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THE COMMON GROUND OF THE CHEMIST AND BIOLOGIST[1]

THE highest type of mind is forever following backward searching for the simple units from which the universe has been built, formulating laws and running forward in thought on the basis of these laws toward the ultimate. The chemist began with the four elements of Empedocles and Aristotle—air, fire, earth and water; then through the long history of the atoms to Dalton's law and Mendelejeff's table; on to ions, electrons and quantums. The biologist began centuries later with the recognition of the cell in the work of Schleiden and Schwann and has progressed from protoplasm to nucleus, to chromosomes, to electrolytes—and here meets the chemist in his search.

For the chemist, however, the *atom* is still the stable unit, just as for the biologist the *cell* is the stable unit. In spite of all the division and subdivision these two working units become only the more veritable, the atom in chemical reactions, the cell in life or living chemistry: each student moves backwards and forwards from these in his analysis and in his synthesis. The common ground then is—how do the atoms of our elements enter into the life of our cells?

We are continuously faced in cell analysis with the fact that all we find in our cells are the same elements that we find in nature outside of these cells. As Paul wrote in his I Corinthians (chap. 15, verse 47) "The first man is of the earth, earthy: the second man is the Lord from heaven." There is only the factor of life to separate the two.

The two sciences, chemistry and biology, have grown so rapidly in the last fifty years that one can scarcely find a master of both. This is true of knowledge in general. It far outstrips the individual mind. As Pope put it even two centuries ago:

> One science only will one genius fit,
> So vast is Art; so narrow human Wit.

The biologist has two great fields to study: first, the unicellular organisms which can be obtained in pure culture in which each cell is a duplicate of all other cells in the mass of culture; and, second, those carefully balanced congregations of cells of many varieties living in communities and constituting animals and plants.

In our disease problems the unicellular organisms often inhabit and live in symbiosis, or with destruc-

[1] From the Hygienic Laboratory, Washington, D. C.

tive parasitism, in certain cells of animals or plants. Tuberculosis is a disease of this type. The tubercle bacillus, a race of several strains, may live in its early life in the animal simply as a symbiete or again as a very destructive parasite within the monocyte, one variety of the cells of that animal. The latter is an ameboid cell known to have several chemical functions of its own in the body.

Thanks to the work of Koch and later to the work of Frouin and others we are able to separate and grow almost any strain of tubercle bacillus on synthetic media, and, based on these two methods, we have the essentials for the chemist—pure controllable substances with which to work.

The whole living bacillus growing in the animal is followed by a series of changes known as cell multiplication, cloudy swelling, caseation and softening. So far as our observation is concerned these changes are morphological, but surely ultimately chemical. The dead whole bacillus also will produce the same changes. It is, therefore, reasonable to suppose that some fraction of the dead bacillus has the same property as the living bacillus and that this fraction can be separated from the dead organism. More than that, such fractions once obtained can be systematically studied for their biological action in the normal and tuberculous animal, for their composition and possible synthesis, and finally for their chemical antagonists.

After years of work the U. S. Public Health Service and the National Tuberculosis Association have developed a plan for definite, systematic study of tuberculosis on this basis. For, as Schiller said, "the head must plan with care and thought before the hand can execute." The work outlined in this plan of careful research, however, can not possibly be done by one man.

You will appreciate that for the animal body or the plant body some of the most active biological principles are present in minute amounts. Yet how powerful is the influence of these principles on the whole intact body of minimal quantity after isolation in relative purity! In the animal body the smallest glands often prepare the most powerful units: for example, adrenalin, pituitrin or insulin. The same is apparently true of the bacteria. The most active substances in them are present only in traces. Therefore, it is necessary to grow these bacteria in enormous quantities for each chemical partition to secure enough of one fraction for biological study. To obtain a sufficiently large quantity of bacteria, a special equipment is required. This is found only in the plants of the manufacturing pharmacist who builds his plant for large production. For careful analytical work the production there, however, must be done under the strictest supervision of the chemist who is chosen to make the analysis. To begin with the glassware and chemicals for the medium, including the water for solution, must remain constants throughout the whole procedure and the only variant should be the strain or race of bacillus used.

After these requirements have been fulfilled and a single strain of the organism chosen and planted on the chosen medium there follows the period of growth at a constant temperature and moisture. With an organism such as the tubercle bacillus, which requires four to six weeks for maturity, the whole quantity is harvested. The bacteria then are separated from the medium and the two resulting fractions, bacteria and media, pass on their way to chemists skilled in special technique for analysis. The procedure for each fraction often requires special methods of separation: for example, in the search for easily oxidized chemical groups the whole process must be followed in an atmosphere of carbon dioxide or nitrogen.

