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CHEMISTRY IN RELATION TO BIOLOGY AND MEDICINE WITH ESPECIAL REFERENCE TO INSULIN AND OTHER HORMONES[1]

YOUR speaker to-day is one who is primarily a worker in the field of experimental medicine; a chemist, if at all, only in so far as an imperfect mastery of your science became necessary for the solution of physiological and pharmacological problems that could not be undertaken or even formulated if their chemical aspects were to be ignored. Under the circumstances I can but feel a sense of deep unworthiness in venturing to address an audience in which are gathered so many distinguished representatives of your noble science. I am highly appreciative of the signal honor conferred upon me by the board of award of the Chicago Section of the American Chemical Society in the bestowal of the Willard Gibbs Medal and I beg the members of the board to believe that I am duly grateful to them.

There exists in our day an essential unity of outlook and interest among the majority of professional chemists, biologists and medical men in respect to the physical and chemical aspects of life. This unity of interest and unanimity of opinion in respect to the applicability of the laws of physics and chemistry to the elucidation of vital processes have their origin far in the past and date from a time long before chemistry had attained to its present dignity as an independent science. It is not my purpose to attempt to record even briefly the history of chemistry or that of medicine, subjects that have been so well treated by many learned men of both professions, but I would ask your forbearance toward an imperfect sketch of the points of contact between your professional ancestors and mine. I leave out of consideration here any reference to such contacts in the ancient or later alchemical periods, or to Arabian science in Western Europe, further than to remark that alchemy, which at its best combined far-reaching metaphysical speculations with a crude experimental chemistry, had, as one of its several aims, not alone the transmutation of the baser metals into gold, thus abolishing that "great disease, poverty," but also

[1] The Willard Gibbs lecture delivered before the Seventh Midwest Intersectional Meeting on the occasion of the award of the Willard Gibbs Gold Medal by the Chicago Section of the American Chemical Society, May 27, 1927.

the cure of fleshly ills and the gift of "perfect health and length of days." Certainly the search throughout the long alchemical period for the "elixir of immortal health" supports the claim for this medical aspect of alchemy, even without proofs on the literary side.

To-day the modern alchemists among you have, in a most remarkable manner and in a most concrete way, actually realized the age-long dream of your predecessors. Paneth well describes the chemical and the medical actions of the modern philosophers' stone, radium, in the following words:

> Thus we see that in a certain sense radium possesses the first and principal property ascribed to the philosophers' stone: it has the power of transmuting elements, although not of producing gold. And, oddly enough, even in respect to the second property which was ascribed to the philosophers' stone radium seems to have gotten something from its fabulous predecessor: it is a very valuable aid in the treatment of some severe diseases, although not a perfect remedy for every illness. So that to a certain degree the radium rays really produce the two very different effects of the philosophers' stone, transmutation and healing.

Even in the later alchemical period the older professions of medicine and pharmacy furnished opportunity, though often grudgingly given, for the development of chemistry, and they may justly be said to have been the parents of modern chemistry. Throughout this period, as in ancient times, there existed a large number of industries, such as the metallurgical industries, enamel- and glass-making, painting, brewing and wine-making, to give only a few examples. But the practice of these ancient arts could not lead to the development of a chemical science as long as the true character of organic principles of the elements and their compounds remained unknown. Especially close was the connection between chemistry and medicine in the days of the iatro- or physician-chemists of the sixteenth and seventeenth centuries. In the first half of the sixteenth century, at a time when the crude chemistry of that day was still entangled with the traditions and even downright impostures of alchemy, there appeared an extraordinary man, Paracelsus (1493–1541), "the very incarnation of the spirit of revolt" (Osler), who must indeed be regarded as one of our ancestors in both branches of learning. Remember that in his day medicine was already a long established and powerful profession and this bold innovator in chemical physiology, pathology and pharmacology, who heaped scorn on Galen and Avicenna, very naturally aroused the hostility of many of the leading physicians of the day.

He is the most notable figure among the earlier physician-chemists and, in the words of the historian E. v. Meyer, to him belongs incontestably the credit of fusing chemistry and medicine in the first half of the sixteenth century, of forcing both into new paths and of freeing chemistry from the shackles of alchemy. Up to our time some of his writings have appeared in no less than five hundred editions. He declared it the true purpose of chemistry not to be the making of gold but the preparation of medicines. "Alchemy is neither to make gold nor silver: its use is to make the supreme sciences and to direct them against disease." This too narrow a conception of the science was soon to be broadened out by the iatro-chemists of the century and more, following his death. He stated clearly that the processes of the animal organism are chemical in their nature and that health is a function of, or dependent on, the composition of the juices and tissues of the body. Even in regard to the rôle played by air in respiration, I find Robert Boyle, more than a century later, citing him in support of his own views, as saying "that as the stomach concicts meat and makes part of it useful to the body, rejecting the other part, so the lungs consume part of the air and proscribe the rest." Medical historians have occupied themselves more with an analysis of the medical achievements of Paracelsus, the Luther of medicine (Osler), than with his chemical discoveries, and his significance is perhaps greater for medicine than for chemistry. He is certainly of great importance in the history of chemical therapeutics and pharmacology. Sudhoff says of his work in these fields:

> He was the first one to show how to separate the active principles from drugs and to use them in tinctures and extracts. He made important discoveries in chemistry: zinc, the various compounds of mercury, calomel, flowers of sulphur, among others, and he was a strong advocate of the use of preparations of iron and antimony. In practical pharmacy he has perhaps had a greater reputation for the introduction of the tincture of opium—''labdanum'' or laudunum—with which he effected marvelous cures and the use of which he had probably learned in the East (Osler).

Naturally, I can not pause to give more than a very incomplete sketch of this innovator whom I here mention because of his constant insistence that physiological processes are chemical processes and that drugs by their chemical properties can bring about favorable chemical alterations in a diseased body.

It has for many years been a custom with me to characterize the vital importance of certain defensive substances and the products of internal secretion present in our bodies in the aphorism: We are walking drug stores. On reading Sudhoff's reprint of the *Labyrinthus medicorum errantium* of Paracelsus (1538), a little meaty classic, I was delighted to find that four centuries ago our author had already elaborated this idea at length:

Also in human beings there is a natural apothecary in which are found all things as in the world (the macrocosm), good and bad, simples and composites, however they be named. . . . As the outer world, the macrocosm, contains visible pharmacies and visible physicians, so in the microcosm, that is to say, in the human being, there is present an invisible pharmacy and an invisible physician who produces, prescribes, dispenses and administers suitable remedies as occasion demands. . . . Let it be known to all men then that had not God created and placed in the bodies of men natural remedies and a natural physician, then, notwithstanding all the efforts of our physicians, not a single creature of earth would remain alive.

