderating alkaline ash, since the regulating mechanism of the body is sufficient to care for any moderate excess of either acid or alkali.

It must not be assumed that all of the mineral matter of the food taken in goes to increase the mineral content of the body, or to change the proportions of the constituents present in the body tissues and fluids. The mineral content of the body remains practically constant under normal conditions, any excess of salts being either not absorbed or promptly excreted. It is only when there is a deficiency of some one element that its administration results in an increased retention of that particular element in the body. In recent years pharmaceutical houses have placed upon the market a large number of salt mixtures which are recommended for use in preventing acidosis and in restoring a normal mineral balance. There is no rational basis for the use of such mixtures, as ordinary food meets every demand.

LECTURE V

FOODS AND METABOLISM (Continued)

Vitamines, Dietetics

Vitamines.—For a long while it was supposed that protein, carbohydrate, fat, and salts were all that were necessary for the diet of an individual, but it was subsequently found that the feeding of purified mixtures of these substances failed to maintain normal nutrition in either animals or man. It then became realized that there were certain substances of unidentified nature occurring in natural foods which were essential for the maintenance of life and health. These substances have been designated as "accessory food factors" or "vitamines." Our knowledge at present includes facts concerning at least five of these accessory food factors. These are designated as vitamines "A," "B," "C," "D," and "X" or "E." The first four are necessary for normal growth and health and the last for the function of reproduction.

The exact mode of action of the vitamines is unknown. The question whether they act to stimulate chemical reactions within the body or whether they supply certain necessary cell constituents is still unanswered. Some have compared the vitamines to the lubrication in a machine. The vitamines, so far as we know, all seem to be produced in the plant world.

The Fat-Soluble Vitamines A and D

Vitamine A is sometimes referred to as "fat-soluble" A because of the fact that it occurs in association with the fats of milk, egg yolk and of glandular organs such as liver. It is present also in the leafy vegetables and, to some extent, in the pericarp of the cereal grains. Relatively small amounts of vitamine A occur in the ordinary subcutaneous fat of animals and there is little, if any, in most of the vegetable oils. One of the richest sources of this vitamine is cod liver oil. Vitamine A is little, if any, affected by ordinary heating or cooking, especially if free access of air is avoided. If, however, a food containing the A vitamine is boiled for a long while, and a current of air simultaneously passed through the mixture, a portion of this vitamine is destroyed.

When the A vitamine is deficient in the diet of young individuals, growth ceases. Fully grown individuals, however, can subsist for a considerable time when this vitamine is absent from the diet. This may possibly be due to the fact that a fair amount is stored in the body in the glandular fats. Ultimately, whether young or old, individuals deprived of the A vitamine develop a chronic conjunctivitis associated with softening of the cornea, the conditions being known as xerophthalmia and keratomalacia. There also occurs a loss of strength and of resistance to infections, especially tuberculosis and sinus infections. Blood regeneration in anemia does not occur in the absence of vitamine A. An atrophy of certain of the endocrine glands has been observed in animals fed on diets deficient in vitamine A.

Vitamine D can best be considered in relation to vitamine A as they usually occur in association, both being "fat-soluble." They do not always occur in the same proportions. Thus cod liver oil contains relatively more vitamine D than does butter. The original source of vitamine D is apparently a green vegetation. Certain marine plants growing near to the surface are a rich source of the vitamine. These plants are eaten by small crustaceans and these in turn are devoured by codfish.

It is probably in this way that the vitamine finds its way to the oil of the cod's liver.

The resistance of vitamine D to heat is about the same as that of vitamine A, but it is not so readily oxidized as is the A vitamine.

When vitamine D is deficient in the diet of growing individuals, rickets occurs. Adding this vitamine to the diet, in the form of cod liver oil, results in a prompt improvement of the condition, provided other disturbing factors are not also present. Lack of this vitamine in the diet of adults is associated with lack of resistance to infection and slow healing of fractured bones. It is an interesting fact that both of the fat-soluble vitamines A and D are associated with the unsaponifiable fraction of natural fats and oils. The substances which do not saponify and which carry the vitamines are sterols, closely related to cholesterol, and comprise not more than one per cent of such a fat as cod liver oil and a smaller proportion of other fats. The discovery that these vitamines are in this small fraction of natural oils has made it possible to prepare the vitamines in concentrated form by separation of the cholesterol fraction so that the vitamines can be administered by mouth in a much more palatable form than cod liver oil ("Oscodal," activated ergosterol, etc.).

Exposure of natural foods to sunlight, or to the rays of artificially produced ultraviolet light, results in the development in these foods of an increased amount of both of the fat-soluble vitamines. Exposure of cod liver oil to ultraviolet light does not increase its vitamine content, but exposure of oils, such as linseed, which normally contain practically none of these vitamines, does lead to a considerable increase. It has also been shown that exposure of a mother to sunlight or ultraviolet light results in the appearance of a larger amount of the fat-soluble vitamines in her milk. Exposure of an individual to sunlight brings about essentially the same physiologic effect as the administration of the D vitamine.

In ordinary diets, the chief source of the fat-soluble vitamines is the fat of milk, the leafy vegetables and the yolks of eggs. An individual taking a reasonable amount of dairy products and leafy vegetables, particularly if supplemented by eggs, receives all of these two vitamines that are necessary. The same cannot be said of a person subsisting upon a diet lacking in dairy products, eggs and green vegetables.

