FRACTIONATION RESEARCH AT THE ROCKEFELLER INSTITUTE

by Professor Lyman C. Craig

IT IS DIFFICULT to estimate how large a proportion of the total effort put forward thus far in chemical research has been concerned with chemical separations of one kind or another, but it is safe to say that the proportion is considerable. Inability to bring about separations with sufficient clarity has been a limiting factor in man's attempt to discover the true nature of many of the things occurring about him from the earliest time. It is still a limiting and often frustrating factor in spite of a tremendous literature on fractionation. For instance, we are quite certain today that inheritance information is transmitted from generation to generation through nucleic acids. Yet we are far from being able to separate a nucleic acid preparation in pure form, preserve it that way and then prove that all the molecules in the preparation are identical.

The terms "separation" and "purification" appear frequently in scientific literature. The exact meaning of each term, however, will depend on the particular scientific discipline involved. In this account only the chemical meaning of the terms will be considered.

To the chemist the separation of the components of a mixture of substances means the division and subdivision of the mixture in such a way as to give a very high proportion of molecules of one kind in each division or subdivision. The manner in which the division and subdivision is accomplished in order to bring about this desired state of affairs constitutes the science and art of chemical fractionation.

No small part of the basic theories on which the science of chemistry now rests has grown out of attempts to separate and isolate certain chemical principles. Even part of the philosophy of the science had its beginnings in this way. For example, the atomic theory was proposed by a group of Greek philosophers led by Leucippus and Democritus nearly 2500 years ago as a result of speculations concerning how far matter could be divided and subdivided (atom, meaning indivisible). The theory was rejected by Aristotle because of lack of experimental proof and was not seriously considered again for over 2000 years.

DALTON'S ATOMIC THEORY

The atomic theory was prominent in the speculations of the English school of scientists of Newton's time, but Dalton just after 1800 is credited with furnishing the first scientifically acceptable proof for its support. Some of the proof is given in a paper read in 1803 which dealt with the differences in solubility of various gases in water. He ascribed the differences to a variation in the weights of the ultimate particles and suggested a table of relative weights. In a paper published in 1808, Dalton concluded that "the ultimate particles of all homogeneous bodies are perfectly alike in weight, figure, etc."

and he reasoned that this must be so with water because no differences in properties such as density could be demonstrated between any given sample of it and another from an entirely different source. He spoke of the ultimate particle as an "atom" and particles resulting from combination of atoms as "compound atoms" or "molecules." His statement that "Chemical analysis and synthesis go no further than to the separation of particles one from another and to their reunion" shows the important rôle of separations in his concept.

CRITERION OF IDENTITY

Dalton assumed that identical molecules could be separated from those that had a different size or shape but the question of how to be sure this had been accomplished with a particular preparation immediately assumed major importance. "Molecules," even as conceived by Dalton, were so infinitesimal that it was evident that there would be countless millions of them in even a microscopic portion of any preparation. In spite of this, the theory steadily advanced because of the working hypothesis that purification processes known since antiquity, such as distillation, sublimation, crystallization and extraction, could indeed sort out the different molecules. If this hypothesis were correct then a preparation would consist of identical molecules if such a sorting process, properly applied, was found to give only fractions whose properties were entirely indistinguishable.

This view quickly became a basic tenet of organic chemistry and remains so today. It is subjected to tests becoming increasingly more critical because of the technical improvement in methodology, a necessary and important fact because larger and more complicated molecules now can be investigated.

If fractionation theory helped establish the molecular theory, it is also clear that (continued on page two)
the molecular theory set the stage for a much better understanding of purification processes. Perhaps the simplest analogy might be to a mixture of marbles of several different colors. Systematic division and subdivision of a sample containing many marbles will finally result in each individual marble being isolated, but much before this in the process it will be found that the distribution of color in the subgroups will not be entirely the same as in the original mixture. The laws of chance come into play. The rather small differences of color distribution in the groups could of course be made much greater if some element of selection could be introduced at each division and subdivision. This is the basis of all separation processes. First there is division and subdivision with the probability factor always involved because of the enormous numbers of molecules, and secondly there is the element of selection superimposed.

The essence of a separation technique is to discover some arrangement of the conditions of division that will give at least a slight bias to the otherwise random disposition of the selected component. From the ancient art of separating things a vast body of technical knowledge has slowly evolved by pure trial and error and the search for the exact conditions required to reach the objectives of the time.

FROM ART TO SCIENCE

Actually, the slow transition from the art to the science of separation and purification has been under way for only a little more than 100 years.

Centuries ago it was observed that water could exist in more than one form—gas, liquid or solid. Under certain conditions two of the phases can exist together in close contact. Individual molecules are free to choose which form or phase they prefer. Thus an element of selection is set up if division and subdivision is made by removing one phase from the other after they have been in contact.

Centuries ago it was also observed that oil and water would not mix. Certain substances (called essences) could be extracted from solids by alcohol but not by water; perhaps with others the reverse. Here was another element of selection involving solubility. Those molecules not able to associate intimately with the solvent molecules would refuse to enter the solvent. A closely related state of affairs was presented by using two solvents not mutually soluble. This was the beginning of fractionation by extraction.

Along with the evolution of the rule that a substance is pure when it cannot be purified further came the observation that with a "pure" substance the transition from one phase to another would take place over a much narrower temperature range than with a less pure preparation. For example a pure solid often would melt (change from the solid phase to the liquid phase) or boil (change from the liquid phase to the gaseous phase) at a precisely defined temperature, while a less pure substance would melt or boil over a range of temperatures. Moreover, the exact temperature of the transition seemed to be characteristic of the substance. Melting and boiling points rapidly came into use as criteria of purity and for identification. Other physical constants such as density, refractive index, optical rotation, etc., came into use.

EARLY BIOCHEMISTRY

When Dr. P. A. Levene began his studies at the Rockefeller Institute in 1905, he was well aware of the importance of separation and purification, as might have been expected of one who had worked with Emil Fischer. The substances he chose to study, however, were of such size...
and complexity as to be generally beyond the separation and purification methods in use at the time. Nonetheless, the progress made was a great tribute to the skill with which he and his co-workers applied those procedures which did afford a degree of separation. The work accomplished up to about 1930 can be considered a phase of empirical investigation necessary to provide information about the properties of the larger molecules before attempting to design the more effective and delicate separation procedures common today. Such empirical studies made wide use of solubility and salting out procedures. It is interesting that the basis for their effectiveness is still not fully explained.

