Fundamentals of Biochemistry in Clinical Medicine

By

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PREFACE

THE physicians and surgeons of today cannot be proficient in medical practice without applying knowledge of the several basic sciences. Unfortunately, altogether too little time is available for the busy practitioner to keep abreast of more than a few medical developments which, because of their very great usefulness, come to his immediate attention. The object of the present work is to present in the form of a short review, the fundamental aspects of biochemistry and its application to clinical medicine, intentionally omitting many details of both subjects.

The book is designed to permit the reader, whose main interest is in some other field, to scan it in a reasonably short time, or to obtain a brief review of whatever subject in this field demands his attention at the moment.

The material is introduced by two chapters devoted to atomic and molecular structure. It has been the experience of the writer that much modern literature becomes more understandable to the medical practitioner if he will devote a few moments to clarify certain elementary definitions. These two chapters do not pretend to go much beyond that. The next seven chapters contain material of more fundamental biochemical nature, while the last nine chapters are dedicated mostly to practical aspects of biochemistry in clinical medicine. It is hoped that this arrangement will facilitate the approach to the various subjects and be time-saving for reviewing. The indicated division of material has not always been followed strictly as convenience has dictated the occasional inclusion of certain clinical aspects in the early part of the book and some theoretical subjects have been discussed in relation to specific disease entities.

Obviously, a book of this nature should not be considered a reference work. The bibliography, following each chapter, to a large extent omits the customary documentary references, the material selected being presented as suitable supplementary reading. Therefore, the bibliography may not necessarily represent, in the author's opinion, the most important contributions to the subject. Many monumental publications have not been listed with the understanding that the reader who seeks more detailed knowledge will resort to larger works.

Buffalo, New York N. C. K.

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N. C. K.

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Chapter 1

ATOMIC STRUCTURE

UNDERSTANDING of the structure of the atom is founded upon an adequate knowledge of the 'particles' which comprise the atom. The definitions of the properties of these particles are derived from a wide variety of experimental work. The particles may not necessarily conform to the way they are pictured or described, but they can be discussed as long as they are defined in terms of properties established by experiment.

Early studies of the structure of the atom were based on observations of electrical discharge in vacuum. Later, the study of radioactivity and transmutation contributed greatly to the increased understanding of atomic structure. In more recent years nuclear fission of certain atoms under special conditions has added considerably to the knowledge of the nucleus. This process has also made available larger amounts of radioactive and isotopic material for experimental work.

An understanding of the nature of electricity underlies all approaches to the study of atomic structure. Electricity is commonly thought of as a form of energy, because it is associated with the ability to perform work. J. J. Thompson showed that electricity consists of distinct particles called electrons. The electron, therefore, is the fundamental unit of electricity and the determination of its electrical charge is of great importance. Millikan established the physical characteristics of the electron with amazing accuracy in his oil-drop experiments.

In studies of the nature of matter, two general laws have been supported by all experimental approaches. These laws state that matter cannot be created or destroyed, and that the same holds true for energy. Of course either one can be altered in form; for instance one chemical substance can be transformed into another, and electricity can be transformed into heat. These two laws have guided practically all physical and chemical research, and they are but two phases of a single principle because matter can be changed into energy and vice versa according to definite laws. The theory of relativity leads to the conclusion that inertial mass of a moving body increases as speed increases. Therefore, a relation between kinetic energy and mass must exist. It is only because of the tremendous disproportion between these two values that the laws of conservation of energy and mass are true for most practical purposes.

In 1905, Einstein formulated the mathematical relationship between energy and mass as follows: $E = mc^2$. In this equation E represents energy of a particle, m its mass, and c the velocity of light. The application of this equation leads to startling consequences. For instance, the conversion of 1 kilogram of mass to energy should produce approximately 25 billion kilowatt hours of energy which corresponds to all the electrical power used in the United States for two months. If energy is measured from the combustion of 1 kilogram of coal, the corresponding figure would be 8.5 kilowatt hours. The only reason why there are no detectable changes in mass in the ordinary chemical reactions is that such changes of mass, equivalent to the ordinary energy changes, are entirely too small to be detected.

ELECTRONS

It already has been stated that electrons represent the unit of negative electrical charge. Electrons have the ability to ionize molecules with which they come in contact. If electrons are discharged in air, they will ionize molecules and make the air a conductor of electricity. This conductivity can be measured with an electroscope, and the effect on the electroscope may be used as a quantitative measure of the flow of electrons.