Vitamine B

Vitamine B is more widely distributed in nature than any of the other accessory food factors. It is present in especially large amounts in the leafy vegetables, in milk, fruits, in the pericarp and germ of grains and in yeast; there are smaller amounts in meat and practically none in fish. Vitamine B is not at all affected by the ordinary temperatures used in cooking. It is also resistant to drying and chemical action of all sorts. Thus vitamine B has been detected in practically normal amounts in whole grain stored for one hundred years.

So widely distributed is this vitamine that almost any individual given a reasonably free choice of food receives a sufficient amount for his needs. It is only on such one-sided diets as are occasionally taken by people in the far east consisting mainly of fish and polished rice that symptoms of vitamine B deficiency develop. When such a deficiency of this vitamine occurs, a condition of polyneuritis known as beriberi develops. With lesser degrees of deficiency, there is loss of appetite and strength.

Though vitamine B deficiency is practically never seen in this country, the use of yeast as a source of vitamines has become a dietary fad, and various yeast concentrates are put up in tablet form and fill the shelves of drug stores. There is very little evidence that the administration of yeast accomplishes any more than to bring about increased intestinal fermentation, thus exerting a laxative effect. Such an effect is observed only in the case of fresh live yeast cultures, however.

Vitamine C

Vitamine C or the antiscorbutic vitamine, occurs in particular abundance in fruits, especially of the citrus variety, in the leafy vegetables, and in tomatoes. Small amounts are present in milk. This vitamine is the only one which is seriously affected by heating. It is rapidly destroyed if heated in an alkaline or neutral solution, but withstands considerable heat in acid solution. It is destroyed, to some extent, by drying and disappears when kept, even at ordinary temperatures, in the presence of alkali. Pasteurization and boiling of milk destroy this vitamine so that infants, whose food consists largely of heated milk, may suffer from deficiency of vitamine C unless it is supplied in the form of orange juice or tomato juice. Tomato juice, even from canned tomatoes, contains a great deal of the antiscorbutic vitamine, this not having been destroyed by heating because of the slight acidity of the tomatoes. In older individuals deficiency of the antiscorbutic vitamine rarely occurs under normal conditions of life. When the C vitamine is deficient in the diet scurvy develops.

Vitamine X or E

Within the last few years, evidence of the existence of a vitamine influencing the function of reproduction has been brought forward by Evans and Bishop. This substance is known as vitamine X or E. Like A and D it is fat soluble and has a somewhat similar distribution in nature. It is especially abundant in the oil of the wheat germ and in the leaves of lettuce. It is also present in olive, cotton seed, maize and peanut oils. It is not associated with the true fat of any of these oils, but occurs in the nonsaponifiable or cholesterol fraction. There is very little vitamine E in animal tissues or in butter fat.

Animals fed on a diet containing an abundance of vitamines A, B, C, and D but lacking in this factor grow at a normal rate and are apparently healthy in every respect, but fail to give birth to young. Absence of the E vitamine in the diet of the male causes destruction of the germ cell; in the female ovulation and conception occur normally, but there is failure to reproduce—the placenta and fetuses being reabsorbed. In this connection the feminine taste for salads with oil dressing may have a biological significance.

It is likely that vitamines other than those now known will ultimately be discovered. Most of our knowledge concerning these elusive but important food substances has come during the last ten or fifteen years and the field is as yet incompletely explored. The whole subject of vitamines has assumed immense importance in the popular mind. Manufacturers of proprietary products have made capital of this recent knowledge and a great many half truths have been stated and restated. A favorite method of exploiting certain foods or vitamine preparations is to present pictures of animals undernourished and sickly side by side with pictures of healthy animals, the latter having received a certain amount of the food or vitamine preparation in question, the conclusion being drawn that a small amount of the particular vitamine supplied in a certain preparation will lead to growth and normal health. The fallacy lies in the fact that the control animals have been fed on highly purified synthetic diets *entirely* lacking in the vitamine and not on an average normal diet. Neither guinea pigs nor human beings fed on reasonable natural mixed diets are noticeably improved by the addition of an extra amount of any one of the vitamines.

We are shown pictures of rats fed on white bread beside those fed on whole wheat bread and are given to believe that we will all be malnourished unless we eat whole wheat. As a matter of fact, if rats or children are fed on white bread, together with milk and vegetables, they will be quite as well nourished and healthy as those fed on the same diet with the substitution of whole wheat bread. In planning a diet a reasonable amount of milk, butter, green vegetables and cereals should be included, and when this is done, we need have no fear of vitamine deficiency. Vitamines should be bought at the grocery store and not at the drug store.

Diets

A proper diet, as has already been seen, has an important influence in the maintenance of health. So long as all the essential qualifications of the diet are met, it is relatively unimportant whether that diet be composed chiefly of vegetables or chiefly of meat, whether red or white meat be taken, whether two meals or four a day, or whether the food be entirely or partly raw. We have with us always the dietary faddists, but the facts remain that the vegetarian Hindu, the carnivorous Eskimo and the omnivorous American are all reasonably healthy and long lived. It is true, however, that the Eskimo would suffer from the cold if required to subsist on the low protein diet of the tropics, and the dweller in the tropics would be uncomfortable if consuming the high protein diet of the Eskimo. A poverty-stricken peasant in Japan or the Philippines may suffer from beriberi as the result of subsisting on a diet composed largely of polished rice and fish, and some of the dwellers of our cities subsisting largely on canned foods, bread and meat and omitting milk, butter, eggs and vegetables from the diet may not receive an adequate supply of mineral salts and vitamines. In general, however, the average mixed diet providing a sufficient number of calories and containing dairy products and leafy vegetables and a minimum of 60 grams of meat protein or 100 grams of vegetable protein will be a suitable one. If the diet contains too few calories, too little protein, and mineral salts or is lacking in any one of the essential vitamines, various disease conditions may result, or the resistance of the body to infection may be lowered, so that the individual succumbs to the bacterial diseases.