Northrop and his collaborators, Butler, Herriott and Kunitz, shortly after 1930 were exploiting the possibility of differences in solubility for purifying enzymes at the Institute. They concluded that there were certain consequences of a relationship developed many years before by Willard Gibbs, known as the phase rule, which could be used effectively for purity studies with larger solutes, such as proteins. This same phase rule explained why a pure substance would give a sharp melting or boiling point if it behaved ideally. When applied to the solubility approach for purification, the rule implied that with a pure sample of a protein the amount of protein in solution at saturation in a given volume of solvent would be independent of the amount of the protein in contact with the solution. Solubility fractionations repeated until "phase pure" material had been achieved resulted in the crystallization of many enzymes and proteins. For this work Northrop shared the Nobel Prize in 1946 (see the Quarterly, Vol. 4, No. 2) with Wendel M. Stanley for crystallizing tobacco mosaic virus and with J. B. Sumner for crystallizing enzymes.

THE ULTRACENTRIFUGE

As a method of working, however, the solubility technique soon began to be supplemented by electrophoresis and sedimentation in the ultracentrifuge. Many of the basic developments in the latter two techniques were worked out at the Rockefeller Institute.

In 1935 Dr. Pickels came to the Institute as a member of the scientific staff of the Rockefeller Foundation to continue studies on an air-driven ultracentrifuge which he and Dr. Jesse W. Beams had devised at the University of Virginia. The refinement of their instrument, now called a "Spinco" ultracentrifuge, was well started before Pickels left the Institute to found the Spinco Company. This firm, which subsequently became part of the Beckman Company, provides nearly all the analytical ultracentrifuges in use today. At first only large molecules could be distinguished by sedimentation techniques, but more recently comparatively small molecules have been successfully separated. Perhaps even more important, the method has also found great use in separating organized cell components from each other.

COUNTERCURRENT PROCESSES

Around 1930 chemists concerned chiefly with the oil industry began to study and greatly improve fractional distillation. It was already realized that the separation effect could be greatly enhanced by use of a fractionation column and that this is a so-called "countercurrent" process in which one passage through a column could be the equivalent of many individual distillations and redistillations without the column. A highly mathematical interpretation of column behaviour soon developed which was based on the theoretical enrichment possible in a single vaporization for a given binary mixture.

The question of adapting experimentally such a procedure to the small amounts of substance available in biochemical problems was one which interested me soon after I became an Assistant of Dr. W. A. Jacobs in 1933. The problem under study at that time concerned the nature of the alkaloids of ergot, expensive drugs available only in small amounts. Although by present day techniques the methods developed for distillation and fractional crystallization do not seem impressive, they were sufficient to purify the small amounts of degradation products formed during the study to the point where reliable analytical data resulted. This contributed greatly to the final success of establishing most of the structural features of "Lysergic Acid" and the ergot alkaloids.

In the next structural study attempted by Dr. Jacobs and his collaborators, miniature fractionating columns of considerable efficiency were developed which would operate with fractions of a milliliter of oil under greatly reduced pressure. These proved adequate to establish many of the basic structural features of the complex veratrine and aconite alkaloids and served to accomplish separations beyond those attainable by any previous workers in the field.

While this work was going on R. Kuhn, M. Lederer, H. Brockman and L. Zechmeister working on natural products, chiefly plant dyes, had revived a technique called "chromatography. It had been proposed nearly 30 years before by a Russian, M. Tswett, for separation of plant pigments. The method, elegant in concept, simply involved percolation of a solution through a bed of a suitable adsorbent. In some of the earliest work on chromatography at the Institute, Jacobs and I found it effective in the veratrine and aconite field for many separations not suited to the fractional distillation techniques. The possibilities in chromatography as a separation tool, however, were not fully realized until A. J. P. Martin and R. L. M. Synge began the classical studies for which they received the Nobel prize in 1952. Their ideas, proposed shortly after 1940, were developed through an attempt to refine liquid-liquid extraction and make this approach suitable for microfractionation of complex water soluble mixtures.

PARTITION METHODS

They conceived the idea of immobilizing one of the two immiscible phases on an inert support so that the other phase could pass over it in countercurrent manner. This type of column proved to be an extremely efficient tool but of course was more like chromatography than liquid-liquid extraction. The suggested term "partition chromatography," however, soon became very popular and the quest for inert supports widened tremendously the whole science of chromatography. Filter paper became an especially interesting material in this connection. Martin and Synge's researches extended chromatography to water soluble substances. Later Martin and James modified the technique to operate with a vapor and a liquid phase. This modification appears to be in many respects the most elegant of all separation procedures. Chromatography in some one of its forms is the most widely used separation method in biochemistry today.

Independently of the English workers, (continued on page four)
I had also taken up the study of liquid-liquid extraction shortly after 1940. However, the investigation resulted in a technique entirely different from partition chromatography to which the name "countercurrent distribution" was given. In order to be sure of the basis of the separations, the method was kept as a strictly discontinuous, stepwise extraction procedure systematized so that the fraction of the original mixture involved in each successive extraction would correspond to a given term of a suitable binomial expansion. Experimentally, this would be a cumbersome procedure without proper mechanical equipment. Such equipment was devised with the aid of ingenious technical help, particularly that of Otto Post who was a technician in Dr. Jacob's laboratory at that time. Mr. Post now owns a small factory which manufactures and installs countercurrent distribution "C.C.D." equipment for use in scientific and industrial laboratories throughout the world.

The C.C.D. technique first made its mark in purity studies in the antimalarial field during World War II. It has made possible many isolations of rare drugs, hormones, vitamins, etc., in pure form for the first time. These include synthetic penicillin G, the pituitary hormones, angiotensin, the parathyroid hormones and many other substances.