Cathode rays represent electrons in motion from the negative cathode to the positive anode of a vacuum tube. The transfer of electrons in a vacuum tube depends on the difference in potential between the cathode and anode and the rate at which electrons are emitted from the surface of the cathode. The hotter the cathode is the more electrons will be formed. Therefore, hot filaments are used in radio tubes, x-ray tubes, etc., to produce adequate streams of electrons.

Electrons are deflected by electrical and magnetic fields according to well-known physical laws. Their motion can be accelerated or decelerated between electrical potentials. Electrons at very high speed are used to bombard elements to transform them into other elements. The high speed of the electrons is obtained by subjecting them to very high voltage fields, or by the use of devices in which the electrical field is changing continually at a much lower voltage. Methods used to accelerate negative particles may also be used for acceleration of positive particles if the electrical or magnetic fields are designed accordingly.

The *Van de Graaff electrostatic generator* has been of outstanding importance in the development of high voltage fields. This machine is based on the principle that a moving belt of non-conducting material can transport electrical charges continually from a generating source to a large closed-surface conductor called a terminal. The terminal is usually spherical, and elementary principles of electrostatics teach that the charges are distributed over the surface, leaving the space inside free of electrical forces. The surface voltage eventually reached depends upon the charging rate and the rate at which the charge is disseminated. Special methods have been used to decrease dissemination of the electrostatic charges; such methods include the use of air low in moisture, air under pressure, and other gases such as neon. Particles to be accelerated are produced by a suitable source inside the terminal and pass through a vacuum tube running from the terminal to the ground. Van de Graaff generators have been built in which particles are accelerated in vacuum between one terminal and another charged at the opposite polarity in order to double the voltage of the accelerating field. The maximum charge obtainable on the terminal is reached when the diffuse dissemination of electrostatic charges is equal to the charges supplied by the belt. It is obvious that surroundings to which the terminal might discharge by sparking across as well as the insulating characteristics of the belt are factors limiting the ultimate voltage. Potentials of over 5 million volts have been created. The maximum energy to which a particle can be accelerated in an electrostatic generator cannot exceed the voltage to which the terminals can be charged. Other devices such as the cyclotron, overcome limitations of the voltage in the available fields by subjecting the accelerating particles repeatedly to the electrical forces. Thus the energy attained by a particle in an electrostatic generator is the result of acceleration in a single step while other devices avoid energy limitations by acceleration in multiple steps.

The *cyclotron* consists of two hollow D-shaped electrodes known as dees. These two electrodes are placed in apposition so that there is a gap between them. The dees are connected to a source of electrical potential of 10 to 100 kilovolts and the polarity across the gap changes at high frequency. The particles to be accelerated are created in the center of the cyclotron and are made to spiral in the hollow dees by a powerful magnetic field. Every time they cross the open gap between the dees the potential across the electrodes causes acceleration. When the spiralling particles have described a 180° arc in one of the dees the polarity changes so that further acceleration occurs while they cross the gap again. Because of the acceleration the particles spiral toward the periphery of the dees and eventually escape tangentially from the magnetic field.

The increase in mass which a particle undergoes during the accelerating process becomes appreciable at high energies. This increase gradually reduces the rotational frequency so that the particles cross the gap at a time when the potential between the dees is less than maximum and converging toward zero. At the zero point further increase in the energy of the particles cannot take place. Thus the relativistic increase in mass places a limit on the energy obtainable in a cyclotron. Two methods suggest themselves to obviate this limiting effect. One is a change in the magnetic field but this is impractical for structural reasons. The other is a gradual reduction in the frequency of the electrical field to synchronize it with the velocity of the particles. Such machines have been constructed and they are called *synchro-cyclotrons.*

The *betatron* uses electro-magnetic induction for the acceleration of electrons. Its construction parallels in principle that of an ordinary transformer in which the secondary coil has been replaced with a circular evacuated chamber called a 'doughnut.' The electrons are made to accelerate in the circular path by the application of a magnetic field. The accelerated electrons may be extracted from the equilibrium orbit in the doughnut by reducing the magnetic flux below the necessary magnitude to maintain a constant radius of the electron path. The electrons may also be extracted by the use of auxiliary coils.