The diet in disease should ordinarily be similar to that in health, with only such modifications as are indicated on account of specific changes in the body present as the result of disease.

The Diet in Fever

In the presence of fever, the metabolism is increased and, consequently, unless an additional amount of food is supplied, wasting of the body occurs. On the other hand, during fever, the appetite is impaired, there is lessened secretion of the digestive juices and poorer absorption from the gastrointestinal tract. This often renders it impossible for the patient to take as much food as during health. In the acute fevers this is of little moment, but in fevers of long duration, as in typhoid or tuberculosis, it is important that an effort be made to supply an amount of calories somewhat commensurate with the consumption. Protein is necessary to overcome the increased protein breakdown, but on account of its specific dynamic action in increasing metabolism, an excess of protein should be avoided. For the adult 0.75 to 1.0 gram of protein per kilo of body weight is an adequate amount and in the presence of fever, should usually not be exceeded. The diet recommended by Shaffer and Coleman for typhoid fever patients supplies rather high calories (60 to 80 per kilogram). The protein need is met by milk and an occasional egg, the remainder of the diet being composed of cream, lactose and a small amount of cereal. In the presence of intestinal complications, such as hemorrhage and perforation, the diet is, of course, promptly altered. Such a high caloric diet is not suitable in most instances during the first two weeks of typhoid.

In tuberculosis the diet should be a liberal one, the caloric intake being in excess of the calculated requirement so that the patient gains in weight. An abundance of the fat soluble vitamines A and D should be supplied in the form of milk, butter and eggs, in order to increase resistance to infection and to promote calcification of tuberculous lesions. The D vitamine seems to aid calcification in this disease as in rickets.

In rheumatic fever the diet need not be different from that in any other febrile affection. There is no good evidence that meat, either white or red, or substances containing the purin derivatives, convertible into uric acid, such as liver, kidneys and sweetbreads, tea or coffee have any deleterious effect on the course of rheumatism, although there is a popular idea that such foods are harmful. As a matter of fact, it has been shown that a purely vegetarian diet may lead to as great an excretion of uric acid as one containing reasonable amounts of meat. Furthermore, we now know that uric acid does not cause the manifestations of rheumatism.

In chronic infectious arthritis, the so-called "chronic rheumatism," there is an abnormal response of the body to sugar, the blood sugar curve following a carbohydrate meal being different than in normal individuals. On this basis it has been recommended that patients with chronic arthritis should receive a diet low in carbohydrate. It has been recommended that the diet be low in calories as well. Recent studies have shown that such low carbohydrate diets do not bring about a change in the response of the body to carbohydrate and a number of observers have found that a reasonable amount of carbohydrate in the diet does not increase the arthritic symptoms.

Diet in Anemia

In the anemias, especially pernicious anemia, it has been shown that there is a special advantage in adding considerable amounts of liver to the diet. There seems to be something in liver which is almost specific in stimulating blood regeneration. This can hardly be due to the small amount of iron contained in liver, for equivalent amounts of iron given in other forms are not as effective. There seems to be a substance in liver comparable to the vitamines which stimulates the regeneration of blood. Minot and his associates in Boston have used a diet containing large amounts of liver with great success in the treatment of pernicious anemia and have recently used the same diet with patients suffering from cancer with reported good results in improving the general condition of these patients. Patients with pernicious anemia should, in addition to the liver diet, usually receive considerable amounts of hydrochloric acid by mouth. In any condition of anemia the diet should be supplemented with liberal amounts of green vegetables because of their pigment content. It has recently been demonstrated that vitamine E has an influence in promoting blood regeneration.

Diet in Diabetes

In diabetes the qualifications for the diet are that the caloric requirements shall be covered, sufficient protein supplied to meet the minimal requirements and sufficient carbohydrate to prevent ketosis. If the body is unable to burn the minimum amount of carbohydrate necessary for this purpose, a sufficient amount of insulin must be given to insure the combustion of adequate carbohydrate. In calculating the diet of a diabetic we have found Shaffer's formula (see page 103) to be of the greatest value. The calculation is made exactly as described in the preceding lecture. The amount of protein is first calculated, allowing in the case of the adult one gram per kilogram of body weight; in children between the ages of ten and fourteen years one and one-half to two grams; younger children, two and one-half to four grams and infants four to six grams per kilogram of body weight per day. The total calories given are based on the calculations previously described. With this information, the quantities in Shaffer's formula are figured out and the necessary minimum amount of carbohydrate given. A reasonable excess, up to as much as 100 grams a day may, to advantage, be given to most diabetics.