**CHROMATOGRAPHY**

At the close of the second World War, Drs. Stanford Moore and William Stein at the Rockefeller Institute turned their attention toward the separation of amino acids by chromatographic procedures, recognizing that this was a basic problem of primary interest in protein chemistry. Their first major contribution to the problem was the introduction of automatic fraction collectors of their own design and the development of a highly sensitive colorimetric assay, the ninhydrin method, for estimating the extremely small amount of amino acid in the fractions collected from the chromatographic column in the fraction collector.

They and their collaborators made extensive studies of various supporting agents as well as other experimental conditions for the most favorable resolution of the amino acids. Starch at first seemed the best support, but in a few years the ion exchange resins, which had been recently proposed for chromatography and found to be very effective in other laboratories for highly charged solutes, proved to be much better. The ion exchange method was steadily improved, particularly with respect to the time required to resolve all the amino acids. Finer particles of the resin uniformly packed in a narrow column gave superior resolutions in much less time when the eluting solvent was forced through the column under considerable pressure.

Finally, in collaboration with Dr. Darrell Spackman, a still further advance was achieved in the construction of a fully automatic recording amino acid analyzer. This instrument performed the laborious work of the ninhydrin analysis and made a complete quantitative amino acid determination possible in less than 24 hours.

While the amino acid separations were being improved in the Moore and Stein laboratory, a number of successful separations of proteins by ion exchange chromatography were also accomplished. Ribonuclease was one of these. After demonstrating its purity, it was degraded enzymatically and many peptides isolated in a pure state by ion exchange chromatography. The separations were sufficient to permit the complete amino acid sequence of ribonuclease (124 residues) to be established.

The technique of electrophoresis, mentioned above, was announced in 1937 by Arne Tiselius of Uppsala, Sweden, who was awarded the Nobel prize in 1948. Electrophoresis takes advantage of the differences in electrical mobility of the components of mixed biological materials, such as the protein constituents of blood serum. Drs. MacInnes, Longsworth and Shedlovsky at the Institute have contributed much to our knowledge of ion mobilities. Dr. Longsworth devised the method currently used for following the movement of solutes in free electrophoresis.

Shortly before 1950 a way of modifying electrophoresis by use of a porous supporting medium was sought. Consden, Gordon and Martin in England tried silica gel, but Durrum in this country and Wieland and Fischer in Germany found moist filter
ROYAL SOCIETY TERCENTENARY CELEBRATED IN LONDON

The Rockefeller Institute was one of a score of universities in this country to be invited to join academic institutions and scholarly organizations throughout the world in celebrating the Tercentenary of the Royal Society in London this summer. Two members of the Institute's faculty, Peyton Rous and Herbert Gasser, Foreign Members of the Royal Society, presided at scientific seminars during the course of the celebrations. George W. Corner, Historian of the Institute and a Foreign Member of the Royal Society also attended the Tercentenary.

Her Majesty Queen Elizabeth the Queen Mother conferred the degree of Doctor of Science, honoris causa, from the University of London on Dr. Bronk, Foreign Member of the Royal Society for the past twelve years, and on the King of Sweden.

The others to be thus honored were Professor Homi Jehangir Bhabha of India, Sir Macfarlane Burnet of Australia, Professor George Charles de Hevesy of Sweden, and Sir Thomas Merton of England.

The public orator, Professor J. R. Sutherland, in presenting Dr. Bronk to the Queen Mother, as Chancellor, said:

"What does science need? What science needs is a mathematician who can do arithmetic, and an average man who can do even easier arithmetic. The world of science has now become so fragmented into so many specialised fields that it grows increasingly difficult for any one man to "grasp this sorry scheme of things entirely." In Dr. Bronk we honour a scientist who first won distinction as a physicist and astro-physicist and then later as a physiologist and biophysicist, and who in all of those fields has made notable contributions to knowledge.

But what has particularly marked him out among the men of his day is his determination in an age of specialised studies to uphold the essential unity of all knowledge. In his valedictory words to the trustees of The Johns Hopkins University, where for five stirring years he proved himself to be an outstanding president, he stressed the fact that understanding requires a comprehension of many related fields of learning and that "unless creative scholars work, and students learn, in universities which stress the unity of knowledge and scholarly endeavour, universities fail to provide the intellectual leadership sorely needed in our complex civilisation." It was therefore characteristic of the man that when he left The Johns Hopkins University to become President of The Rockefeller Institute he proceeded to transform that famous centre of advanced medical studies into a postgraduate university.

As an administrator and co-ordinator of research he has played a unique part in the modern history of the United States of America. Honours have flowed in upon him from all sides. He is now serving for a third term as President of the National Academy of Sciences, and he must have formed about the largest private collection of honorary degrees of any man now living.

We in London are proud to think that we have some small share in this remarkable career and, we believe, a lasting hold on his affections. In the late twenties and early thirties he worked from time to time at University College and one of his old friends there records how on one occasion Dr. Bronk, who after all, is a countryman of James MacNeill Whistler, remarked to him that Gower Street (near the University) on a foggy winter day is a very lovely place. He has travelled far and achieved much since those early days at University College: but with it all he has retained the essential humanity of a great man, known by his familiar name of "Dett" to a very wide circle of friends and fellow-workers, from President Eisenhower down to his junior colleagues, and to many old friends and well-wishers in this country.
Donald K. David, Vice Chairman of the Ford Foundation, has been a Trustee of the Institute since 1950. Formerly Professor and Dean of the Graduate School of Business Administration at Harvard University and now Chairman of the Committee for Economic Development, Mr. David has been concerned all of his life with relationships among business, education, and the community.

Born in Moscow, Idaho, son of a pioneering merchant, Mr. David very early resolved to study business, and upon graduating from the University of Idaho he went to the Graduate School of Business Administration at Harvard University. Harvard had drawn him like a magnet and it has remained a dominant interest in his life ever since.

After he received the degree of Master of Business Administration at Harvard in 1919, Mr. David became instructor and in 1920 was made Assistant Dean of the Graduate School of Business Administration, the first assistant dean at Harvard. He served as assistant dean and as assistant professor, then associate professor of marketing until 1927. Harvard was the first to teach marketing, and Mr. David was the first to teach some aspects of it at Harvard. Faced with a new field, he wrote his own textbook: "Retail Store Management Problems," published in 1922, and with Malcolm P. McNair he published another book, "Problems in Retailing" in 1926.

