SCIENTIFIC SECTION

PREPARATION FOR PROGRESS.*

BY GEORGE D. BEAL.[1]

There has never been a time when public attention was so largely focused upon the subject of research as at the present. One of the most potent sales arguments used by advertisers, stock salesmen and other promoters is that underlying the proposition or the product offered for sale is a history of intensive research. Furthermore, financiers regard a program for future research as a guarantee of the soundness of an investment, and as insurance that new developments or proposed processes will be of more than ephemeral value.

The American wood distillation industry a few years ago was regarded as one most soundly entrenched. Because of the excise taxes upon grain alcohol even in pre-prohibition days, its use as a solvent in many industries was hampered. Accordingly wood alcohol, or methanol, in spite of the unfavorable physiological properties of its vapor, acquired an entrée into many operations. The legalization of denaturing processes for ethyl alcohol, instead of cutting into this market, furnished an additional outlet for methanol as one of the most desirable denaturants. The development of phenol resins, of the types of Bakelite, Redmanol and Condensite, further stimulated this industry by creating a new and large market for formaldehyde, obtained by the oxidation of methanol.

About three years ago the chemical interests of this country were stirred by the announcement that synthetic methanol was being imported into the United States, and at a price of one-half to one-third of that previously commanded by the wood distiller's product. This news was disastrous for those who had been contentedly drawing dividends from our American hard woods. To the American chemical industry as a whole, the effects were not so serious, for among the users of these products were certain far-sighted individuals who had realized the uncertain character of their source of supply. As a result of a research program, wisely indulged in, a long established industry may be left with nothing to show for years of work but a useless group of buildings and retorts.

Some theoretical economists have acquired the idea that research is a stabilizer of business. Research on the contrary has proved to be an upsetter of business as far as many organizations have been concerned. A fortunate research development may cause control to pass over night, as it were, and antiquate what may until that time have been regarded as one of the most modern of processes. The wise industrial organization is the one which insures its future progress through a research branch proportioned to the balance of the organization, and which ever has in mind the state of the business to-morrow. Such a group will prove the soundness of the doctrine of "eternal vigilance."

Research is variously spoken of as "pure" or "applied," the latter designation being reserved for that to which is ordinarily assigned a direct dollars and cents

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valuation, or which is defined in another way as "industrial" research. It is difficult for one to find any basis for this arbitrary division. An appraisal of the fields of investigation in the sciences, mathematical, physical or biological, will fail to show wherein the pure research has been lacking in its practical application to human comfort, luxury or welfare. The pure science of yesterday is the applied science of to-day. The metaphysicians and the alchemists of the later middle ages laid the foundations for the physics and chemistry of modern times. The iatrochemists, boldly asserting the connection between vital activity and chemical reaction, were the predecessors of the biochemists who have given us such agents as adrenalin, thyroxin and insulin.

There is really no aristocracy of research based upon lofty reasoning. Faraday, asked by a parliamentary commission regarding the value of his researches into electricity, replied, "some day you can tax it." The seemingly crude inventions of Morse, Bell, Brush and Edison have been brought to their modern perfection by the theoretical studies of Steinmetz, Langmuir and Pupin. And yet there have been no more important contributions to pure science than the results of these same investigators.

A prophet is not without honor save in his own country. Josiha Willard Gibbs, as a professor of mathematics in Yale University, contributed a series of papers to the Connecticut Academy of Sciences, dealing with certain mathematical relationships between series of systems having components in common, though in possibly different states of dispersion. The importance of these relationships was recognized by Europeans before they attracted the attention of the author's own fellow-countrymen. In fact, it was only after the death of Willard Gibbs that American chemists saw in his so-called "phase rule" one of the most important single contributions to theoretical chemistry that has ever been made.

By means of this law, originally regarded by many as only of interest in mathematical theory, many of the developments of the steel industry have been brought about. This is true especially of the steels which are adapted for special purposes, prepared on prescription, one might say. This applies also to ceramic materials, cements and other building materials, and to many other chemical processes, organic or inorganic. Without it, these industries might have failed in some of their most successful accomplishments, and their developments would certainly not be at all understood.

The contributions of Pasteur to organic chemistry, to biology, to agriculture and to medicine mingled most happily the theoretical and practical aspects of the research method. The demonstration of the relation of crystalline forms and spatial relations to optical rotation, the discovery of the cause and the method of control of silk worm diseases, thus saving to France an important industry, the control of alcoholic fermentations, all of these were steps, theoretical or practical, leading up to the masterpiece, one of the greatest contributions to the happiness of every human being, the real foundation of the germ theory of disease. The most romantic story of science is found in Vallery-Radot's "Life of Pasteur," which deserves thoughtful reading by all seeking to progress through research.