The patient is put on the diet thus calculated and the effect is observed. If glycosuria occurs, the total amount of sugar eliminated in twenty-four hours is estimated and a sufficient amount of insulin administered, in divided doses, to prevent glycosuria and to maintain an approximately normal blood sugar level. The amount of insulin necessary for this purpose is approximately 1 unit of insulin for each 1.5 to 2.0 grams of glucose excreted per day. The number of injections given daily depends upon the severity of the diabetes. If the daily insulin requirement does not exceed 10 units, all of the insulin may be given in a single injection before breakfast, which is made the largest meal. Even such a case, however, is more easily controlled by two daily injections, one before the morning and the other before the evening meal. If the amount of insulin necessary exceeds 20 units, it is best to give three meals of equal size and three injections of insulin—one preceding each meal. When diabetes is very severe, the effect of the evening injection may be gone before the next morning, and the blood sugar may mount well above the threshold for urine excretion. In such instances, the patient should receive a fourth dose of insulin at midnight. It is not usually necessary to starve the diabetic patient in order to determine his sugar tolerance, as was the practice before the days of insulin. The principle of treatment now is to calculate an ideal diet, give it to the patient, and administer sufficient insulin to insure utilization of the available carbohydrate.

The treatment of acidosis occurring in the course of diabetes has been detailed in the lecture on acidosis.

Diet in Nephritis

Diet in nephritis has received a great deal of attention. It is questionable whether human nephritis is ever the result of an improper diet, although it has been claimed that a high protein diet, at times, produces nephritis in rabbits. Certainly human beings can take very large amounts of protein without any apparent deleterious effects on the kidneys. An increasing amount of evidence is accumulating that nephritis is the result, primarily of infection, and that consequently the important element in the treatment is the control of the infection rather than administration of a particular diet. Once nephritis has developed, however, a special type of diet is usually indicated, and the character of this diet will depend upon the type of nephritis present.

In the more or less pure type of tubular nephritis or nephrosis in which there is no retention of nonprotein nitrogen and no increase in the blood pressure, a high protein diet is indicated, the patient receiving as much as 2 or 3 grams of protein per kilo of body weight. The complete proteins of milk, meat and eggs are distinctly preferable to the vegetable proteins. The need for protein in this condition is for the replacement of serum protein lost by passage into the urine and by transudation into the tissues. Liver and green vegetables, especially spinach, are of value in overcoming the anemia always present in this type of nephritis. Water intake rarely needs to be limited, but salt should be moderately restricted when marked edema is present.

In glomerular or interstitial nephritis associated with high nonprotein nitrogen in the blood, hypertension and hematuria, the amount of protein in the diet should be limited to that necessary for maintenance (0.75-1 gram per kilo). Vegetable proteins are particularly undesirable in the case of glomerular nephritis with hematuria, since these proteins, being incomplete, are only partly available for the reconstruction of body tissues, and consequently give rise to considerable amounts of nitrogenous waste products, which must be eliminated by way of the urine. Cereals containing much protein are inadvisable, but such pure starches as arrowroot may be used. Starches, fats, and sugars should supply most of the calories. Soups, except cream soups, should not be taken because of the possible deleterious effects of the salts and meat extractives. Salt should be restricted, but the diet need not be entirely salt free. The patient should be allowed no salt meats, and the butter used should be unsalted. The water intake should not be limited, on the contrary the drinking of water should be encouraged.

In glomerular nephritis with hematuria, it is of advantage to institute at intervals of a week or ten days, a "sugar diet" for a day. On the "sugar day" the patient receives ten grams per kilogram of cane sugar in one liter or 1500 c.c. of fruit juices and nothing else.

Diet During Pregnancy

During the course of pregnancy, there is an increased need for certain food elements in order to provide for the development of the fetus. There is also a small additional need for calories. It is especially important that the diet should contain a sufficient amount of the fat-soluble vitamines A and D and sufficient lime. The best sources of lime and of the vitamines mentioned are milk and the leafy vegetables. The milk consumption should be not less than one pint a day, preferably more. This need not be taken as a beverage, but may be cooked in foods or taken as ice cream. The administration of cod liver oil is advisable, but, as this is distasteful to most adults, one of the newer preparations of cod liver oil in tablet form may be substituted. (Oscodal.) The D vitamine alone may be given in the form of activated ergosterol. It has been shown that when the diet of the mother is deficient in the antirachitic vitamine (D) during pregnancy, the infant is likely to suffer from rickets, even though given cod liver oil from the time of birth.

During pregnancy the liver often suffers some temporary damage. One of the results of derangement of liver function is a tendency to the development of ketosis. In order to protect the liver and to prevent ketosis a diet containing relatively high carbohydrate is advisable. The carbohydrate taken should be well spread out over the day so that the blood sugar never falls very low. When the manifestations of toxemia with vomiting occur, additional carbohydrate should be given early in the morning and at midnight. When the vomiting is persistent and little or no carbohydrate can be retained by mouth, the intravenous injection of 10 per cent glucose is indicated, the amount of solution given being 20 to 25 c.c. per kilogram of body weight. Some glucose may also be absorbed when given rectally.

When vomiting occurs, there is a loss of acid and a tendency to the development of the condition of alkalosis. In such cases the administration of from one-half to one c.c. of dilute hydrochloric acid three times a day is indicated. A mistake frequently made is the giving of alkali to patients suffering from vomiting during pregnancy. This increases the alkalosis and may lead to such a serious manifestation as tetany convulsions.