In this quite modern fashion Paracelsus here restates the enduring canon of Hippocrates—Νούσων φύσιες ιατροί—better known to us in its later paraphrased form as *vis medicatrix naturae.* Professor Max Neuburger, the learned professor of the history of medicine at Vienna, truly remarks that the problem of nature's healing power is probably the most weighty of all that have engaged the thoughts of physicians during thousands of years.

The iatro-chemists were the physiological chemists of their day. They possessed the highest scientific and humanistic culture of the time and historians of science agree in the opinion that chemistry profited greatly by passing into their hands. The study of their attempts to elucidate the phenomena of life and the chemical alterations associated with disease is a fascinating one. The physiologists, biochemists and pharmacologists of our day have at their disposal a great wealth of discovery in the more exact sciences—the gifts of the intervening centuries, but even with all this assistance modern iatro-chemists still find themselves trying, though confidently, to hack their way out of the jungle so boldly and gaily entered by their predecessors nearly three hundred years ago.

Naturally you will call to mind also, as every one must, the iatro-physicists of this period. It is thought that the physiological speculations of Descartes, as given in his treatise *De Homine,* had a great influence in turning men's minds to the possibility of basing physiology on physics and chemistry, but there is little doubt that the teachings and discoveries of Harvey had the greater influence on the development of iatro-physics. This phase of science, however, lies outside our present discussion.

I must content myself with recalling to your minds a few of the names of the iatro-chemists of this period —van Helmont and Sylvius, of whom Michael Foster, with a first-hand knowledge of their writings and those of their pupils, has given such an enlightened and sympathetic account in his Lane Lectures on the History of Physiology in the sixteenth and seventeenth centuries—Tachenius, Willis, Mayow, Lémery, Hooke, Peyer, Brunner and many others of this time might be named who forwarded both chemistry and medicine in the latter half of the sixteenth and well on into the seventeenth century.

One great man, Robert Boyle, nobleman of wealth, stands out prominently in the seventeenth century, one whose name is revered alike by physicists, chemists and medical investigators. This greatest chemist of his day, though not trained as a medical man, nevertheless, says one of his biographers, Thomas Birch, "went very accurately through all the parts of Physic." A study of his writings furnishes ample evidence of his acquaintance with medicine and the medical theories of his day. This great man even occupied himself with therapeutical questions and published "collections of choice and safe remedies, for the most part simple and easily prepared, very useful in families and fitted for the service of country people." The historian Neuburger in his scholarly treatise entitled "Die Lehre von der Heilkraft der Natur im Wandel der Zeiten" devotes several pages to Boyle's views in regard to the respective rôles of "nature" and the physician "in restoring the distempered body to its pristine state of health," and states that Boyle's opinions on these matters were not without value and precipitated many controversies.

Boyle was particularly fascinated by that fundamental problem—the nature of the respiratory process —of which he says that "it is a subject of that difficulty to be explained and yet of that importance to human life that I shall not regret the trouble my experiments have caused me if they are found in any degree serviceable to the purpose for which they were designed." I have been surprised to learn, in my study of his writings, with what ardor Boyle pursued the effects of diminished air pressure, with his improved Guericke "pneumatic machine," on a great variety of animals. Bees, flies, butterflies, caterpillars, humming birds, sparrows, larks, mice, fishes, eels, unborn puppies, all served as objects of experiment in the study of this great problem which was to occupy the attention of his successors down to our day. At a time when, in spite of some earlier approaches to the truth, it was still generally held that the sole purpose of breathing is to cool the blood, Boyle's experiments forced upon him the conviction expressed as follows:

Without denying that the inspired and expired air may be sometimes very useful by condensing and cooling the blood that passes through the lungs, I hold that the depuration of the blood in that passage is not only one of the ordinary, but one of the principal uses of that passage. But I am also apt to suspect that the air doth something else in respiration which hath not yet been sufficiently explained.

The last sentence suggests that Boyle may have had a prevision, years before the discovery of oxygen, that this "something else" is the respiration of the tissues themselves.

After citing the opinion of Paracelsus, an opinion not based on experimental evidence, that "the lungs consume part of the inspired air and proscribe the rest," Boyle, on the basis of his own extensive experimentation, makes the prophetic statement:

It seems we may suppose that there is in the air a little vital quintessence, if I may so call it, which serves to the refreshment and restauration of our vital spirits, for which use the grosser and incomparably greater part of the air being unserviceable, it need not seem strange that an animal stands in need of almost incessantly drawing in air.

This "vital quintessence" is of course the later oxygen of Priestley and Scheele.

All of his experiments lead him to support

the theory of Moebius that the genuine use of respiration is the ventilation not of heart but of the blood in its passage through the lungs, in which it is disburthened of those excrementitious steams proceeding for the most part from the superfluous serosities of the blood.

Truly, Boyle could touch no subject without leaving his mark on it. For example, the respiration of fishes, "being animals without lungs," also excited his curiosity, and he "thinks it not altogether absurd to say that their gills seem somewhat analogous (as to their use) to lungs." His experiments with the air pump had taught him that there is "wont to lurk in water many little parcels of interspersed air, whereof it is not impossible that fishes may make some use, either by separating it when they strain the water through their gills or in some other way."

Time and occasion permit only of a glance at a few other great peaks in the panorama that we are so hastily surveying. Let us pass at once from Boyle to Lavoisier, another immortal, one of the greatest among the founders of your science, often, indeed, called the creator of modern chemistry, but also one who made fundamental contributions to the theory of respiration. He mistakenly held that combustion occurs only in the lungs. Thus, in the well-known joint memoir with the great mathematician Laplace, published in 1780, the conclusion is arrived at:

Respiration is therefore a combustion, slow, it is true, but otherwise perfectly similar to the combustion of charcoal. It takes place in the interior of the lungs without giving rise to sensible light because the matter of the fire (the caloric), as soon as it is set free, is forthwith absorbed by the humidity of these organs. The heat developed by this combustion is communicated to the blood which is traversing the lungs, and from the lungs is distributed over the whole animal system (Foster's translation).