The specialized chemist having supervised the harvesting begins his peculiar analysis. After he isolates the fraction which especially concerns him at the moment he passes it through the committee[2] to the biologist specially concerned with its reaction in the normal and tuberculous animal.

It is superfluous to-day to emphasize the differentiation that has come in this field of technique and method. Among the biologists we have many specialists as we have among the chemists. We have those who study the influence of a special chemical unit in the normal animal body; those who follow it in the pathological body; those who study its effect on the cells, and those who are skilled in its influence on the body fluids. We have those who dig deeper and follow its influence in the almost fathomless depths of oxidation and reduction both *in vivo* and *in vitro*. For this reason in the isolation of a new chemical unit a sufficient amount must be isolated to retain a sample for later comparisons and to distribute the necessary quantities for each special biological study.

The result of the biologists' work is the guide to the chemists in further purification and fractionation; for, where a specific biological fraction remains intact there will the chemist follow further in his partition.

It will be seen from this brief outline that the great essential is the definition of the problem. The whole problem must be analyzed into its various phases and each phase placed in the hands of the

[2] Committee on Medical Research, National Tuberculosis Association; see SCIENCE, 64: 265, 1926; Tr. Nat. Tuberc. Assoc., p. 74, 1926.

student best fitted for its study and possible clarification. Each step in the process must be recorded with the same patient care that the good researcher follows in recording the methods and observations of his work. This necessary record involves with so large a program a machinery of its own, for, on the foundation of the records, is built both the ability to reproduce and to correlate the results. The task of synthesizing the knowledge gained is a very difficult one, for men's thoughts are much harder to unite than simple chemical units. To accomplish this, however, we have adopted a system of juries—each jury being carefully chosen for its ability for criticism and constructive suggestion. Before a chosen jury the researchers discuss their work and the committee and student are often safely guided by the uniform advice of such a group of critics.

It must be borne in mind, however, that to secure the best minds for such a duty the problem must be of such importance in human welfare that all are willing to help.

The final synthesis of the knowledge gained will be perhaps more difficult, but it is hoped that it will enable us to control this sickness in a much more effective way than we are able to do at the present time.

Up to to-day in the tuberculosis work there have been isolated some nine or ten fractions from the human tubercle bacillus which have definite physiological action. I will mention only two in illustration—a protein and a phosphatide fraction.

The *protein fraction* belongs to square R of the Johnson plan for analysis.[3] The whole living bacilli separated by filtration from the synthetic medium on which they were grown at constant temperature were washed, dried at 37° C., ground in a ball mill and plasmolyzed with ether. The residue, insoluble in ether, was desiccated in vacuum at the same temperature and extracted with cold water. This extract was clarified by the supercentrifuge and filtered through a Berkefeld filter of known porosity. These steps follow the processes A, B, C, E, G, R and S in Johnson's chart. The cold water extract contains the albumin globulins, nucleic acids and non-protein amino acids and some unknown substances. It is found, however, to possess all the properties of crude tuberculin in the proportion of ten milligrams to one cubic centimeter of the Bureau of Animal Industry crude tuberculin.

Crude tuberculin has not changed in the last twenty-five years. It is a dirty compound of many substances concentrated from a boiled beef broth medium and bacilli and yet it is used as the basis for destroying millions of dollars worth of cattle annually and for the diagnosis of human tuberculosis. It is effective, but it would be infinitely more effective if purified to the point of knowing the chemical composition of its potent fraction, of having this in the condition of procuring known dilutions and of being able to compare it with the same fraction of other well-known strains of bacilli, such as avian, bovine and lepra.

The newly isolated tuberculin fraction distributed to biologists has been found to have very specific action in the normal and tuberculous animal. It produces typical skin and tissue reactions in the tuberculous animal,[4] cellular reactions,[5] individual cell reaction differing in type, whether introduced by the micropippet within the cell or allowed to bathe the environment of the cell,[6] antigenic properties in studies of serum.[7] On the basis of these studies further work on isolation and purification is clearly indicated.

In this relation it is significant to record that the sulphur mechanism of the human tubercle bacillus is peculiar. This knowledge is in large measure due to the refined technique of the secretary of this division, Dr. Sullivan. Dr. Sullivan, Dr. Smith and the author, working in the Hygienic Laboratory,[8] have shown that the sulphur complex in H37, the type of culture used in this preliminary work, has apparently a peculiar sulphur mechanism. For both the chemist and the biologist to-day the operating mechanism of such elements as sulphur, phosphorus, boron, silicon, iron, hold apparently the key to many of our difficult problems of oxidation and reduction in living chemistry.