In 1927 Mr. David left the academic world for a time to become Executive Vice President of the Royal Baking Powder Company. He held this post until his election as President in 1929 when he was also elected Vice-President of Standard Brands, Inc. From 1930 until 1941 Mr. David was Vice President of the Great Island Holding Corporation, and from 1932 to 1941 he was President of the American Maize-Products Company of which he is a Director today.

After more than a dozen years away from Harvard Mr. David was persuaded by President Conant to return in 1942 as Associate Dean of the Business School to become Dean upon retirement of Dean Donham. His term as Dean at Harvard from 1942 until his retirement in 1955 was a time of vigorous development of the Business School. Mr. David considered it important that such key figures in American business and finance as Henry Ford and John D. Rockefeller, Jr., should be familiar with the Harvard Business School. In acquainting Mr. Ford with the School, he inevitably acquainted him with himself. As a result of their friendship, Mr. David was among those to be invited by Mr. Ford in 1948 to become the first Trustees of the Ford Foundation to be elected outside the immediate circle of the Ford family. Later he was among the first of those outside the Ford family to be elected Director of the Ford Motor Company. Upon his retirement from Harvard in 1955 Mr. David became Chairman of the Executive Committee of the Foundation and a few months later he was elected to his present position as Vice Chairman of the Board.

Mr. David’s association with Mr. Rockefeller arose in a similar way. Mr. Rockefeller initially announced that while he was interested in the School of Business Administration he was not prepared to give it money. But after he received a letter from Mr. David describing his plans, Mr. Rockefeller’s interest heightened and one day he asked if he might send one of his investigators to the School.

Mr. David agreed. The investigator, "who looked under every rug and behind every door" as Mr. David puts it, was Dr. Lindsley Kimball, now the Institute’s Treasurer. Mr. Rockefeller decided to offer $5 million to Harvard for the School of Business Administration provided the University would match it with a similar amount within a year, a proviso which was met successfully.

Mr. David was asked in 1950 to become a Trustee of the Institute when Mr. Rockefeller retired from the Board. In discussing the matter with Mr. Rockefeller, Mr. David demurred, saying he knew nothing about administration of medical research. Mr. Rockefeller replied, "Oh, that will be all right; we have many who know all about it!" Mr. David soon knew more, for almost immediately after his election to the Board he became a member of the Trustees’ Committee to consider the future of the Institute. Mr. David recalls that in the course of the numerous and intensive meetings of the committee that went on for more than a year under the Chairmanship of Dr. Bronk while he was President of Johns Hopkins University it became obvious that Dr. Bronk would be the ideal future President for the Institute, a conclusion which subsequent events have proven to be eminently wise.

Mr. David is Chairman of the Committee for Economic Development, an organization of 200 top-ranking business men and educators with the function of using objective research to determine private and public policies which will promote economic growth and stability in our free society.

In addition to these many activities, Mr. David is also a Director of the General Electric Company, the Ford Motor Company, the Great Atlantic and Pacific Tea Company, Aluminium Ltd., R. H. Macy & Co. and Boys Club of America. He is a member of the Business Advisory Council to the U.S. Department of Commerce and on the Board of Managers of the Silver Hill Foundation.

Mrs. David is the former Elizabeth Soulen, daughter of a member of the faculty at the University of Idaho. The Davids were married in 1917 while he was still in graduate school, and having been the wife of a graduate student herself Mrs. David’s sympathy for students’ wives led her, as the Dean’s wife, to organize a club for wives of the students of the Harvard
THE TRUSTEES continued

Business School. The Davids have two children, each of whom has three children. The Davids consider their home to be Osterville, Massachusetts, on the Cape, for though his office is in Manhattan, Mr. David believes it to be essential to have a place "where you can get your feet on the ground." A Westerner, fond of the out-of-doors, Mr. David's relaxations are rose gardening, golf, tennis, fishing and camping.

FRACTIONATION RESEARCH
(continued from page four)

paper more successful. Dr. Henry Kunkel of the Institute worked for a year in the laboratory of Tiselius in Sweden refining the filter paper method then returned to the Institute to introduce potato starch, a plastic resin (Geon) and other supporting agents. These researches made electrophoresis a much more versatile method for separating proteins and peptides.

Only a few years ago, a search was undertaken in our laboratory at the Institute and by Drs. Porath and Flodin in Sweden at the University of Uppsala for a countercurrent method which would separate molecules exclusively on the basis of their size and/or shape. The Swedish research led to a polymerized dextran gel called "Sephadex" which seemed to have pores with the right properties so that differences in the rate of diffusion into and out of the pores could be exploited. When used like a chromatographic supporting agent, Sephadex permitted surprisingly good separations, mostly based on size and shape.

Our work led to study of the factors controlling the rate of diffusion through semipermeable membranes under a concentration gradient only (simple dialysis). Surprising selectivities were found when the pore sizes of the membrane were adjusted to a critical point. This method, like the Swedish work, is still under active development, but it holds promise of revealing considerable information about the shape and conformational stability of large molecules when the results are interpreted together with the type of results obtainable with the ultracentrifuge.

Certainly one of the areas in biochemistry in which great advances have been made is that of isolation and purification of the components of complex biological materials. Before 1940 the purity and actual molecular weight of nearly all solutes with molecular weights greater than a few hundred was in grave doubt. Now it is possible to fractionate and purify substances 100 times as large with about the same confidence as with the smaller molecules before 1940. The very complex mixtures resulting from degradation of the large molecules can also be fractionated successfully today. The main techniques which make this possible are chromatography, electrophoresis, countercurrent distribution and the ultracentrifuge.