The Diet in Obesity

When the food provides more calories than are necessary to meet the energy requirements of the body, the remainder is stored, largely in the form of fat. There are no particular foods which are specifically "fattening." Any food supplying calories, when given in excess, leads to the deposition of fat. Protein, because of the fact that it stimulates metabolism and thus increases the energy output, is less likely to lead to the laying down of fat than are the other foods.

In order to bring about a reduction in the weight of an obese patient, the first essential is that the diet be one which supplies fewer calories than the daily energy requirements, the remainder of the requirements will then be met largely by the utilization of stored fat of the body. In planning a diet for an obese patient, one should calculate the approximate food requirement in terms of calories and then give a diet containing from 500 to 1000 less calories per day than the calculated needs. The diet should contain a fair proportion of protein, as this increases the energy output by its specific dynamic action. Bulky foods, such as green vegetables, bran bread, and similar articles are useful because they bring about a sense of satisfaction by filling the stomach, yet fail to supply very many calories. During reduction in weight, some patients suffer from a feeling of weakness between meals, which may be attributed to hypoglycemia. These symptoms may be relieved by the taking of a cup of hot tea with a moderate amount of sugar.

Diet and Pellagra

There is no condition in which diet produces a more marked effect than in patients suffering from pellagra. The feeding of a diet very high in protein and B vitamine, and low in carbohydrate, but containing moderate amounts of fat results in remarkable improvement in the majority of cases of pellagra, all of the symptoms, including the skin manifestations, showing prompt recession.

Diet During Infancy

The high mortality rate among infants is due chiefly to improper methods of artificial feeding. Infants nursed at the breast succumb to the nutritional and diarrheal diseases very seldom as compared with those fed on the bottle. By far the greater part of this mortality is preventable. Much of the failure of artificial feeding in the past has been due to lack of information concerning the nutritional needs of the infant and the processes of digestion. In order to feed an infant satisfactorily a few fundamental requirements must be fulfilled and these can be stated briefly.

In the first place, any food, no matter how digestible, will be unsuitable unless it supplies a sufficient number of calories. Failure to give sufficient calories has been the cause of more difficulties in infant feeding than any other one factor. A normal infant will rarely thrive unless he receives approximately fifty calories per pound of body weight per day. An undernourished infant will not thrive unless he receives almost as many calories as a normal infant of the same age. For example, a normal infant of six months, weighing fifteen pounds, will need approximately fifteen times fifty calories a day, or seven hundred and fifty calories, as a total. An undernourished infant of six months, weighing only eight pounds, will also require very close to seven hundred and fifty calories, which will be almost one hundred calories per pound. The calculation of calories in the diet is extremely simple. Milk contains twenty calories per ounce and sugar one hundred and twenty calories per ounce.

The second requirement for successful infant feeding is that the diet must contain certain essential elements in sufficient amounts. These are protein, carbohydrate, mineral salts and vitamines. The requirements for protein, mineral salts and some of the vitamines are met if the infant receives one and one-half ounces of cow's milk per pound of *expected* body weight per day. With lesser amounts of milk than this, nutritional disturbances are likely to result, although an infant may, for a time, thrive on as little as one ounce of milk per pound of body weight. The proportion between milk and sugar is of importance. One part of sugar to eleven of milk is the most suitable proportion. The amount of milk just recommended fails to supply all of the vitamines necessary, so that two additional vitamine-containing foods should be added to the dietary of all infants. These are cod liver oil and orange juice. Cod liver oil administration should be begun during the first month in doses of one-half teaspoonful three times a day. This may be given with a dropper or added to the feeding. By the age of six months the infant should be taking one teaspoonful of cod liver oil three times a day. One or two tablespoonfuls of orange juice should be given daily after the first month.

The third requirement is that the food must be uncontaminated by harmful bacteria. The most satisfactory method of accomplishing this is to boil all milk given to the infant. Boiling milk for two minutes will suffice.

The boiling also renders the food more digestible and does not impair its nutritional value. Pasteurization is somewhat less effective. Raw milk should, under no circumstances, be fed to babies.

The fourth fundamental requirement of the feeding is that it must be digestible for, if such is not the case, the baby will fail to make use of what is offered him, and undigested food remaining in the intestinal tract is likely to be acted upon by bacteria with resulting intestinal disturbances. Cow's milk is not as digestible as breast milk. This is due largely to the fact that it contains substances which neutralize the digestive juices. Some infants are able to take straight cow's milk up to the limits of the capacity of their stomachs and digest it well, but the majority cannot. It is therefore necessary, in most instances, to give the infants a lesser volume of cow's milk than they would be taking if they were receiving breast milk. This is most simply accomplished by diluting the milk during the early months of infancy and later leaving out the water as the infant's digestive capacity increases with age. If cow's milk is artificially soured by the addition of acid or by the growth of acid-producing organisms, it becomes approximately as digestible as breast milk and can be given in the same amounts—or, in other words, need not be diluted.

The practical application of the principles just laid down is simple. Cow's milk and sugar furnish the basis of the diet. No patent baby foods are necessary or desirable. The cow's milk used should be preferably from a mixed herd of ordinary cows. Jersey or Guernsey milk is not suitable. The sugar used is ordinary granulated sugar or Karo corn syrup, each of which can be bought in a grocery store. Of the two sugars, corn syrup is somewhat preferable.