In spite, however, that the place where oxidation occurs is erroneously inferred to be in the lungs only rather than in the hidden recesses of the tissues of the body, Lavoisier is nevertheless the first chemist or physiologist to *prove* that the respiration exchange is the result of a combustion and he was the first to make quantitative measurements during respiration of the intake of the "respirable part" of the atmosphere (the oxygen of Scheele and Priestley, later so named by Lavoisier) and of the output of the "aeriform calcic acid" (the carbon dioxide or "fixed air" of Black). It is quite comprehensible that the creator of gravimetric analysis and the discoverer of the principle of the conservation of mass in chemical operations should have made this quantitative experiment in animal physiology.

There is not time while we are on this subject of the respiration to consider the work of Joseph Black, Robert Hooke, Richard Lower and others of that time. The physician-chemist John Mayow (1643–79), however, can not be passed over without a word. Like Boyle, Mayow saw clearly that respiration is supported, not by the air as a whole "but by the more active and subtle part of it, the spiritus nitroaerius," or spiritus igneo-aerius, and both by experiment and inference demonstrated the analogy between respiration and combustion. The increase of weight attending the calcination of metals he declares also as due to the absorption of the *spiritus* of the air. Mayow had sound notions in regard to the relation between increased muscular work and increased respiration a full century before Lavoisier and Priestley, but unfortunately, in conformity with the conceptions of his day, he states that his nitroaerial spirit is separated from the blood in the ventricles of the brain and passes thence in supposed nerve tubules to the muscles where it combines with "sulphur," in consequence of which union muscular contraction results. The numerous and ingenious experiments of Priestley (1733–1804), one of the last phlogistonists, on respiration, combustion and calcination, as detailed in his memorable treatise, Experiments and Observations on Different Kinds of Air (1774), must also be passed over.

The latter part of the eighteenth and the first quarter of the nineteenth century were days of great discoveries of inestimable value to mankind, discoveries that inevitably and finally raised chemistry to the status of a great science, a younger sister of physics, though in our day the exponents of the older science claim, and perhaps justly so, that your science will ultimately be incorporated into the body of physics and that instead of atomists you will become mathematical energeticists, dealing primarily with protons and electrons and quanta and other concepts of their wizardry.

In this period the elemental or composite character of the various "airs" that had so puzzled the men of Boyle's day was determined: oxygen, nitrogen, hydrogen, methane and the composition of water and carbon dioxide came to be known. The chemical balance came into daily use. New elements were discovered and new inorganic compounds were made. An increasingly large number of organic compounds were being isolated as definite chemical individuals from a variety of vegetable products and from the tissues and secretions of man and animals. In this period falls the discovery and isolation of some very important products of animal metabolism, as urea (1773), uric acid (1776), allantoin (1800), cystine (1810), creatine (1835), glycerin (1779) and other chemical principles, the study of which was later to exert so great an influence on the development of synthetic chemistry. In this period also the pharmacist-chemists isolated quinine from the cinchona bark, that beneficient febrifuge (*Pulvis febrifugus orbis americani*) introduced into Europe from the new world nearly two centuries before; that gift of the gods, the juice of the poppy, was made to yield in crystalline form its analgesic morphine and its less valuable sister alkaloid, codeine (1803–1823). The seeds of the strychnos tree yielded up strychnine and brucine; hellebore and cevadilla seeds, veratrine; ipecacuanha, emetine; tobacco, nicotine; and a little later atropine was isolated from belladonna. A discovery of fundamental importance for chemistry, medicine and the arts was Faraday's isolation of benzene from gas distillation residues in 1825. Of his "bicarburet of hydrogen," by which name the new hydrocarbon was designated, Thorpe wrote a quarter of a century ago: "the work which has accumulated around this single substance during the 75 years which have elapsed since it has been known constitutes one of the most astonishing records of intellectual and industrial activity of which history has any record."

But the first quarter of the nineteenth century was a period when men did not solely occupy themselves with the isolation of elements and new compounds but, as in the quarter of a century that we have just lived through, minds of a high order also developed theoretical principles. Years after the enunciation of Boyle's Law and more or less coincidently with a host of brilliant discoveries of the very greatest importance in various departments of physics and in applied mathematics appeared Avogadro's law and Dalton's atomic theory. I need only recall to your minds the names of some of the greatest investigators in physics of this era, as Faraday, Ampère, "the Napoleon of electricity," Oersted, Ohm, and preceding them, Galvani, Volta and Coulomb among those who laid the foundations of electro-dynamics; of Thomas Young and Fresnel in the field of light, of the great Carnot and of Fourier in that of heat, of Gay-Lussac and Mariotte in the field of the gases, of Dulong and Petit, who showed that the atoms of elementary substances have the same capacity for heat. The important discovery that substances having an identical elementary composition may yet differ in their chemical or physical properties or both —isomerism—also falls in this period (1823), as also the enunciation by Grotthus (1818) of the fundamental principle underlying all chemical processes involving the absorption of light energy. It was indeed a remarkable period. Science and biology have been benefited as much or even more in consequence of these discoveries in physics of a century ago than by the chemical additions to knowledge that were coincidently made.

The formulation of such general statements capable of mathematical treatment is, as is known to all, the highest aim and the ultimate goal of the scientist's activity. We, who deal with the chemical and physical complexities of living organs, where the variables are not only very numerous but also where the dependence of each of these variables on one or more of the others must be taken into account, can but regard the full attainment of these highest aims of biological science as something that lies in the far future.

It should be stated, however, that many special topics in the broad field of plant and animal physiology are already capable of quantitative treatment, and many of my colleagues will feel that I have understated our case. They will call to mind investigations in relation to vision, muscle contraction, the nature of the nerve impulses, the neutrality mechanism, respiration and metabolism, to cite only a few examples from physiology to which quantitative methods are applicable.

But let us trace still further the relationship between chemistry, biology and medicine. The character of this relationship is now becoming reversed. No longer are the devotees of the biological and medical sciences foster-parents or foster-brothers of yours as in the old days. It is we who are now dependent in a large part of our work upon you and your fellow scientists, the physicists.

The reason for this change in relationship is not far to seek. It lies primarily, as stated above, in the fact that your science has devised many more diverse and accurate methods of measurement.

