are simply trying to get more money for a lot of men who are there now." Well, I was not. I was trying to build up a great Office, or help to. It is a great Office now, but I was trying to improve it, but that is the spirit that Congress displayed. They treated it exactly as if it were any clerkship that was under discussion; and the Office cannot get by it, but men like you can; if you will give the matter sufficient thought, and make up your minds that it is right, and bring influence to bear upon Congress, the matter can be rectified.

The equipment is also insufficient. For example, there is a library of technical books and technical literature. You gentlemen all know that the technical literature of the world is very large, and constantly increasing. Congress allows three thousand dollars a year for the Patent Office to keep up with all the technical literature of all the arts. It ought to be fifty thousand dollars, and it ought to be whatever is necessary beyond that; and yet it was absolutely impossible for me to get one dollar beyond the three thousand dollars a year while I was there. There was a separate set of German patents, two hundred thousand in number, which we wished to bind by classes according to German classification, so that searches might be made through them by the public who are interested. Instead of making a list of all the patents that dealt with electrical motors, for example, and then going through twenty-one hundred volumes to get at them, we wanted to have four or five volumes of electrical motor patents, and so with the other arts. It took me three years to get an appropriation of twenty thousand dollars to bind them, and during that whole time they were tied in bundles, because we did not dare open the bundles for fear numbers would be lost.

There is another matter of great importance. These young men and these older men, the examiners, instead of being obliged to get knowledge from books only, ought to be able to go out and see what the manufacturers are doing in their establishments. They ought to learn the arts as they are actually practiced, so that their judgment would be sound. I sent out as many as I could; I would have sent all of them out from time to time to make investigations if I had been permitted to do so. I could have raised a fund of fifty thousand dollars easily by voluntary subscription from concerns that had applications pending, but sending the young men out by the use of funds raised in that way would have put the Office under obligations, and it would have placed the assistants in positions where they might be open to suspicion and criticism because they had a pleasant trip to Chicago, or St. Louis, or elsewhere; and Mr. Lane, I think properly, said he would not permit it. But here was a fund which I used for that purpose. It was five hundred dollars. There are now four hundred and nineteen in the corps; this sum was about \$1.25 apiece for these men. I tried my best to get Mr. Lane to agree to ask Congress for thirty thousand dollars for that purpose, and he said it was absolutely useless; he would not do it; he knew it would not be granted. But an appropriation like that, properly presented to their congressmen, by people who know the importance of it, might easily be secured.

I wish to speak also of the position of the Office in the governmental system. The Patent Office is a bureau of the Interior Department. When I went into office I did not know Secretary Lane. He sent for me shortly before I was appointed and I then met him for the first time. I formed an intimate friendship with him, our relations were most cordial, and I regard him as a great man, and yet, in spite of that, I am obliged to say after a four years' experience as Commissioner that the Office gains nothing by being a bureau of the Interior Department, and that it is seriously handicapped by the connection. It ought to be an independent office, answerable to nobody but the President and Congress, just as the Agricultural Bureau was before the present Department of Agriculture was created. The reason is that it is one of eight different bureaus, unrelated,

the work in one not similar to the work in another, the needs of one not similar to the needs of another. But, if an attempt is made to increase the salaries in the Patent Office, or to increase the personnel, immediately the question arises, "What about the Land Office? Won't the Commissioner of Pensions want salaries raised?" Thus a comparison is made between the Patent Office and its needs, and the needs or demands of other offices having no relation to it whatsoever. That comparison the Secretary could not fail to make, no matter how well he might understand the conditions in the offices, because he would arouse jealousy. And if he made up his mind that one office needs better salaries than the others, because it is engaged in a higher class of work, and were to pass that recommendation on to Congress, the Congress itself would make the very same comparison and he would not get anywhere.

If the Office were an independent bureau, it could fight its own battles without any such disadvantageous comparisons, and I believe that if that change were made and gentlemen such as you would interest yourselves, and get your local bureaus and your legal departments to interest themselves, in any way you may see fit, in the needs of the Office, we might get the necessary assistance from Congress, and we could build the Office up to the point where it would be, in fact as it should be, the most superb patent office in the world—and its judgments would be far more certain and trustworthy. I think such action would save every year, in the relief of business from the uncertainty of wrongly granted patents, millions of dollars over all that it would cost.

It is constantly said, when the subject of increased appropriations for the Patent Office is raised, that the Office pays its own way. In the last five years it has turned back into the Treasury about one million dollars over the entire appropriation for it, and the building which it occupies was largely built out of surplus which had accumulated in the Treasury from Patent Office fees. But there is no reason why public money should be wasted, no matter where it is drawn from, and the income of the Office is not the measure of its needs, nor of the service it renders to the public. If the Office must be kept self-sustaining, it is an easy matter to increase the fees for patents, and I think that the business interests of the country would stand it. I do not think that is important. The important thing is that the needs of the Office should be intelligently studied by Congress, and when ascertained they should be provided for, without any regard to whether the Office costs one million dollars over what it receives in fees or not.