A suitable formula for infants during the first year of life is prepared by adding three ounces by volume of corn syrup to one quart of cow's milk. This provides the proper proportions between sugar and milk. Such a mixture has a fuel value of thirty calories per ounce. For infants during the first month of life, this mixture should be diluted with an equal volume of water in order that the infants will not receive more cow's milk than they are able to digest. If all goes well, the proportion of water may be decreased gradually until, at the end of the third month, the infant will be receiving two parts of milk mixture to one part of water. By the age of five or six months the infant's capacity for digestion will usually have increased to such an extent that the milk and sugar mixture may be given undiluted.

The mixture should be boiled in all instances. Ordinarily the bottle should not be offered more often than every four hours and the infant should be allowed to take about as much as he desires. Five feedings a day are usually sufficient and after the fourth month many infants fed in the method described will not need more than four bottles a day.

If acid milk is used instead of sweet milk, it is not necessary to dilute the formulas at all, even for young infants. Lactic acid milk may be prepared by the addition of one and one-half drams of lactic acid U.S.P. to the quart of milk, or five drops to each ounce of milk.

Lactic acid milk with corn syrup added in the proportion of three ounces to the quart is given undiluted to infants throughout the first year and is offered at four hour intervals. This food is concentrated and the final mixture contains thirty calories to the ounce. From this figure the number of calories taken by the baby may be readily calculated. It will be seen that the infant needs to take a relatively small number of ounces in the day in order to meet his food requirements. Infants fed on lactic acid mixtures are often satisfied with four feedings a day after the first month.

The formula may be prepared from *unsweetened* evaporated milk. This is to be distinguished from *sweetened condensed* milk, which latter should, under no circumstances, be used in infant feeding. Unsweetened evaporated milk is simply cow's milk evaporated to one-half of its volume and sterilized. In using the evaporated milk one part of milk is mixed with one part of water and this gives whole milk which may be used in the same way as in the formulas already mentioned. Lactic acid milk also may be obtained in dried form.

Cod liver oil and orange juice are given daily throughout the first year. At the age of six months, the infant should be given well cooked cereal from a spoon and should also receive well cooked and finely chopped spinach and other green vegetables. After the infant has begun to take a considerable amount of cereal, one-half of the sugar added to the milk may be omitted. At the age of one year, all the sugar may be omitted from the milk formula.

The simple mixtures recommended are all that are necessary for the feeding of normal and most sick infants and are superior to any of the patented baby foods on the market.

LECTURE VI

THE ENDOCRINES

A full consideration of the endocrine glands, and the substances elaborated by them, would require much more time than that allotted to a single lecture. Volumes have been written on the subject, but there is perhaps no field of medicine in which fallacies have so exceeded facts as in that of endocrinology.

Proof that internal secretions or "hormones" are produced by various glands, has been obtained experimentally by observing the symptoms produced following the extirpation of the glands, and in certain instances the effects of the feeding or transplantation of glands, or the injection of active extracts. Through such experiments evidence has been obtained that the thyroid, parathyroid, pancreas, adrenals, pituitary, ovaries and testicles produce active internal secretions. In the case of other glands, such as the thymus, pineal, carotid, tonsils, kidneys, liver and spleen, the production of internal secretions has been postulated but positive proof of the existence of such is lacking. In some instances, as in the case of the thyroid and adrenals, active constituents have been isolated and chemically identified. In other instances an active substance in impure form has been isolated which has not been chemically identified, for example, the secretion of the pancreas (insulin) and of the parathyroid glands (parathormone). In some instances the active chemical principle isolated is not the sole product of the gland. The thyroid gland secretes something besides thyroxin and the adrenals something besides epinephrin.

With the exception of the thyroid, and possibly the anterior pituitary principle, the active principles of the endocrine glands, whatever they may be, are practically completely destroyed during the processes of digestion, so that when these various glands, or their extracts, are taken by mouth, no physiologic effect is observed. In some cases the endocrine hormones seem to be closely associated with proteins which explains their destruction by tryptic digestion. In others, as epinephrin, there is an alteration in the character of the active chemical substance during digestion. It is fortunate that such destruction takes place in the intestinal tract, as otherwise it would not be safe for one to eat any of the organs having internal secretions.

The wholesale use of the various polyglandular tablets now on the market is entirely unjustified by any facts yet discovered. In general, any such preparations administered by mouth are ineffective, with the single exception of thyroid and possibly pituitary. Traces of active substances from other glands may possibly be absorbed from the intestinal tract, in the same way that undigested proteins are occasionally absorbed, and certain molecules comprising the products of the breakdown of active endocrine substances may be absorbed and utilized by the endocrine glands of the body, if present and functioning, but when these glands are present and functioning there seems to be no need for such an extra supply of materials. In human beings there are a few definite, clear-cut diseases which are due to lack of secretion of the endocrine glands, such as cretinism, diabetes, parathyroid tetany, eunuchoidism, dystrophia adiposogenitalis and Addison's disease. A great variety of other conditions have been described as due to endocrine dysfunction ranging all the way from "that tired feeling" to nephritis, Mongolian idiocy, and the criminal personality.