THE ERA OF CHEMICAL SYNTHESIS

Hardly had the first quarter of the nineteenth century passed when new developments arose, more especially in organic chemistry, that were destined to push forward in an immeasurable degree not only man's ultimate conquest of nature but also his ability to control or conquer disease and to prolong life, and hence, in so far as this may contribute to that end, to increase the sum of human happiness. The new era that has brought priceless gifts to mankind is the era of chemical synthesis. In conformity with my plan of emphasizing the importance, for the biological sciences and medicine, of only the great achievements of your science in this era I must limit myself to a brief survey of the discoveries of a few among the great men whose work happens to be of especial significance for these sciences. Let me begin with Liebig, whose contacts with medicine came through pharmacy, to which profession he was apprenticed in his early youth, and who later continued his chemical studies in Paris under Gay-Lussac. In his "Organic Chemistry in its Applications to Physiology and Pathology," published in 1842, after stating that "the great physicians who lived toward the end of the seventeenth century were the founders of chemistry and the only philosophers acquainted with it," and deploring the fact that "modern chemistry, with all its discoveries, has performed but slender services for physiology and pathology," he gives expression to his belief that:

> The most beautiful and elevated problem for the human intellect, the discovery of the laws of vitality, can not be resolved—nay, can not even be imagined—without an accurate knowledge of chemical forces: of those forces which do not act at sensible distances; which are manifested in the same way as those ultimate causes by which the vital phenomena are determined; and which are invariably found active whenever dissimilar substances come into contact. . . . Before the time of Lavoisier, Scheele and Priestley, chemistry was not more closely related to physics than she is now to physiology. At the present day chemistry is so fused, as it were, into physics that it would be a difficult matter to draw the line between them distinctly. The connection between chemistry and physiology is the same and in another century it will be found impossible to separate them.

After this confession of faith by Liebig we can no longer wonder that this great chemist concerned himself during many fruitful years with numberless questions touching the life processes of plants and animals; that he should be remembered to-day not only for his lasting achievements in organic and in technical chemistry, for having been a great teacher and inspirer of young men, but also as the founder of agricultural chemistry and as the most notable among the modern founders of biological chemistry since Lavoisier.

You all know that to the beautiful friendship which existed between him and the great Wöhler, unique in the history of science, and to the fortunate collaboration of the two in research, we owe some of the very greatest contributions ever made to the subjects now under consideration. Friedrich Wöhler studied medicine as a young man, taking his degree in medicine and surgery at Heidelberg in September, 1823. While a lad at the Gymnasium, he devoted himself passionately to chemical experimentation and to the collection and study of mineralogical specimens, much to the neglect of his school subjects. At Heidelberg he came into close contact with the chemist Gmelin and with the physiologist Tiedemann. Before he had taken his degree the young Wöhler had already completed four investigations dealing with selenium and with cyanic compounds and the year (1824) after his graduation he published a very comprehensive study, originally intended for a graduation thesis, of the excretion in the urine of a very large number of substances, including iodine, carbonates of the alkalis, saltpeter and other inorganic compounds; numerous organic acids, including benzoic acid, substances that color the urine, as indigo and rhubarb, and such as impart an odor to this secretion, as turpentine and asparagus. This paper, entitled "Experiments on the Passage of Substances into the Urine," was awarded a prize by the medical faculty of Heidelberg, and can be read to-day with profit by physiologists and pharmacologists, not alone for its numerous references to the work of other investigators of that time, but also because of the wonderful acumen with which the youthful investigator discusses the true function of the kidneys and the cause of the acidity of the urine. He sums up his deductions in regard to the kidney in the following passage:

> The kidneys are organs that serve the purpose of secreting a fluid composed in part of such substances as

pass in the unassimilated condition into the blood, being incapable of serving as replacers of bodily constituents, and in part of such as are produced during digestion and during the interchanges of material in the animal body (intermediary metabolism) or which are finally thrown off as being of no further use in these interchanges; they are therefore organs that serve to maintain the composition of the blood in a state necessary to the maintenance of life, without themselves producing any new substance whatever.

Pharmacologists of a later day were to show that Wöhler's "physiological deductions" needed to be modified in that the kidneys have a definite though limited power of synthesis and physiologists have also proved that, in addition to the kidneys, the respiratory function serves also to maintain the composition of the blood and tissue juices in the chemical equilibrium necessary to life.

Fortunately for both medicine and chemistry, Liebig and Wöhler in 1837 elected to attack the problem of the chemical constitution of that important metabolite, uric acid, first isolated by Scheele from urinary calculi in 1776, which up to that time had been of interest only to medical investigators and practitioners because of its connection with gout. As A. W. Hofmann so aptly remarks, this constituent of our body has shown itself to be a very protean among organic chemicals.

The results obtained by these two great investigators in their study of this acid and of the more than sixteen entirely new derivatives which they were able to prepare from it, as also of the many previously known substances that were encountered by them during their oxidation and reduction experiments in this field, have been described in detail by A. W. Hofmann and have also been outlined in a fascinating manner by T. E. Thorpe in his essays on historical chemistry. These memorable researches on uric acid excited the highest admiration of the chemists of the day, and I need not comment further on their significance for organic chemistry or for the future development of chemical physiology.

I need not comment either at length on the great consequences for organic chemistry and for medicine that flowed from the collaboration of the pair in their researches on the nature of the oil of bitter almonds, suggested by Wöhler to Liebig in 1832 as a suitable subject for a joint research. It must have been something akin to inspiration, says Thorpe, that led Wöhler to suggest the subject. I have often wondered whether the germ of the idea could not be traced to Wöhler's wide knowledge of medicinal substances. Oil of bitter almonds had long been in use as a domestic remedy, and Wöhler, who, in addition to his professorship at Göttingen, also held the post of supervisor of pharmacies for the Kingdom of Hanover, must have been well aware of the medicinal properties of the oil. The discovery of the compound radical benzoyl (and of benzoyl chloride) and the proof that numerous correlated bodies could be grouped around it were epoch-making in their far-reaching consequences and will always remain, historians of science are agreed, one of the greatest achievements in organic chemistry.

Wöhler's discovery in 1842, made also independently by Alexander Ure, of Edinburgh, in 1841, that ingested benzoic acid is paired in the animal organism with glycocoll, or amino-acetic acid, and excreted as hippuric acid, which, from a purely chemical point of view, may be regarded as only a minor addition to the "benzoyl" edifice, became nevertheless of the greatest significance for physiology and pharmacology as constituting the first demonstration that the animal organism has the power to combine chemically dissimilar substances into new compounds—a capacity for synthesis that up to that time was believed to be confined solely to plants. This discovery naturally led to wider views in respect to the nature of intermediary metabolic processes. Since 1842, biochemists and pharmacologists have discovered innumerable other instances of the very considerable synthetic power with which animal tissues are endowed and the conception no longer excites wonder by its novelty.