THE FUTURE

One might logically inquire as to the direction future separation research in biochemistry is likely to take. It seems safe to say that further attempts will be made to improve the over-all selectivity and at the same time provide a more gentle environment. The achievement of higher selectivity has shown that often a slight transformation hitherto overlooked may occur during fractionation with even the most gentle methods. It is likely that more attention will be given to the separation of the organized entities just above the size of single molecules such as viruses. The ultracentrifuge and electrophoresis have already been found useful in this problem. Recently liquid-liquid systems have been developed by Albertsson at Uppsala which are so gentle that even intact viruses may be separated. Remarkable selectivities in a single stage are often found. Countercurrent distribution may increase the selectivity still further for those systems showing less selectivity. Separation research is likely to be important for a long time to come.
DAVID PORTRAIT OF THE LAVOISIERS
IN THE LIBRARY OF WELCH HALL

The magnificent portrait of the Lavoisiers which has hung in the Library of Welch Hall for 30 years has become so familiar a part of the daily scene that no doubt many fail even to see it or, seeing it, fail to appreciate its great worth. Yet since Mr. John D. Rockefeller, Jr., gave the painting to the institute it has been sought for loan by great museums and governments abroad, copied in oil for other institutions, reproduced in numerous books on science and art, and copied hundreds of times for various other uses throughout the world.

That the Institute possesses this much-sought treasure of art and the history of science is characteristic of Mr. Rockefeller's benefactions. The way in which he explored the matter before making a gift of the painting is equally characteristic of his wisdom in wishing always to make accessible the best while leaving freedom of choice to those about him. In a letter to Dr. Flexner on April 30, 1927, Mr. Rockefeller wrote in part: "Since you and [the Trustees] of the Institute feel so confident that the possession by the Institute and its display there of the David portrait of Lavoisier and his wife are both appropriate and altogether to be desired, I am happy to present the portrait to the Institute. Because we dislike to bind those who come after by fixed and hard agreements ... it is my desire to have the picture belong to the Institute, to be used, enjoyed, and if that should ever seem wise, disposed of by the Institute as the judgment of the ... Trustees may from time to time dictate."

The painting is treasured, not only because it was painted by Jacques Louis David in 1788 at the very peak of his career, but because it is the only authentic likeness of its subject, Antoine Lavoisier. Lavoisier, the distinguished French chemist, was also a financial speculator and a man of aristocratic tastes. In 1769 he acquired a post as Farmer-General, and later as a wealthy aristocrat he was able to commission David, the leading painter of his day, to paint the portrait.

The Lavoisiers were a devoted couple, and their pose together in David's portrait, surrounded by chemical apparatus, is not altogether artistic fancy. Madame Lavoisier served as her husband's laboratory assistant. She was also a portrait painter herself, as well as an expert engraver. She engraved the illustrations for her husband's "Treatise on Chemistry," and she executed a portrait of Benjamin Franklin for which he praised her warmly. In 1794, as a result of a decree of the French Revolution against all Farmer-Generals, this remarkable man who revolutionized chemistry was sentenced to death by the guillotine in spite of his philanthropies, his learning, his appointment to the Constituent Assembly in 1789 and his appointment as Commissioner of the Treasury in 1791. David fared better. Joining the revolution, he became a member of the governing body of France and its leading painter. Fortunately, Madame Lavoisier escaped her husband's fate and in 1805 she married the physicist, Count Rumford, though they separated soon after.

Mr. John D. Rockefeller, Jr., purchased the Lavoisier portrait in 1925, and in the Fall of that year he arranged a private showing at the Institute. The painting was then hung at the Metropolitan Museum on loan. In 1926 the design of Welch Hall
was undertaken, and from the beginning thought was given to providing a place in the new building, either in the library or in the dining room, where the portrait might be hung. The architect and those responsible for the design decided upon the north end of the main reading room of the library where the painting hangs today.

Since 1927, when Mr. Rockefeller made a gift of the painting to the Institute, it has repeatedly been sought for exhibition, both here and abroad. It has actually been removed, however, only three times. The first occasion was the exhibition of Masterpieces of Art at the New York World's Fair in 1940. When the organizers of the Fair appealed for help in view of the virtual impossibility of obtaining paintings from abroad because of the war, the Trustees relaxed their strict policy against lending the portrait. It was also the war which resulted in the painting's second absence for it was placed in a vault for the duration. The Trustees again relented, to honor the bicentennial of David's birth, and the painting was exhibited during the summer of 1948 at the Musée de l'Orangerie des Tuileries in Paris.

Once thereafter the painting left Welch Hall, but only to be moved into an improvised studio at the Institute where a full-size copy in oil was painted by Mr. Fred Wright. That painting is now the central ornament of the Lavoisier Library at the DuPont Company's research laboratories in Wilmington, Delaware. This, incidentally, was the second time the painting had been copied in oil. In 1934 a small copy was made for the Laboratories of Physiological Chemistry at Yale University.

Photographs and reproductions of the painting have appeared throughout the world. It even appeared (on its side) in the New York Daily Mirror as it was leaving the New York World's Fair. A full color reproduction was published recently in the Metropolitan Museum of Art's Miniature Album. The latest case in which permission to reproduce the portrait has been sought was for Gerald Holton's Foundations of Modern Physical Science.

Sigma Xi Chapter Elects Honorary Members

The Rockefeller Institute Chapter of the Society of Sigma Xi announced the election of three honorary members, the first to be elected since this category of member was created last Spring. Honorary members are, Drs. John H. Northrop and Carl TenBroeck, members emeriti of the Institute, and Dr. Ernest W. Smillie, Assistant Business Manager until his retirement two years ago.

Executive Editor Joins Cytology Journal Staff

Dr. Raymond B. Griffiths will join the staff of the Journal of Biophysical and Biochemical Cytology in December as Executive Editor. Dr. Griffiths, most recently Editorial Director with the American Cancer Society, received the Ph.D. degree in biology from Princeton in 1940 and an M.D. degree from Northwestern University in 1946.

Dubos Chairs Dartmouth Great Issues Convocation

Professor René J. Dubos was Chairman of a Convocation on the Great Issues of Conscience in Modern Medicine attended by more than 2000 at Dartmouth College, September 8, 9 and 10. In his opening address Professor Dubos stated that ethical and social problems arising from the advances of modern medicine have become so complex that their solution must rest with the whole of society, not with medical scientists alone.

The Convocation was attended not only by scientists including such distinguished men as George Kistiakowsky, Ralph Gerard, Herman J. Muller, and Sir George Pickering, but also Brock Chisholm, Aldous Huxley, Sir Charles P. Snow, and other men of law, medicine, philosophy, literature, science.