The action of any given hormone may be altered, or even reversed, depending upon the condition of the body as a whole, and upon the simultaneous excess or deficiency of other hormones; for example, injection of extracts of the posterior lobe of the pituitary may cause either diuresis or suppression of the urine. Epinephrin normally leads to a rise in blood sugar and insulin to a fall in blood sugar, but the simultaneous injection of pituitary principles modifies or entirely prevents either of these effects. Insulin under certain conditions, increases the rate of the heart beat, but when the adrenal glands are removed from an animal, no such acceleration of the heart rate occurs. Changes in the activity of one endocrine gland may, as is well known, cause marked changes in other glands, for example, following castration the pituitary enlarges, and following removal of the pituitary changes in the ovary occur. For these reasons it is often difficult to determine, in a clear-cut way, the action of the individual endocrine hormones.

The facts concerning epinephrin, and the active principles of the thyroid gland, are so well known that it would be useless to recite them at this place. It may, however, be profitable to consider some of the recent work on the active principles of the pituitary, pancreas parathyroid and ovarian follicles.

The Pituitary Hormones

The pituitary or hypophysis is not a single gland but consists of two parts, which are entirely different in structure and function. In the anterior portion of the pituitary, there is elaborated a substance which has an influence upon growth. Young animals, from which the anterior lobe has been removed, do not grow at a normal rate, and retain their infantile characters. In human beings, the clinical condition of dystrophia adiposogenitalis (Fröhlich's syndrome) is believed to be associated with a deficiency of the anterior lobe of the pituitary. There is a considerable amount of evidence to the effect that an excess of the anterior pituitary hormone is responsible for the condition of acromegaly.

Brailsford Robertson has isolated from the anterior lobe of the pituitary a lipoid substance to which he has given the name of "tethelin." This substance seems to have a specific action on growth. It resembles in some respects the A vitamine. It is possible that there may be other active substances in the anterior lobe. When anterior pituitary gland is administered by mouth some absorption of the active principle occurs, at any rate in the case of amphibians.

The posterior lobe and intermediary portion of the pituitary body produces a substance or substances which have marked physiologic actions. It is a mooted question whether all of these actions are the result of a single substance or of more than one substance. When the posterior lobe is extracted with alcohol, a substance is removed which resembles histamine. A similar substance can, however, be removed from other glands and tissues, and this may be considered an incidental constituent. This substance, when injected, leads to capillary dilatation and to a fall in blood pressure.

The more specific constituent of the posterior lobe exerts a wide variety of effects. When injected, it brings about capillary constriction with a resultant rise in blood pressure. The posterior lobe principle also causes contraction of the musculature of the uterus. This latter effect is observed in vitro, even in such a dilution as one to one hundred thousand million parts. It is this substance in posterior pituitary extracts which is of use in obstetrics. A further action is to increase the flow of milk of the lactating mother. This latter effect, however, is only transitory and consists chiefly in a forcing out of milk already in the mammary glands. If the total milk obtained is measured over a period of days, it is no greater than when pituitary is not administered. The posterior pituitary hormone, when injected into normal individuals or into those suffering from diabetes insipidus exerts an antidiuretic action; but Abel has shown that when given to animals fed entirely on green vegetables for several days the effect is that of diuresis. When given to individuals in whom diuresis has been produced, by sodium chloride or urea or following the administration of anesthetics, the diuresis is not diminished, but increased. The posterior pituitary hormone prevents the *hyper*glycemia following the injection of epinephrin and the *hypo*glycemia following the injection of insulin.

The active principle or principles of the posterior pituitary seem to be of the nature of polypeptides, that is, protein derivatives intermediate between amino acids and proteoses. These substances are not destroyed by pepsin but are destroyed by trypsin. The posterior lobe of the pituitary, when fed by mouth, is therefore, ineffective.

The Pancreatic Hormone (Insulin)

Evidence that the pancreas produces a hormone was first obtained by Minkowski and von Mering in 1889. They found that when the pancreas was entirely removed from dogs, hyperglycemia and glycosuria resulted, and also that when small portions of the pancreas were grafted under the skin, the glycosuria ceased but reappeared when these grafts were removed. It was subsequently found that when the pancreatic duct was blocked so that degeneration or sclerosis of the pancreas occurred, glycosuria did not result. Autopsies on animals so treated revealed the fact that the pancreas was extensively atrophied and sclerosed with the exception of certain "islands" of cells which had been described previously by Langerhans. Subsequent histologic investigations by Bensley of Chicago led to the discovery that there are two types of cells in the pancreatic islands, the alpha and beta cells, which are responsible for the production of a substance necessary for bringing about the normal metabolism of sugar in the body. Over a long period of years many fruitless attempts were made to isolate the active substance. A reasonably pure active substance was finally isolated from the pancreas by Banting and his collaborators and named by them "insulin."

Insulin seems to be related to the polypeptides. It is destroyed by tryptic action and by alkalies; it is, however, stable in acid solution and may be heated to boiling temperature for a number of hours without being destroyed. It is easily adsorbed by proteins. It is precipitated in fairly pure form at a pH of 5, but is redissolved when the solution is made as alkaline as pH 6.5 or as acid as pH 4. Precipitation of the active substance at a pH of 5 (its isoelectric point), the method described by Shaffer, is now in general use. Insulin may also be precipitated by picric acid.