The significance of Wöhler's discovery in 1828 of the artificial formation of urea by the molecular transformation of ammonium cyanate is known to every freshman in our schools of chemistry and medicine. This discovery, the significance of which was fully realized by the young Wöhler, effected a revolution in the ideas of men and showed that the organic substances present in bodies of animals and in plants can not be the products of a mysterious vital force but are subject to the same laws as those that are encountered by the chemist in his laboratory while occupying himself with bodies of purely inorganic origin.

Of the chemists of the period under consideration who were intensely interested in the chemical phenomena presented by plants and animals, I can refer here only to the great French chemist, Jean Baptiste André Dumas, the contemporary of Wöhler and Liebig. At the age of eighteen, the young pharmacist detected the presence of the newly discovered iodine in burnt sponge, a substance employed at the time in treatment of goiter, and later worked in conjunction with the physiologist Prévost on the active principle of digitalis, on the transfusion of blood, on the seat of formation of urea in the body, on the chemical changes accompanying the embryonic development of the chick and many other chemico-physiological questions. Naturally, even a man of Dumas's ability could not, at that time, make any significant advance in our knowledge in his too brief excursions into these difficult fields. He and Prévost were, however, the first, as far as I am aware, to demonstrate by experiments on nephrectomized animals that urea is not formed in our kidneys but elsewhere in the system, as they were still able to detect it in the blood of the nephrectomized animals.

In his later years, long after he had won his place among the great chemists of his time, Dumas returned, says Thorpe, to many of the chemico-physiological problems with which, in association with Prévost, he had begun his career as an investigator. In this later period fall his studies with Boussaingault on the formation of fat in the animal body and his own studies on the origin of bees'-wax. He proved that bees, even when fed exclusively on sugar, still retained the power of producing wax, contrary to the opinion of his predecessors, who believed that the bee secretes the wax while extracting the honey from flowers and that there is no necessary connection between the two processes. The nature of alcoholic fermentation and the treatment of the silkworm disease induced by *Phylloxera vastatrix* were among the later interests in the life of this gifted and many-sided man.

Having unfortunately little leisure for the pursuit of historical studies, I am fully conscious of the fact that I have given you a very sketchy outline of the points of contact between chemistry and medicine from Paracelsus to the time of Liebig, Wöhler and Dumas. The problem of animal respiration we had left in the state in which it was formulated by Lavoisier. But even after Spallanzani and others had shown early in the nineteenth century that consumption of oxygen takes place in the tissues themselves rather than in the blood, a true solution of the problem could not be arrived at without quantitative data in regard to the oxygen and carbon dioxide content of both arterial and venous blood. Here a non-medical investigator, Gustav Magnus, professor of physics at Berlin, came to the rescue of physiology in 1837. By means of the mercurial air pump he was able to liberate oxygen and carbon dioxide from both arterial and venous bloods and to show that the percentage of oxygen is greater in arterial blood while that of carbon dioxide is greater in venous blood. These determinations by Magnus were afterwards amplified by the physiologists Pflueger, Ludwig and his pupils, among whom was Lothar Meyer, later to win distinction in pure chemistry, and their work, in conjunction with the labors of many other investigators during the last half of the nineteenth century, has given us a theory of both internal and external respiration which the science of our day has only been able to expand but not to overthrow. The historian Fielding H. Garrison pithily remarks that "the development of the physiology of respiration from Borelli to Magnus was almost exclusively the work of three mathematicians, two physicists and five chemists."

In respect to the further developments in regard to both internal and external respiration, I can not do better than transcribe the concise description by one of your own guild, Professor W. Mansfield Clark:

> In all science there are few developments as beautiful as those which have given us the precise knowledge of the blood equilibria. There have been found: a quantitative relation between the iron of the blood pigment and the oxygen combining capacity; quantitative data for the equilibria between partial oxygen tensions and degree of oxygen saturation of haemoglobin; preliminary data on the Donnan equilibrium between the oxygen-carrying blood pigment, trapped within the semipermeable membrane of the red cell, and the plasma; exact relations for the bicarbonate equilibria of the plasma and the acid-base properties of the oxygen carrier; the mechanisms for the maintenance of constant hydrogen-ion concentration of the blood and the control of lung ventilation by the activation of a nerve center called the respiratory center. Of this Haldane says, "A rise of 0.2 per cent. or 1.5 mm. in the CO_2 pressure of the alveolar air and arterial blood causes an increase of about 100 per cent. in the resting alveolar ventilation. The outstanding delicacy of the regulation of blood reaction is thus evident. No existing physical or chemical method of discriminating differences in reaction approaches in delicacy the physiological reaction."

The prophecy of Liebig has been realized. In our day chemistry and physics have become fused into the very structure of the biological and medical sciences. But despite the fact that chemists during the past seventy-five years have necessarily concerned themselves largely with the development of their science along inorganic, synthetic, physicochemical, quantitative and, in recent years, more and more along electrochemical and mathematical lines, they have nevertheless, as in earlier times, continued to take an interest in the chemistry of life processes. It would too greatly lengthen this paper to give even a brief outline of the hundreds of contributions that have been made by the chemists of all countries to biochemistry since 1860 or thereabouts.

An outstanding example or two of the contributions of chemists to biology from that time to ours must suffice. And here there naturally comes first to mind the name of Emil Fischer, one of the very greatest experimental chemists of all time, whose outstanding contributions toward the solution of the most difficult and important among biochemical problems will always be looked upon with veneration by those who are conversant with the researches of this genius and have a first-hand knowledge of these difficult subjects. His researches on the chemical structure of the sugars and on the very specific ferments that liberate them from their derivatives, and on the structure of the proteins and their primary and secondary cleavage products effected a revolution in our chemical concepts of these products of vital activity and opened up new vistas in regard to biochemical processes. An analysis and a description of his monumental discoveries in regard to the members of the purine group and their allies, as found in both animals and plants, would carry us back to Scheele's discovery of uric acid in urinary calculi and then to a consideration of the earlier discoveries of his predecessors, Wöhler, Liebig, Fourcroy, Grimaux, Baeyer, Strecker, Horbaczewski and others. Suffice it to say that the contributions of Emil Fischer surpass in their ultimate significance for chemical physiology those ever made by any other man in the entire history of biological and medical science.