Perhaps more significant even than the protein fractions are the *fatty acid* series. Anderson,[9] using the same base line organism, H37, by a process described in his paper in a constant atmosphere of carbon dioxide, isolated certain *phosphatide* fractions. These, under the study of Sabin and Doan[5] and Reznikoff and Chambers,[10] have so far been found to possess characteristics peculiar to them. Especially is this true of the stimulating action possessed by the phosphatide fractions for the rapid multiplication of the special cell of the body which responds to infec-

[3] *Am. Rev. Tuberc.*, 14: 169, 1926.

[4] Smith, Maurice I., unpublished; Long, Esmond R., unpublished.

[5] Sabin and Doan, *J. Experimental Medicine*, 46: 645, 1927.

[6] Chambers and Reznikoff (in press).

[7] Pinner, Max, Public Health Reports, Bulletin No. 57, p. 20, 1926.

[8] White, Smith and Sullivan, *American Review of Tuberculosis*, 13: 77, 1926.

[9] Anderson, R. J., *J. Biological Chemistry*, 74: 537, 1927.

[10] Chambers and Reznikoff, Tr. Nat. Tuberc. Assoc. (in press).

tion with the living tubercle bacillus. The *phosphatide fraction* introduced into the peritoneum produces a veritable tumor of monocytes, the one variety of mesoblast cells that constitutes the tubercle. This function has later been shown to be possessed, after a finer fractionation, by the *saturated fatty acid* of this phosphatide portion of the tubercle bacillus, H37.

The proportions in which these fractions are obtained are indicated in the several papers referred to, but their significance has a direct bearing on another feature of the same combined study being carried out by Dr. DuBois (not yet published) and his associates at the laboratory of the Russell Sage Foundation of Cornell University Medical School in which it is found that phosphorus is an element of the most vital importance in the whole tubercle process. How far this will lead us in lipin metabolism, carbohydrate metabolism, living cell function and primary life functions no one to-day can predict.

In this program of research there are now cooperating three government divisions, eight universities, four endowed laboratories, two manufacturing chemical plants, seven volunteer health bodies and two semi-governmental bodies.

Scientific research has always gained and suffered from the belief that isolation and untrammeled labor is the birthright of its devotees. This came from a day when fear and accusations of witchcraft followed the pursuit of knowledge and from a time when the well-equipped brain was rare. To-day conditions are vastly different. Our equipment of real students is very large, but in the United States our physical equipment of laboratories and apparatus is far greater than our capacity to use them well. Then there is now a sort of hysterical worship of research, and much passes for research that is only mimicry. Still, there is no nation with our potential for the purest type of research, if we only realize our opportunity.

For those interested in research in its truest sense I can speak with some experience. I have yet to meet one, no matter how abstract his problem, who is not happy to give of his time and his knowledge for the advancement of human welfare if he can see the direct application of his special knowledge in the solution of a problem of general welfare and importance to mankind. Not only that, he is also the most honest member of society in his cooperation and seldom loses sight of his high purpose in his selfish desires. They all seem imbued with the thought of Lord Kelvin, who said "There can not be a greater mistake than looking superciliously upon practical applications of science. The life and soul of science is its practical application."

Therefore, I wish to state again that the carefully defined *problem* is the essential thing, and its analysis and apportionment to the proper student is the road to success. There is little need for new institutes of research with their need of robbing other institutes to man them. It is better to apportion the task to a man where he is and to strengthen him in the environment of his growth. Problems must be viewed in their relation to the nation and to the welfare of man and the more widespread our centers of study the more powerful our reserves, for there are always the oncoming students from which we must draw our future strength.

From the example I have given you of research in tuberculosis you will appreciate that the method of systematic study of pure bacteria on synthetic media, with chemist and biologist working in conjunction, is applicable to many of our disease conditions in plant and animal; but far wider is its application to problems of nutrition and bacterial processes in industry and to the problems of life itself. From a study of the simple units of life we shall probably grow into a knowledge of the congregate groups of life undreamed-of before. This is the more likely since there is no living plant or animal that exists free from myriads of these unicellular organisms performing probably the most necessary functions for existence.

Finally, the greatest difficulty comes, as I have noted above, in the correlation and final synthesis of the knowledge gained. One always has to remember the remark of Jean Jacques Rousseau, "I know only that truth is in the things and not in the mind which judges them; and that the less I put my mind in my judgments about them the more sure am I to come near the truth," and so careful record, rechecks by repetition of the things we record, are necessary before we commence synthesis, lest mixing an impure observation we pollute our conclusion. Time alone can tell the success that will follow our efforts, but already the results have abundantly justified the method. Our endeavor should always be

> To search through all
> And reach the law within the law.
>
> —*Tennyson.*

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THE MECHANICS OF MATERIALS—A CONTRIBUTION FROM APPLIED SCIENCE TO PURE SCIENCE

During recent years we engineers have been frequently reminded of our debt to "pure" science and