Research is at times based upon the wish for improvement, and at other times upon the necessity therefore. The present development of the automotive industry owes its existence to both. The desire to eliminate the inconvenience and danger of hand cranking brought about mechanical starting, which was only rendered possible by the development of a compact, fool-proof electrical system, and particularly of a storage battery of the highest efficiency yet obtainable.

Foreign control of rubber production, coupled with the enormous consumption of rubber in tires, stimulated research upon rubber as never before. One of the most important contributions in this field was the knowledge that rubber, once used, was not junk. Now reclaimed rubber is used in combination with virgin rubber in exactly the same manner as shoddy wool is mixed with virgin wool, and steel scrap used open hearth steel. The material which was formerly used only in compounding the cheapest of rubber goods is now the material that has broken the back of the foreign rubber monopoly, and is holding the price of tires within the range of our pocketbooks until our own interests, rudely awakened from their state of complacency, shall be able to meet the demand through American-owned plantation rubber.

It is dangerous business to enjoy too complete a monopoly of the supply of any material as necessary to welfare, comfort or luxury as rubber has come to be. Restriction of production and other artificial methods of maintaining unfairly high prices are, in this era, only an invitation to the research laboratory to discover either a reclamation method or a substitute. Substitutes are not necessarily inferior replacements, and once a product is replaced, even in part, by another material of equal or superior quality, its preëminence is gone, and a world market may be lost.

To continue with the automotive industry for but a moment, there is one development which should be mentioned as a triumph of organic chemistry. Automobile fabrication is rapid, but automobile finishing, with our former knowledge of paints and varnishes, was slow. Cars dragging through the finishing processes represented entirely too large a volume of frozen assets. Intensive study of rapidly drying lacquer finishes produced results just at the correct time to enable American manufacturers to convert their large plants which had been erected and equipped for the manufacture of nitro-cotton and the solvents necessary for its conversion into smokeless powder.

The lacquering process as at first applied was in essence a matter of celluloid plating. Solvents required for this purpose were few in number and generally of the acetone or simple ester type. Experience soon demonstrated, however, that such finishes lacked body, covering power and texture, and that they did not have the proper resistance to weathering and temperature changes, particularly those involving thermal expansion of the metallic under-body. These qualities have been secured by the addition of gums, some of natural origin, and others, so-called ester gums and synthetic resins, products of the laboratory whereby the nature of native vegetable and fossil vegetable resins have been imitated. Practical experience again has shown that solvent mixtures, rather than simple solvents, must be used, and that low, medium and high boiling fractions of the solvent mixtures are needed, controlling covering power, initial set, final drying and necessary plasticity of the lacquer film.

Important corporations have grown up in the solvent trade. Natural gas, containing hydrocarbons of the olefin series, is the basis for one group of materials. Ethylene glycol, a little sister of glycerin, has grown in four years from a laboratory curiosity to an importance in industry equal to that of glycerin. Not only has it important qualities itself, but its ester and ether combinations have solvent properties of an importance equal to that of the glycol. And with these developments, other uses have also come. As an antifreeze compound, it has been found to be unexcelled. With a molecular weight of 62 as against 92 for glycerin, one gallon will have the same effect in reducing the freezing point of a water solution as one and one-half gallons of glycerin. Low toxicity and volatility and lack of corrosive effect cause it to compare favorably with glycerin, in addition to the greater activity above mentioned. Another important industrial use came from the discovery that nitrated it had, molecule for molecule, practically the same explosive force as nitro-glycerin, with the result that an increased number of sticks of dynamite per pound could be obtained.

Biological reactions are becoming of increasing importance in the field of solvent manufacture. With the knowledge gained from the study of the alcoholic fermentation of sugar as a starting point, the action of other enzymes from yeasts, molds and bacteria upon sugars and starches has been studied. Thus in particular normal butyl and iso-amyl alcohol are being obtained from corn starch, adding not only these alcohols but their esters and other derivatives to the list of commercial solvents and organic chemical reagents.

Some scattered attempts have been made to adapt these new solvents to pharmaceutical practice. Long and intensive research in this field will undoubtedly prove fruitful. It may seem that ethyl alcohol was intended by Providence as the ideal solvent for pharmaceutical and chemical operations because of its wide range of solvent power, its degree of miscibility and its low absolute toxicity. Possibly, however, there has been too much blind acceptance thereof. Pharmacists should study in detail the solvent powers of the other alcohols, determine in what way their physical properties lend themselves to pharmaceutical operations, investigate all of their chemical and biological effects, including possible decomposing actions upon plant educts, preservative effect against fermentative and putrefactive changes and, most important of all, their own effects upon the animal organism.