By substitution, degradation and especially synthesis, he established the genetic relationship between uric acid, xanthine and hypoxanthine and their multitudinous substitution products and showed that they may all be considered as derived from a substance $C_5H_4N_4$, for which he proposed the name purine (from *purum* and *uricum*) and which, although purely hypothetical at the time, he afterwards succeeded in synthesizing. In the field of the sugars, with the aid of phenylhydrazine, which he himself had discovered at the very outset of his scientific career (1875), he was able to isolate in pure form not only the few then known natural monosaccharides, but a host of others whose existence he predicted from the van't Hoff theory of the asymmetric carbon atom and which he synthesized by the skillful application of a number of general reactions, and in this way established the structures and configurational relationships of this very important group of substances. He also studied in detail and clarified the chemistry of the glucosides, their structure and spatial configurations and especially their behavior towards enzymes. The ester method for the separation of amino acids which he devised enabled him to determine much more nearly quantitatively than had hitherto been possible the composition of the complex mixtures resulting from the hydrolysis of proteins, and led to the discovery of several still unknown amino acids in such mixtures. These amino acids he succeeded in condensing with each other in amide-like union to substances which he called peptides and which, as the number of the amino acid residues of which they were made up was increased, approached closer and closer in physical and chemical properties to the peptones obtained from natural products. Similarly, he found that the tannins are glucosides of ester-like combinations, "depsides" (from δεψειν, to tan), of phenolcarboxylic acids joined to each other through a phenolic hydroxyl group of the one and the carboxyl group of the other. As in his protein work, after having determined the nature of the component units of the natural products, he synthesized numerous compounds more and more resembling these natural products in their chemical reactions and physical properties.

As I am noting here more particularly the contributions of certain leaders among so-called pure chemists toward the elucidation of the chemical occurrences in living things, rather than those of biochemists, pharmacologists and physiologists, significant as these have been, it is only natural that I should refer to the work of Willstätter, A. v. Baeyer's distinguished pupil. You are all familiar with the brilliant researches of this master and his pupils on the chemical nature of chlorophyll and with their success in isolating in crystalline form the chemical individuals that had originally been grouped under that comprehensive term. It has been said that if it can be assumed that one thing is of more importance than others, then chlorophyll is undoubtedly the most important and the most indispensable of all things. The epigram contains a larger element of truth than is usually inherent in pithy sayings. Certainly the chloroplast of the green leaf, one of the most wonderful of all chemical laboratories, activated, as it is, by the sun's radiations, taken into consideration with the chemical activities of the other plant physiological mechanisms, offers problems that challenge the highest skill of the chemist and bio-physicist. And here in this broad field of photo-synthesis we find pure chemists, plant chemists and physicists combining forces in our day as never before, in the solution of problems of the greatest significance, both from a theoretical and a practical point of view.

Willstätter and his collaborators, building on the foundations laid by earlier workers, Hoppe-Seyler, Gautier and others in the eighties of the last century, v. Nencki, Küster and others since 1900, have finally given us a clear picture of the chemical relationship that exists between haemoglobin, the respiratory pigment of our blood, and the assimilatory chlorophyll pigments of plants. The relationship is of philosophical as well as bio-chemical interest. Both classes of pigments have essentially a comparable structure, the basic complex of each, called aetioporphyrin by Willstätter, being a compound consisting of four substituted pyrrole nuclei united through two carbon atoms. The blood pigment contains iron and the plant pigment magnesium in combination, partly through normal and partly through secondary valences, with the nitrogen atoms of the pyrrole groups in the aetioporphyrin complex. On degradation the two pigments yield the red, metal-free porphyrins which are broken down by oxidation into the anhydride or imide of haematinic acid and this by loss of carbon dioxide gives methylethylmaleinimide.

A second field of the greatest importance to both plant and animal physiology which has been greatly advanced by Willstätter's researches is that of the enzymes or organic catalysts. These products of vital activity, in contrast to inorganic catalysts, such as the acids, the various elements and metallic compounds employed in our laboratories, are so highly specific in their action that a particular biose, as milk sugar, cane or malt sugar, for example, is only capable of being hydrolyzed by a special enzyme, the only one, indeed, that is capable of effecting its hydrolysis. By devising new and ingenious modifications of a method long employed in biochemistry, that of adsorption, this investigator has been able to separate from their mixtures, and to obtain in a high degree of purity, many enzymes and to differentiate, for example, two such closely related sugar-splitting enzymes as saccharase and maltase. The skilful employment of metal hydroxide gels, more particularly the various structural modifications of aluminium hydroxide, enabled Willstätter to effect these extraordinary separations of enzymes from the various impurities and the activating and inhibiting substances that are always associated with them in the naturally occurring mixtures with which we have to deal. The new methods may truly be described as selective adsorption methods, as has been done by Willstätter, and it is interesting to note, as he points out, that this selective adsorption is determined, not by the degree of dispersion or other physical state of the adsorbing compound, but rather by its chemical structure.

The researches of a century have shown how very numerous are the specifically acting enzymes that are present wherever protoplasm functions, whether in single-celled organisms or in the more intricate structures of the higher plants and animals, and how varied are the chemical operations whose entire course, that is to say, whose rates of reaction and elaborated products are determined by these unique agents of vital activity. Admittedly, the further elucidation by chemists of both the dynamics and the organic structural problems here presented will yield results of the greatest significance both for chemical science and for the better comprehension of the life processes. For your consideration as chemists, I shall conclude my remarks on this aspect of biochemistry by the citation of a passage from a recent address of Willstätter on "New Methods in Enzyme Research":

> Of the characteristics of enzymes only the structural chemical and probably also the stereochemical specificity are uninfluenced and constant. The sugar-splitting enzymes show the strictest specificity in both respects, as regards chemical constitution and arrangement in space; the fat-splitting enzymes have a wider range of activity on structurally different, ester-like substrates. But they appear to be more finely differentiated in their stereochemical specificity. If we compare the lipases of the pancreas, the liver, the stomach and the fungi as to their action on the same racemic substrate we find all different from each other in their selective action, preferring, now in the one case, now in the other, the d- or the l-form, if only we use a sufficiently large number of the racemic esters, as, for example, of the mandelic acid group. This configurational specificity can so far be considered as an enzyme constant. Thus far there has been observed no case where the influence of foreign bodies determines the direction of the rotation of the preferred compound.