Lancefield Honored by Whitney Foundation

Professor Rebecca C. Lancefield received the third T. Dukett Jones Memorial Award of the Helen Hay Whitney Foundation on October 8, 1960. The award, in the amount of $6500, was conferred for "her long and continuing studies which are so largely responsible for the present knowledge of the biology of hemolytic streptococci." The citation and presentation were made by Professor Maclyn McCarty at a dinner in honor of Dr. Lancefield at the Princeton Inn held during the Helen Hay Whitney Foundation's third annual meeting of its research fellows and established investigators.

Dr. Lancefield's research has made important contributions to understanding streptococcal infections and their two most important sequelae: rheumatic fever and acute glomerulonephritis.

FIFTY YEARS AGO AT THE ROCKEFELLER INSTITUTE

Advances in Biological Chemistry

In his Obituary Notice of Simon Flexner written for the Royal Society, Peyton Rous records that "wherever Flexner asked in New York about a chemist for the Institute all answered, 'Whatever you do, don't get Levene.'" Flexner boldly ignored this advice and appointed the Russian P. A. T. Levene, then at the Pathological Institute of the New York State Hospital. Levene assembled a number of able young associates including Walter A. Jacobs and Donald D. Van Slyke, now Members Emeriti. With this group he began a structural analysis of nucleic acids and nucleoproteins which led to a discovery of far-reaching importance, the identification of ribose as the carbohydrate in certain nucleic acids.

By 1910 this work was becoming known abroad and justified Flexner's perception and courage. Emil Abderhalden, a famous German biochemist, wrote to Dr. Flexner in August 1910: "The greatest joy during the past few months has come to me over the wonderful works of Levene, Jacobs, and Van Slyke on nucleic acids. Such a great result of systematic work in so short a time has seldom occurred."
**Academic Honors**

**DETELV W. BRONK**  
Sc.D., University of London

**RENE J. DUBOS**  
D.Sc., University of Brazil

**Academic Appointment**

**ROBERT L. SCHOENFELD**  
Adjunct Professor, Polytechnic Institute of Brooklyn, New York

**Lectures, Conferences and Symposia**

**EDWARD H. AHERNS, JR.**  
Participant, International Symposium on Glyceride Physiology and Biochemistry, sponsored by Centre National de la Recherche Scientifique, Marseille

**CARL BERKLEY**  
Participant, Third International Conference on Medical Electronics, London

**DETELV W. BRONK**  
Opening Address, National Academy of Sciences Transportation Study  
Dedication Address, Marine Biological Laboratory new Research Building

**MERRILL W. CHASE**  
Lecture, Department of Pathology, Cornell University Medical College

**GEORGE W. CORNER**  
Participant, Opening by Queen Elizabeth II of new buildings of the Royal College of Obstetricians and Gynaecologists, London  
Participant, Symposium on Endocrine Control of Labor, Lund, Sweden  
Theme Address, International Conference on Congenital Malformations, National Foundation, London

**LYMAN C. CRAIG**  
Lecturer, National Science Foundation Summer Conference for College Teachers, Purdue University

**ARPAD I. CSAPO**  
Participant, International Symposium on Endocrine Control of Labor, Lund, Sweden

**RENE J. DUBOS**  
Dedication Address, University of Kentucky Medical Center  
Chairman, Convocation on the Great Issues of Conscience in Modern Medicine, Dartmouth College

**RICHARD M. FRANKLIN**  
Summer Course, Long Island Biological Association, Cold Spring Harbor, New York

**WALther F. GöEBEL**  
Participant, International Colloquium on the Biochemistry of Sugars, Gif-sur-Yvette, France  
Lecture, Wander Forschungsinstitut, Freiburg, Germany

**MARGERIS A. JESAITIS**  
Participant, Gordon Research Conference on Proteins and Nucleic Acids

**DANIEL E. KOSHLAND, JR.**  
Participant, Symposium on Reaction Mechanisms, Princeton University

**FRITZ A. LIPMANN**  
General President and participant, Symposium on Protein Biosynthesis, Wassenaar, Netherlands

**KARL MARAMOROSCH**  
Lecture, United Nations Hour, Philippine Radio, Manila  
Lecture, The Weizmann Institute of Science and Institute for Biological Research, Rehovoth, Israel  
Participant, XIIth International Congress of Entomology, Vienna

**MACLYN MCCARTY**  
Participant, International Colloquium on the Biochemistry of Sugars, Gif-sur-Yvette, France  
Participant, Symposium on Immunochemical Approaches to Problems in Microbiology, Institute of Microbiology, Rutgers

**S. WILLIAM PELLETIER**  
Participant, International Union of Pure and Applied Chemistry Symposium on Natural Products, Melbourne, Australia  
Lecture, Presidency College, Madras, India  
Lecture, The Weizmann Institute of Science, Rehovoth, Israel

**GERTRUDE E. PERLMANN**  
Lectures, The Weizmann Institute of Science, Rehovoth, Israel  
Lecture, Hebrew University, Jerusalem  
Lecture, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science, Prague  
Participant, Symposium on Macromolecular Structure and Biological Function, Stockholm

**KEITH R. PORTER**  
Participant, European Regional Conference of Electron Microscopy, Delft  
Participant, Xth Congress of the International Society for Cell Biology, Paris  
Chairman and Lecturer, Session on Microsomes and Protein Synthesis, IUB/IUBS International Symposium on Biological Structure and Function, Stockholm

**HOWARD RASMUSSEN**  
Invited Speaker, First International Congress of Endocrinology, Copenhagen  
Participant, The Laurentian Hormone Conference  
Participant, Symposium on Proteins, Brookhaven National Laboratory  
Lecture, Massachusetts Institute of Technology  
Lecture, University of Alabama Medical School, Birmingham

**MARIA A. RUDZINsKA**  
Participant, 5th International Congress of Gerontology, San Francisco

**RICHARD E. SHOPE**  
Participant, Gordon Research Conference on Cancer  
Address, Conference on Zoonoses, University of Illinois
PHILIP SIEKEVITZ
Participant, Symposium on Membrane Transport and Metabolism, Prague
Participant, Symposium on Protein Biosynthesis, Amsterdam
Participant, Symposium on Biological Structure and Function, Stockholm
Lecture, Xth Congress of the International Society for Cell Biology, Paris