Changing economic, political and moral policies stimulate research along new lines. With the onset of national prohibition, the open manufacture of alcoholic beverages became a thing of the past. The study of fermentation, for the production of new industrial solvents, has facilitated the conversion of certain distilleries into scientific biological workshops, as previously mentioned. Various breweries have taken up the production of sugars of commercial importance, notably maltose and various types of malt syrups. This, in turn, has stimulated research in baking. The growth of yeast during the leavening of dough has been dependent in the past partly upon the conversion of starch to soluble fermentable sugars by amylolytic enzymes accompanying the zymase of yeast. Now by the use of malt syrup in a dough mixture the time of fermentation is notably shortened by furnishing the yeast with a readily available carbohydrate upon which it may feed.

The fermentation of sugar by yeast is in part an oxidative process, the oxygen required being obtained from the atmosphere. It has been found that certain oxidizing agents, notable bromates and iodates, used in small amounts, have a remarkably stimulating effect upon the yeast cells. Again, in the growth of yeast, protein is formed, the nitrogen for this purpose being obtained from proteins in the flour. As this involves an initial decomposition of the protein a search was made for a more readily available form of nitrogen. This was finally obtained by providing, with the oxidizing agent, an ammonium salt, ammonium chloride proving suitable.

Without going into a discussion of the merits of the case, we may mention briefly the "yeast for health" campaign. Interest in vitaminous diets and theories regarding the control of intestinal flora by implantation came to the rescue of distillers having an over supply of yeast. Investigation showed that fresh yeast had qualities which were beneficial to some persons, and probably had ill effects for none. Here was a fortunate combination which appealed most strongly to the writer of advertising copy, with the result that the manufacturer in question need worry no longer over the disposition of his production of yeast.

Especially significant work is in progress on the physiological effects of ultraviolet light. Curiously or not, certain striking relationships have been discovered between the effects of these wave-lengths of light and the effects of certain vitamines. The irradiation, by ultraviolet light, of various oils duplicates almost entirely in the oils the properties of the fat-soluble vitamines in which these oils have been found deficient. Even more striking results have been obtained by the irradiation of certain wax alcohols of the sterol type, which are found in traces in the unsaponifiable fraction of many fats, in the secretions of various glands and in the blood stream.

Others have reasoned, since ultraviolet light indirectly has this beneficial effect upon health, why should we not pay more attention to its direct action. A part of the activity in this direction is of course explained by the readiness with which the public makes a fad of any new scientific development of unusual interest. However, some questions of real importance have been brought out as a result. First is the relationship of glass to ultraviolet radiation. Ordinary glass is practically opaque to ultraviolet light, while fused quartz, transparent to ordinary rays, is almost completely transparent to these other rays as well. Transparent quartz being out of the question for windows, research attention has been directed to the preparation of glasses or substitutes therefore which have, as far as possible, the property of ultraviolet transmission. Certain of the organic substitutes, based upon celluloids or resins, have desirable transmissibility, but fail in other respects. Lacking a vitreous hardness, they scratch easily, they may fail under a heavy load, and more serious yet, because of the well-known effect of actinic rays on organic compounds, they gradually undergo some decomposition, with darkening, which lessens their transmission of visible rays.

Certain true glasses have been developed which have a very fair degree of transmission, as compared with quartz. These, at the present time, command high prices, and some, unfortunately, do not justify the claims which have been made for them. A new difficulty has also come to light. Many, upon prolonged solarization, lose fifty per cent or more of their transmitting power in the vital range. The effect is more pronounced in the light of a mercury vapor lamp, because of the greater percentage of short wave-lengths, but is quite appreciable with sunlight. This is only a surface effect, and the transmissibility is at times restored by heating, while the opaque portion may also be removed by grinding and repolishing. By a systematic investigation of the silicates, however, it seems quite likely that glasses having relatively high transmission and stabilized against solarization will be developed, and that the physical properties of these glasses will lend themselves to manufacture by the modern processes.

This general field is not only of interest to those concerned with the public health, which group includes all of us, but is of particular interest to pharmacists for other and more personal reasons. Both ultraviolet light, which of course covers a broad range of wave-lengths, and polarized light, have a decided chemical effect upon many medicinal agents. As a result we must, in our study of glass containers, take into consideration not only the effect of the constituents of the glass upon the medicating agent, but also the necessity for using such compositions of glass as will preserve galenicals by preventing the passage of actinic wave-lengths.