Even a rapid survey of the many other fields in which chemists and biologists have an interest in common would transcend the limits that time and a consideration for your patience impose upon me. There remain, for example, the problems that arise in connection with the nature of the oxidation and reduction processes that are carried out in our bodies at 37.5° C—problems that stand in the closest theoretical relationship to the efforts of your fellow chemists to explain the true mechanism of even the simplest of oxidations, as that of carbon monoxide to carbon dioxide. My personal interest in this most fundamental of biochemical problems stands in inverse ratio to my ability to treat it adequately, even were there time at my disposal to do so. Fortunately I can refer you to the concise and elegant outline of this subject that was given us in Baltimore two years ago by Professor Stieglitz in his Dohme lectures. This field, I am happy to say, is being tilled intensively by the younger physical, organic and biochemists of the day. The earlier experimental observations of pharmacologists and physiologists in respect to the influence of a change in the *milieu* on the oxidative capacity of cells are now receiving an interpretation more in accord with our newer conceptions and more capable of mathematical treatment. Thus, W. Mansfield Clark, who has distinguished himself in this field, points out in one of his recent papers how intimately related are the oxidation-reduction systems and acid-base systems of the animal organism, and adds:

This has long been suspected to be a matter of profound importance in physiology, but it is believed that this (his) is the first systematic presentation among the numerous theoretical possibilities among the interrelated acid-base and oxidation-reduction equilibrium states.

I have also no time to comment on the reasons that induce the pharmacologist to follow your investigations with an absorbing interest and with keen enthusiasm. Some of these reasons are found in the biochemical problems outlined above, the essential parts of which are woven into the very texture of his thought, if I may say so. But quite aside from these more fundamental problems, there exists also a community of interests between us concerning the invaluable remedies with which chemists, working often in close cooperation with the pharmacologists, are enriching our *materia medica*. Occasionally, alas, in their cooperation in this field, both parties have fallen into the very human error of exaggerating the practical importance of their discoveries and researches—which latter, indeed, are often too solely and too transiently utilitarian in purpose and in character to redound to the credit of either party to the transaction.

In regard to the influence that our American predecessors and our own contemporaries in this country have had in shaping the future course of the biological and medical sciences I need not speak at length. Your influence, direct and indirect, on these sciences can be traced in the pages of the admirable historical review of your activities during the past half century published in the Golden Jubilee Number of *The Journal of the American Chemical Society,* though evidently the biochemical implications of this half-century's work could not always be brought out by the writers of that volume. As never before in our history, our younger biological and medical investigators are utilizing in their investigations the methods and principles of the various divisions of your science. A study of the various chemical, biochemical, biological, pharmacological, physiological and experimental medical journals of the country will furnish conclusive evidence that our countrymen are making fine progress in the broad fields covered by these journals.

PHYSICAL CHEMISTRY AND BIOLOGY

I come now to a consideration of some special points of contact between the physical chemist and the biologist, quite apart from the numerous references that have already been made to such contacts in earlier passages of this lecture. These contacts are conditioned by the composition and structure of the living substance—protoplasm—and the multifarious units—the cells of plants and animals—to which the protoplasmic structures are confined. The cell doctrine, far-reaching in its influence upon medicine and biology, as finally formulated by Dutrochet, Schwann and Scheiden before the middle of the last century, is to be counted among the very greatest discoveries of that century, comparable in its consequences for biology to those that followed the acceptance of the atomic and molecular hypothesis in chemistry.

The mysteries of life lie concealed in these units, individually of microscopic size only, and specialized in structure and function in the multicellular plants and animals. Naturally, I can not here comment on the reasons that necessitate a minimum external surface area for a cell, nor can I consider the influence of cells upon one another, nor the inadequacy of the cell theory to cover satisfactorily all the facts of development, as is claimed by a few biologists. The individual cell, wherever found, must be regarded as a congeries of minute, discrete chemical factories, standing in a possibly mobile spatial relationship to one another and working together in a beautifully harmonious manner. Surfaces, internal and external, and surface energies are of paramount importance in these individual units of life, as they are also when the units are aggregated in a manner to produce areas astonishingly large in dimension. The total internal surface of a given single cell, when the extensive colloidal interfaces, not to mention the limiting surfaces of the nuclei, nucleoli, chromosomes, plastids, zymogen granules, vacuoles or other microscopically determinable components, would, if computable, be found to be very large in comparison with that of its outer envelope. These internal surfaces, or boundaries between contiguous phases, are the seats of all manner of changes and operations, not merely all such as are broadly described as physico-chemical in character (electric charges, etc.), but I venture to assert that all those protoplasmic processes that are usually defined as purely chemical in character, that is to say, oxidations, reductions, syntheses, hydrolytic decompositions, etc., are likewise surface actions. In the living cell, then, we have a system, the *microphysical* or *ultramicrophysical structure* of which differentiates it entirely from the systems of our test tubes and enables the cell to carry on all of its manifold processes at 37.5° C., more or less, as the case may be.

The labile oriented molecular arrangement in space and time of the surfaces of discontinuity of the phases of the various heterogeneous systems of the living cell and the constant interaction of these surfaces with sources of free energy of the environment, may account for the continued differentiations, apparently purposeful and directed, that characterize living things, as compared with the trend of non-living things toward less complex states. It may well be that an increase in our knowledge of molecular mechanisms in both fields will prove that the difference in behavior of living organisms and matter devoid of life is, in the last analysis, one of degree and not of kind.

I have said above that considerations of surface are of paramount importance in biology. Nature has found a means of producing very large surfaces by the aggregation of countless cells, as in leaves, root tendrils, capillaries and innumerable other structures. Krogh has calculated that if we suppose the total weight of a man's muscles to be 50 kilograms and his capillaries to number 2,000 per square millimeter of cross section, the total length of the capillaries of our muscles alone would be something like 100,000 kilometers, and their total surface 6,300 square meters. Our lungs, when collapsed, are small organs, but in them are found 725,000,000, more or less, of little pockets or alveoli where our thin-walled capillaries exchange carbon dioxide for oxygen. The total internal area of these lung terminals or alveoli is close to 100 square meters, enough for thirty suits of clothes, as Sir Arthur Shipley puts it in his valuable little book entitled "Life." The thin-walled capillaries of the lungs, one thousandth of a millimeter in wall thickness, make it possible for the slow process of diffusion to do the work necessary for the maintenance of life in less than the four seconds of each respiratory act. And so everywhere throughout the body we find these enormously extensive areas of cell surfaces—mechanisms for effective adsorption, secretion and excretion in the unit of time.