EDWARD L. TATUM
Participant, International Conference on Congenital Malformations, London

A. CECIL TAYLOR
Lecture, Second International Course on Lyophilization, Lyon, France
Participant, Symposium on Cell Movement and Cell Locomotion, Society of Cell Biology, Leiden, Holland

WILLIAM TRAGER
Discussion Leader, Conference on Obligate Parasitism, Monticello, Illinois

PAUL A. WEISS
Moderator, International Conference on Congenital Malformations, London

CURTIS A. WILLIAMS, JR.
Lecture, Mexican Society of Biochemistry

HENRY N. WOOD
Participant, Symposium on Activation of Metabolic Systems During Development, AIBS Meetings, Stillwater, Oklahoma

VLADIMIR K. ZWORYKIN
Participant, Third International Conference on Medical Electronics, London

Society Elections

CARL BERKLEY
Member, Executive Committee, International Federation for Medical Electronics

DETLIEW W. BRONK
Honorary Member, The Royal Institution

KARL MARAMOROSCH
Official Representative, American Phytopathological Society and Entomological Society of America, Xth International Congress of Entomology, Vienna
Member, Committee on Archives, American Phytopathological Society

WILLIAM TRAGER
President, Society of Protozoologists

VLADIMIR K. ZWORYKIN
President, International Federation for Medical Electronics

Other Appointments and Distinctions

DETLIEW W. BRONK
Vice President, 9th International Congress of Linguistics

GEORGE W. CORNER
Executive Officer, American Philosophical Society

DANIEL E. KOSHLAND, JR.
Member, Biochemistry Study Section, Public Health Service

KARL MARAMOROSCH
Certificate of Appreciation, Government of the Philippines

PEYTON ROUS
Chairman, Board of Scientific Consultants, Sloan-Kettering Institute for Cancer Research

RICHARD E. SHOPE
Vice Chairman, Research Advisory Council, American Cancer Society
Member, Board of Medical Education and Research, University of Pennsylvania

EDWARD L. TATUM
Member, Board of Scientific Consultants, Sloan-Kettering Institute for Cancer Research

PAUL A. WEISS
President, Xth International Congress of Cell Biology
Member, International Editorial Board, Medical Abstracts
Member, Advisory Board, Theoretical Biology

New Appointments to the Faculty

MURIEL M. ANDREWS, Research Associate with Professor Archibald. Formerly member of scientific staff of the Medical Research Council, Chemotherapeutic Research Unit, Glasgow.

RUTH ARNON, Research Associate with Associate Professor Perlmann. On leave from The Weizmann Institute of Science, Rehovoth, Israel.

ALBERT A. BENEDICT, Guest Investigator with Associate Professor Chase. On leave as Associate Professor, Department of Bacteriology, from the University of Kansas.

CARLOS E. BIRO, Guest Investigator with Professor Lipmann; Helen Hay Whitney Foundation Fellow. Formerly Research Fellow, University of Pennsylvania, and Resident in Allergy and Immunology at University of Pennsylvania Hospital.

FILIPPO CAVALLERO, Research Associate with Professor Northrop. Formerly Assistant at the Institute of Microbiology, University of Genoa.

FRANCOIS CHAPEVILLE, Guest Investigator with Professor Lipmann; Helen Hay Whitney Foundation Fellow. Formerly Research Fellow, French Atomic Energy Commission.

HARTWIG CLEVE, Research Associate and Assistant Physician with Associate Professor Bearn. Formerly Research Associate, Pasteur Institute, Paris.

SAMUEL DALES, Research Associate with Professor Porter. Formerly Postdoctoral Fellow of the National Cancer Institute of Canada at Ontario Cancer Institute.

EDWARD DE MAEYER, Research Associate with Dr. Rous, Member Emeritus. Formerly Research Fellow, Harvard Medical School and Children's Hospital in Boston.

LUDWIG EDELSTEIN, Professor of Philosophy. Formerly Professor of Humanistic Studies at The Johns Hopkins University.
Departures from the Faculty

OLGA STEIN, Guest Investigator with Associate Professor Dan Moore. On leave as Research Associate, Department of Experimental Medicine and Cancer Research, Hebrew University, Hadassah Medical School, Jerusalem.

YEHEZKIEL STEIN, Guest Investigator and Assistant Physician with Professor Ahrens; Fellow, U. S. Public Health Service Training Program. On leave as Physician, Hadassah University Hospital and Lecturer in Medicine, Hebrew University, Hadassah Medical School.

PRZEMYSLAW SZAFLRANSKI, Research Associate with Professor Lipmann. Formerly Assistant Professor, Institute of Biochemistry, Polish Academy of Sciences.

HIROSHI TAKEDA, Research Associate with Associate Professor Csapo. Instructor in the Department of Physiology, School of Medicine, Kyushu University, Japan.

COURTNEY T. WEMYSS, JR., Guest Investigator with Assistant Professor Williams. Associate Professor of Biology, Hofstra College.

NEW APPOINTMENTS continued from page eleven

JACK C. GEER, Guest Investigator with Associate Professor Dan Moore; U. S. Public Health Service Senior Research Fellow. On leave as Assistant Professor of Pathology, Louisiana State University School of Medicine.

AHARON GIBOR, Research Associate with Associate Professor Granick. Formerly Senior Plant Physiologist, Resources Research Institute, Washington.

EICHI HASEGAWA, Research Associate with Professor Lipmann; formerly Guest Investigator.

MITSUO IZAWA, Research Associate with Professor Mirsky. Formerly graduate student at Nagoya University, Japan, where he received the degree of Doctor of Philosophy.

KENNETH M. JONES, Research Associate with Professor Woolley. Formerly Guinness Research Fellow, Department of Biochemistry, Oxford University.

DAVID KESSLER, Guest Investigator with Professor Archibald. Fourth year medical student at New York University College of Medicine.

PETER J. LACHMANN, Guest Investigator and Assistant Physician with Professor Kunkel; Fellow, U. S. Public Health Service Training Program. Formerly John Lucas Walker student in the Department of Pathology, Cambridge University.