Research upon glass which will conduct vital rays is again focussing attention upon a problem which interested the people some fifteen years ago. Even the most actinic of glasses will conduct only such vital rays as actually reach the incident surface. Loading the air of cities with smoke has been looked upon as an economic crime, because of the loss of fuel power represented by the smoke and because of the grime added generally to buildings, their contents and clothing. The annual fall of soot in a city such as Pittsburgh is estimated at 1400 tons per square mile per year. It was formerly stated by authorities during certain earlier investigations that soot, while dirty, was not unwholesome. We know now that soot, in the form of smoke, does cut off vital rays, and as such is unwholesome. Elimination of smoke will speed the time when rickety children and pneumonia-stricken adults will be a very occasional specimen.

In conclusion, it might be well to speak of some problems in pharmacy where research will undoubtedly be well rewarded. When fluidextracts, freshly prepared, are stored in well-filled, closely stoppered containers in cool, dark places, precipitation very frequently takes place. These conditions are not things which, while not actually set down by the hand of God, just exist, or come into being. Having in mind the fact that many of the plant educts are colloids, and that these, with many other principles, are sensitive to very slight changes in environment, an investigation of the tinctures and fluidextracts of the U. S. P. along physico-chemical lines is indicated. By determining the actual physical characteristics of the inerts which are of colloidal nature, it should be possible to rapidly age galenicals by adjustment of the hydrogen-ion concentration immediately to the isoelectric point for these substances, favoring thereby the rapid formation of precipitates which will be easily and readily removed. At the same time hydrolyses, either as the result of enzyme action or acidity, and whether desirable or not, will be more readily induced or prevented. Therefore our galencial preparations should be the next field for physico-chemical study.

Another investigation which is warranted, and which has been carried on haphazardly except by a few, is upon the subject of extraction. Friedrich Rochleder, of Prague, in 1858 called attention to the fact that as there were different types of cell individuals in each drug, we might expect to find as many different types of cell constituents. These, being chemically different, might reasonably be expected to undergo reactions when brought together outside of the cell, *i. e.*, when dissolved by a menstruum. These reactions, he pointed out, are governed, of course, by the nature of the menstruum. On these grounds, it seems, there is ample cause for a systematic investigation of extraction methods, all the more so because of the present restrictions upon the use of that which we have come to regard as the ideal, if not the universal, solvent.

A third type of investigation desirable, I believe, is upon the state of aggregation of galenicals. We have learned that in many cases the unwise or improper application of heat, especially with our lack of knowledge of the effect of p_H variation, brings about serious decompositions. These effects have been recognized in other industrial operations with organic fluids of similar nature, with the result that by the judicious application of heat practically complete dehydrations can be effected without in any way affecting the other characteristics of the material.

This operation is well known in the case of milk, is applied successfully to other liquids, and it is believed has been attempted with various galenicals commonly prepared by water extraction. The process referred to is that known as spray drying, wherein evaporation of the solvent takes place from the liquid in mist form, and under such conditions that heat contact is short and air is absent. These operations are not feasible for the retail pharmacist, because of the equipment required, but their results, and especially the elimination of alcohol, should be of benefit to him. At least, we should inquire into whether we use liquid extracts because custom so rules, or whether there are other desirable qualities at present only assumed.

The AMERICAN PHARMACEUTICAL ASSOCIATION is preparing a wonderful opportunity for pharmacy in its Headquarters Building. Many things have been said about the purposes of the building, its offices, its museum, its library and its research laboratories. All have their function, and all will be, wisely administered, of the greatest benefit to American Pharmacy. However, with our subject that of Research, we are thinking more of the plans and facilities for such, as they will be governed by the library and laboratories.

In the first we hope to see a national library of pharmacy, where the best of pharmaceutical and related literature of the world will be found. This should be a center where students, not only from all over the country, but from all over the world, will come for the exchange of thoughts and the recording of progress.

In the laboratories we hope to see the most constructive work that pharmacy has witnessed. Such studies should be for the betterment of pharmaceuticals, wherein natural and synthetic products alike will be investigated, and wherein the development of the assay process as a means of regulation will always be of secondary interest. Scientific pharmacy must be constructive, not repressive, and pharmaceutical research will do well to model itself upon the systems that have so well served other industries.

Research is governed in part by systematic plodding, by patiently fitting together the mosaic blocks until the completed picture is on view. It is no less constructively served by imagination, by the ability to always see the final picture, lacking in polished detail, of course, from having viewed the developments as they take form. Both are equally necessary in the execution of the masterpiece, one to plan, the other to patiently complete the details.