I can not close this outline of "contacts" without a few further words on the bearings of physical chemistry on physiology and medicine. Every scientist of our day has learned that our countryman, J. Willard Gibbs, a man of the highest genius, by his fundamental and profound researches first placed the theory of surface phenomena on a truly scientific basis and made it capable of statistical and thermodynamical treatment. Since his day our knowledge of the actual molecular structure of the surfaces of both simple and heterogeneous systems has been greatly extended by scientists in this and in foreign countries —in this country by Langmuir, Harkins and others. Now, for more than half a century, physiologists and pharmacologists have been impressed, by the nature of the problems they were facing, with the need of more accurate knowledge of the physicochemical and chemical occurrences at the interfaces and limiting membranes of living structures. Naturally, their problems are bound up with questions involving adsorption and surface tension, colloidal sols and gels, the influence of the ever-varying chemical state of cell membranes, catalysis and related actions. Pharmacologists have always been confronted by the physico-chemical difficulties encountered in their attempts to analyze and understand the effects of drugs, including the powerfully acting hormones of our body, on both unicellular organisms and on the more complex structures of the animal body. My collaborators and I, to give but one example, have encountered such difficulties in our attempts to explain the increased susceptibility of the central nervous system of frogs to certain dyestuffs (ordinarily harmless) when administered subsequently to certain, otherwise trivial, injuries which so greatly increase the permeability of the capillaries and the adsorptive power of the cells of the brain and spinal cord that the ordinarily harmless dyestuff now reaches such a concentration in these cells (as can be shown by color tests) that violent strychnine-like convulsions immediately follow.

Workers in the medical sciences, as in biology, are bound to profit greatly, if not at present, then later, by the newer revelations in regard to the molecular structure of surfaces, more particularly those of micro-heterogeneous systems. They will agree with Professor Donnan when he gives expression to his conviction that "the newly recognized 'two-dimensional' molecular world . . . and the new knowledge of the structure of this 'surface world' presents phenomena of molecular orientation of the highest importance for the understanding of great regions of natural phenomena." Even though physical chemists are at present in disagreement in respect to many points in connection with this "two-dimensional" molecular world, the biologist must greet with enthusiasm every new and undoubted fact here discovered and the future theoretical developments in relation to it, even though he may only imperfectly comprehend the latter.

I realize fully that it is not within my competence to speak authoritatively in regard to the contacts between physical chemistry and vital occurrences, but I can not forbear citing, as a conclusion to my remarks on this subject, a heartening passage from Professor Donnan's address "On the influence of J. Willard Gibbs on the science of physical chemistry":

> In physiology the power and value of thermodynamical methods have been fully recognized only in comparatively recent times. Perhaps after another century of research in this science there may come another Willard Gibbs, who will discover the fundamental equations of the living cell, where the unseen of the past seems to reach out and grip the future. But for that we shall require something more than linear differential equations.

The biologist, having in mind the ambitious attempts of the iatro-physicists and the iatro-mathematicians of the seventeenth century, as Borelli and others, to reduce physiology to physics and "to ornament and enrich it by mathematical demonstrations," and while not unmindful of the great value inherent in the contributions of these pioneers to haemodynamics and the mechanics of muscular movement, will feel, nevertheless, that the physical chemists of our day, like their mathematical predecessors three centuries ago, do not always take into account the complexities encountered in this laudable purpose of reducing life phenomena to fundamental equations. It is not specialized mechanisms, as the muscle, the selective permeability of membranes or certain definite chemical and physico-chemical processes like those of the respiration, which are already capable of thermodynamical treatment, that offer difficulties to the realization of this laudable ambition, but the more general cytological problems of biology such as are encountered in the study of cellular processes as a whole, of cell organization into highly differentiated structures, and of development in general, together with the difficult problems of heredity, that will tax the power of the Gibbses of the future. Or, consider the difficulties that will confront the mathematician of the future in his efforts to express the entire life processes and the reproductive powers of a single-celled organism only, as, say one of the paramoecia, in the form of valid general equations. To the biologist, it must appear that not one Gibbs but perhaps a half dozen or more will be required and their genius will be able to achieve results of value only after many more quantitatively determined biological facts shall be at their disposal than is now the case. The writer is an optimist in regard to the mental powers of the elect of our species, but he can not but feel that a single century will hardly suffice for the realization of these hopes, which biologists in general cherish equally with physicists and chemists.

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(*To be concluded*)

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

GRANTS IN AID OF RESEARCH, FOR 1928

THE allotment of American Association grants for 1928, in aid of research, will occur next December and all applications to be considered in that allotment must be in the Washington office by December 1. While the amounts of these grants are never large, being usually for sums less than five hundred dollars, yet this annual allotment constitutes an important part of the work of the Association. It is intended that the grants to individuals shall be specially useful in making possible the completion of important pieces of research already begun or that they shall be the means of supplying special apparatus or facilities, in cases where adequate funds can not be secured elsewhere. They are generally announced in January and the funds become immediately available. A grant may be disbursed in a single sum or in suitable installments according to the wishes of the grantee. All undisbursed grants or undisbursed portions of grants revert to the treasury on October 1 of each year, unless special arrangements have been previously made with the permanent secretary's office to have them made available for the next fiscal year. It will be remembered that the official year of the association extends from October 1 to the following September 30.

It is specially important that members of the association should be alert to the possibilities of these small grants and that the older members should give advice and suggestions to the younger members in this connection when occasion arises, to the end that the grants may be allotted to persons who will make the most of them and for projects that are of outstanding and pressing importance. Applications for grants may be made at any time, but no allotments are made excepting at the time of the annual meeting of the association. A special form of blank is now provided for applications. Copies of the blank are to be had from the permanent secretary's office. Each application should be supported by letters from at least two persons who are acquainted with both the applicant and the research project for which a grant is needed.

All applications for grants are referred to the Committee on Grants for Research, which makes allotments in December of each year. At the annual meeting the council makes an appropriation for grants allotted by the Committee on Grants. Each applicant receives a notice in January, informing him whether or not his application has been favorably acted upon. The permanent secretary acts as secretary of the Committee on Grants, but he is not a member of the committee and has no vote. The membership of the Committee on Grants for 1927 is as follows: Dr. Aleš Hrdlička (for Psychology, Anthropology, Education, Economics), *chairman*; U. S. National Museum, Washington, D. C. Dr. B. M. Davis (for Botany); University of Michigan, Ann Arbor, Mich. Dr. Joseph Erlanger (for Physiology); Washington University School of Medicine, St. Louis, Mo. Dr. Nevin M. Fenneman (for Geology); University of Cincinnati, Cincinnati, Ohio. Dr. L. G. Hoxton (for Physics); University of Virginia, University, Va. Dr. Vernon Kellogg (for Zoology); National Research Council, Washington, D. C. Dr. W. Lash Miller (for Chemistry); University of Toronto, Toronto, Canada.