Although all the evidence points to the fact that insulin is produced only in the pancreatic islands, it can be extracted from other organs of the body. Much of the insulin of the body appears to exist in combined and unavailable form. It is stated that enough insulin may be extracted from the blood of a rabbit to cause the complete disappearance of sugar from the blood of three or four other rabbits, though injection of the blood alone, untreated by the extraction method, produces no such effect. In the case of a patient dying from diabetic coma, enough insulin was extracted from the pancreas to have kept a total diabetic alive for as long as one month.

The physiologic action of insulin is to increase the rate of oxidization of glucose and to promote its synthesis into glycogen. The disappearance of the glucose after administration of insulin can, however, not be entirely accounted for either by combustion or conversion into glycogen; but there is good reason for supposing that a certain portion of the sugar is converted into fat. The administration of insulin to a normal individual as well as to a diabetic, results in a distinct lowering of the sugar of the blood; when this falls to as low as 400 or 500 mg. per 100 c.c., characteristic symptoms known as the insulin or "hypoglycemic" reaction occur. A moderate lowering of the blood sugar is associated with hunger contractions of the stomach and an increase in appetite.

When insulin is administered to diabetics, these patients as a class tend to become excessively fat. Whether this is due to an increased conversion of sugar into fat or to a decrease in the utilization of fat is not known, but the clinical fact remains. A similar effect is observed in nondiabetics. This has been taken advantage of in the treatment of malnutrition. Attempts have been made to improve the nutrition by the feeding of considerable amounts of carbohydrate together with the injection of insulin. Excellent results have been obtained in the case of infants and young children, and the method is one which should be equally applicable to adults.

When either epinephrin or extract of the posterior lobe of the pituitary is injected, the effect of insulin is antagonized. Insulin produces a much more marked effect in the presence of thyroid deficiency than under normal conditions. It also produces a more marked effect in the presence of anhydremia.

Since insulin is destroyed by tryptic digestion, pancreatic products administered by mouth are entirely ineffective, although it is claimed that a small amount of insulin may be absorbed through the mucous membrane of the mouth.

Within the last few months Frank, working in Minkowski's clinic, has synthesized a substance "synthalin" closely related to guanidin which has a physiologic effect approximating that of insulin. It is stated that this substance is absorbed by the intestinal tract and may, therefore, be administered by mouth. Further developments will be watched with interest.

The Parathyroid Hormone

It has been known, for many years, that accidental removal of the parathyroid glands is followed by the appearance of the clinical condition of tetany characterized by muscular spasms or convulsions. The calcium content of the blood falls coincident with the onset of the spasms. (See Lecture III.) This observation seemed to indicate that a substance, produced by the parathyroid glands, was necessary for normal calcium metabolism. The administration of parathyroid glands by mouth was, however, found to be entirely ineffective in preventing the symptoms of tetany or in altering the calcium content of the blood.

Very recently Collip, using a technic similar to that used for the preparation of insulin, has prepared an active extract of the parathyroid glands (parathormone) which, when injected, leads to a prompt increase in the blood calcium. In the case of tetany the increase in blood calcium occurs simultaneously with relief of the symptoms. The effect is somewhat more marked when calcium salts are simultaneously administered by mouth. With a normal or small intake of calcium salts, the increase in blood calcium is at the expense of the calcium of the bones and tissues and negative calcium balance occurs, that is to say, calcium is actually lost from the body, even though it is increased in concentration in the blood. The parathyroid hormone has been shown to be of distinct value in the treatment of those forms of tetany associated with a low calcium content of the blood, namely parathyroid tetany and infantile tetany; it is less effective in the tetany due to alkalosis. The parathyroid hormone, when given in excessive amounts, leads to an increase of blood calcium above the normal, and this may lead to intravascular coagulation and death. This hormone also leads to an increased excretion of phosphates by way of the urine and is, therefore, theoretically indicated in the case of nephritis with phosphate retention and a low blood calcium content.

It has been shown by Aub and his coworkers that the administration of the parathyroid hormone to patients suffering from lead poisoning leads to a passage of lead from the tissues into the blood and to its final excretion from the body. The hormone must, however, be used very cautiously in lead poisoning, as an increase in the concentration of lead in the blood may bring about active symptoms of plumbism.

Ovarian Hormones

In the ovarian follicular fluid of animals there occurs a substance which, when injected, causes a recurrence of the oestrus cycle in ovarectomized animals. This substance has been purified by Allen and Doisy and has been subjected to clinical use. It is stated that, in the case of ovarectomized women or in those suffering from ovarian amenorrhea, the injection of this extract prevents the atrophy of the uterus and leads to subjective improvement. It has not, however, been possible to bring about normal menstruation through its use.

That there are other hormones produced in the ovaries is certain. They have, however, not as yet been isolated in a state of purity, or made available for parenteral administration.

The Outlook in the Field of Endocrinology

There are doubtless hormones as yet undiscovered which are elaborated in other glands of the body and which will sometime be made available for clinical use. Certain glands have a structure which would seem to indicate that they are organs of internal secretion, yet no evidence is forthcoming as to the nature or action of the secretions. The thymus gland, for example, may be completely extirpated without any effect on the animal, so far as has been observed. Whether such organs as the liver, spleen and kidneys produce internal secretions is as yet undetermined.

The accomplishments of endocrine therapy in the case of thyroid, pancreas, and parathyroid disturbances are little short of miraculous, but we should not be misled by these successes into the supposition that very many of the ills of mankind may be benefited by the administration of endocrine products or that any besides cretinism may be influenced by the feeding of pills containing organ extracts.

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