FRANCIS L. LAMBERT, Jacques Loeb Associate in Marine Biology. On leave as Assistant Professor of Biology, Union College, Schenectady.

BYRON LANE, Research Associate with Professor Lipmann. Recently associated with Department of Biochemistry, University of California School of Medicine, San Francisco.

THOMAS A. LANGAN, Guest Investigator with Professor Lipmann; National Science Foundation Postdoctoral Fellow. Formerly Postdoctoral Fellow, Medical Nobel Institute, Stockholm.

TAPANI LUUKKAINEN, Guest Investigator with Associate Professor Csapo; Foreign Scientist Research Fellow of the National Institutes of Health. Assistant Physician, Women's Clinic, University of Helsinki.

YOSHIHIDE MANO, Guest Investigator with Professor Lipmann; Rockefeller Foundation Fellow. On leave as Lecturer, Faculty of Medicine, University of Tokyo.

THEODORE F. MEDREK, Research Associate with Professor Lancefield. Candidate for Degree of Doctor of Philosophy at Cambridge University.

P. RAJAGOPALAN, Research Associate with Professor Craig. Formerly Research Associate, New York University School of Medicine.

ERWIN RUDE, Research Associate with Professor Goebel. Formerly graduate student at University of Freiburg from which he has just received the degree of Doctor of Philosophy.

DEREK G. SMYTH, Research Associate with Professor Stein. Formerly Postdoctoral Fellow in Biochemistry, Yale University School of Medicine.

LEONARD B. SPECTOR, Assistant Professor associated with Professor Lipmann. Formerly Associate Biochemist, Massachusetts General Hospital, Boston.
MAN-CHIANG NIU, Assistant Professor, left his laboratory at the Institute to become Associate Professor in the Department of Biology, Temple University, Philadelphia.

JOHN K. ROSE, Guest Investigator associated with Professor McCarty and Assistant Physician to the Hospital, left September 15 to go to the Bacteriology Department of the Karolinska Institute, Stockholm.

SEIYO SANO, Research Associate with Associate Professor Granick, left at the end of June to work with Dr. C. Rimington in the Department of Chemical Pathology, University College Hospital Medical School, London.

New Grants and Contracts
From the United States Public Health Service:
To Dr. Ahrens for his study of the effect of dietary fat on tissue fatty acid turnover $53,857
To Dr. Archibald for a study of enzymes of osseous and cartilaginous tissues $25,929
For continuation of Dr. Archibald's work on post-menopausal osteoporosis $21,476
To Dr. Armin Braun for his research on factors influencing recovery of plant tumor cells $12,701
To Dr. Chase for his study of inhibition of delayed-type hypersensitivity $14,432
For Dr. Chase's work on genetic selection for experimental drug allergy $23,000
To Dr. Craig, for correlation of membrane diffusion and sedimentation data $96,140
To Dr. Dole for his research on the metabolic activity of non-esterified fatty acids $24,645
To Dr. Edelman for study of interaction and energy transfer in biological systems $22,322
To Dr. Franzl for investigation of the nature of the antigenic stimulus $47,395
To Dr. Granick for his study of the enzymes of porphyrin biosynthesis $9,750
To Dr. Hartline, for continuation of his research on the electrical activity of single receptors and neurones of the eye $46,411
To Dr. James Hirsch for his study of bacterial mechanisms of phagocytic cells $9,890
For Dr. Lancefield's study of cellular antigens of streptococci $15,927
To Dr. Lloyd, for a program of investigations in neuroglialular physiology $22,867
To Dr. Lynch for her study of the genetics of tuberculosis in mice $18,740
For Dr. McCarty's studies on the cell surface of Group A streptococci $27,335
To Dr. Palade for investigation of transport mechanisms in the wall of blood capillaries $50,071
To Dr. Pelletier for his work on the chemistry of the aconitum and delphinium alkaloids $19,890
To Dr. Rasmussen for his isolation and characterization of parathyroid hormone $13,052
To Dr. Siekevitz for the continuation of his work on biochemical properties of microsomal membranes and ribonucleo-protein particles $18,805
For Dr. Tatum's study of biochemical genetics of microorganisms $14,145
To Dr. Trager for a project of research into biochemical changes accompanying malarial infection $8,980
To Dr. Woolley for his work on the isolation and structure of growth promoting peptides $19,813
For Dr. Woolley's study of the mechanism of action of serotonin and related hormones $13,476
For Dr. Zworykin's work on electronic data processing in hematology $29,900

ALUMNI

WILLIAM F. ARNDT, JR., PH.D., 1959. Research Associate, Department of Bacteriology, Georgetown University Medical School.

JOHN J. CABRA, PH.D., 1960. Postdoctoral Fellow, Department of Biophysics, The Weizmann Institute of Science.

GERALD M. EDELMAN, PH.D., 1960. Assistant Professor and Assistant Dean of Graduate Studies, The Rockefeller Institute.

CHANDLER M. FULTON, PH.D., 1960. Instructor, Department of Biology, Brandeis University.

IRVING H. GOLDBERG, PH.D., 1960. Assistant Professor, Department of Medicine and Biochemistry, University of Chicago.

JOHNS W. HOPKINS III, PH.D., 1960. Instructor, Department of Biology, Harvard University.

SANFORD A. LACKS, PH.D., 1960. Instructor, Department of Biology, Harvard University.


SUYDAM OSTERHOUT, PH.D., 1959. Associate, Department of Medicine, and Instructor, Department of Bacteriology, Duke University School of Medicine.

LEE D. PEACHEY, PH.D., 1959. Assistant Professor, Department of Zoology, Columbia University.

MALCOLM L. PETERSON, PH.D., 1960. Assistant Professor of Medicine, Washington University.

HOWARD RAMMUSSEN, PH.D., 1959. Assistant Professor and Associate Physician to the Hospital, The Rockefeller Institute.

MARTIN A. RIZACK, PH.D., 1960. Assistant Professor and Associate Physician to the Hospital, The Rockefeller Institute.

HAROLD J. SIMON, PH.D., 1959. Assistant Professor of Medicine and Medical Microbiology, Stanford University School of Medicine.