The *synchrotron* combines the principles of the betatron and the cyclotron. The initial phase of operation consists of acceleration by the betatron principle of electrons injected at nearly the speed of light. Subsequently the electrons are accelerated to high energies by application of a constant frequency field similar to that employed in the cyclotron.

The electron is the smallest known mass. Its mass in grams would require 27 ciphers after the decimal point before the first significant figure. Electrons are constituents of all matter; chemical properties of matter depend exclusively on the arrangement of electrons in the atom as described later.

POSITRONS

C. D. Anderson, in 1932, discovered the existence of another particle in the atom equal in mass to the electron, but of opposite charge. This particle has been termed the positron. The positron has a very short life. When its energy has fallen to a relatively low value it is annihilated on encountering an electron with a consequent release of radiation of the gamma-ray type, with energy equal to the sum of the two particle masses.

PROTONS

If a cathode tube is constructed with a perforated cathode, rays extend behind it, and it can be demonstrated by use of an electrical field that these rays carry a positive charge. Electrons issuing from the cathode will collide with atoms of gas in the rarefied atmosphere of the tube, and an occasional collision will knock other electrons from the orbit of these atoms; thus the remaining part of the atom will carry a positive charge. These particles form the rays observed behind the cathode. If the atom is hydrogen, the resulting positively charged particle is called a proton.

Figure 1 shows diagrammatically the formation of a proton by collision of an electron with a hydrogen atom. The bombarding electron has enough energy to carry away the orbital electron of the hydrogen atom, leaving the positively charged nucleus (the proton). Because of its positive charge the proton will be attracted by the negative cathode and, if the electrical forces are adequate, it will continue its path through the perforations of the electrode. The positive ray can be deflected in electrical or magnetic fields. A measurable degree of deflection requires more electrical force than in the case of the electrons. This is due to the greater mass of the positive-ray particles.

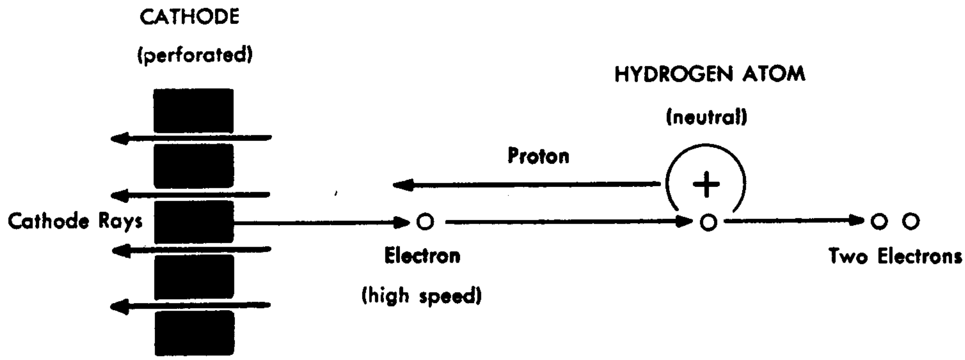

FIG. 1

The proton, the lightest of the gaseous ions, weighs approximately 1,840 times as much as the electron.

NEUTRONS

The existence of the neutron was predicted by Rutherford in 1920, later they were demonstrated by Joliot and Curie in France, and by Chadwick in England. If radiation from radon strikes a target of beryllium, a flow of radiation from the beryllium results. This radiation is capable of ejecting protons from the atoms of many elements. Energy calculations applied to such experiments show that the radiation from beryllium can be explained only by assuming that it contains particles of unit mass and without charge. In other words, these particles are of the same mass as a proton, but do not carry an electrical charge. They are called neutrons.

Neutrons, having no charge, are hard to detect because they cannot be deflected by electrical or magnetic fields. This characteristic gives neutrons the important property of being able to penetrate the electron shells of atoms and enter the atomic nuclei. Neutrons which have been slowed down by passage through screens consisting of material containing hydrogen (water, paraffin, etc.) are more useful for the penetration of atomic nuclei than high-speed neutrons. The atoms of nearly all the known elements interact with neutrons and five main types of behaviour have been observed. These are the emission of:

a) A proton
b) An alpha particle
c) Gamma radiation
d) Neutrons
e) A positron

Neutrons will eject protons from a screen containing hydrogen atoms, and it is for this reason that water, instead of lead, is used as a protective wall for