As I have said, the Office is absolutely unable to help itself. Anybody who as Commissioner starts in to get something for the Office is immediately accused of trying to get something for himself. But intelligent bodies, and influential bodies such as this, can influence and should influence Congress. Here is a field for constructive work, where the results will be to the interest and advantage of all of us. I trust that you will make it a matter of serious thought and concerted action. I thank you very much for the opportunity to bring the subject to your attention.

160 BROADWAY
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THE PHARMACEUTICAL CHEMIST AND THE SCOPE OF HIS WORK¹

By FRANK O. TAYLOR

Each of us is prone to magnify the importance of that particular branch of chemistry in which he is actively engaged, so perhaps I may be pardoned for what, to many of you, may seem a biased and erroneous opinion, or evidence of a dense ignorance concerning other fields of chemical endeavor, when I say that I believe no field of chemistry is of greater scope or more varied character than that of pharmaceutical chemistry. And

¹ Address before the Detroit Section of the American Chemical Society, January 16, 1919.

yet, I hope to give you such reasons for the faith that is in me that, if not fully agreeing, you may at least recognize a measure of justice in this claim and have a better understanding of the reasons back of it.

Pharmacy has to do with the compounding and dispensing of medicinal products and is most frequently thought of in the very narrow sense of mere mixing together of various individual substances, or the extraction of drugs with the proper solvents and dispensing in suitable form for use, the whole process involving only a very moderate degree of chemical knowledge.

It is to this extremely limited scope that the term "pharmaceutical chemistry" is all too frequently confined. I wish to direct your attention, however, to pharmaceutical chemistry in its broadest sense as being the chemistry of medicinal substances, pertaining to their origin, preparation, dispensing, and effects, and the remarkable and varied ramifications of these subdivisions. Far from being a limited and somewhat isolated division of chemical science there is, I believe, no other branch of chemistry that needs for the solution of its diverse problems so many otherwise distantly related portions of chemical knowledge.

The metallurgist, who from the iron ore of northern Michigan produces by reactions in blast furnace and Bessemer converter, iron and steel of varied composition; or from the scarlet cinnabar of southern California wins the mercury for use in physical instruments and amalgams; or from the ores of Missouri obtains in giant smelters the zinc for innumerable industrial uses, may often forget that iron is intimately associated with vital processes as in the red blood corpuscles and plays an important rôle as a curative agent; that the mercury salts are used in combating some of the most deadly and insidious diseases, or as highly effective germicides and antiseptics; that the zinc in one form may be intensely escharotic and in another may be the basis of mild and healing ointments of wide use.

The agricultural chemist, who makes two blades of grass or ears of wheat grow where only one grew before, may also develop digitalis or belladonna or hydrastis or cannabis in greater abundance or of higher potency.

The glass chemist may have his skill taxed to produce ampoules of glass free from excess alkali and easily workable in a blow-pipe flame or free from soluble iron salts that rapidly decompose such substances as hydrogen peroxide or adrenalin.

The coal-tar industry contributes from its cruder products the so-called "dead oils" as a basis for disinfectants of considerable potency; pure cresylic acids, to make antiseptics for surgical or general use; and phenol for use as such or in various compounds such as phenyl salicylate (salol) or the phenolsulfonates of zinc and calcium.

The dye chemist furnishes for medicinal use such things as phenolphthalein, so widely employed as a laxative; phenolsulfonaphthalein as a test for activity of the kidneys; scarlet-red for stimulating healthy and rapid growth of skin over surfaces denuded by burns or other accidents; acriflavine, but recently recommended in solution as a surgical dressing for extensive wounds, to be used in a manner similar to the sodium hypochlorite solution, known as Dakin's Solution, being destructive to bacteria in high dilution and apparently harmless to living tissues; malachite green proposed and widely experimented with for the same purposes; or methylene blue, so extensively used in certain types of urethritis.

Physical chemistry lends its aid in the production of such remedial agents as colloidal solutions of silver, mercury, sulfur, etc., obtained either by direct electrolytic action or in the presence of proteins, and adds to our slowly acquired empirical knowledge of emulsions an understanding of the reasons why, and the conditions under which the best results may be obtained.

Radiochemistry finds its pharmaceutical application in the use of ultra-violet rays for sterilizing water or various solutions, or the employment of radium salts and radioactive solutions in the treatment of various diseases, notably cancer.

The petroleum industry gives to the pharmaceutical chemist solid and liquid petrolatum of varying degrees of purity ranging from cruder petrolatum for veterinary ointments to the most highly purified liquid oil intended for human use as an intestinal lubricant, and paraffin as an ingredient of ointments or base of surgical dressings for application to extensive superficial wounds or burns.

The consideration of oils and fats, both vegetable and animal, applied one way or another to medicinal use, opens up another wide range through which our chemical investigations may lead us, including such things as the familiar castor and cod-liver oils; the intensely active cathartic, croton oil; that relic of old-time pharmacy, citrine ointment, made from lard, nitric acid, and mercury by a process similar to the familiar elaidin test for olive oil; the comparatively little known chaumooogra oil, which has been used with some measure of success in the treatment of leprosy in India and our own southern states, and was some years ago the subject of extensive chemical investigation; oil of chenopodium or American wormseed, used first as an ordinary anthelmintic and more recently as a highly successful agent in destroying the hookworm, the bane of existence to so many thousands of people in warmer climates; and a great array of other fixed and volatile oils. And these things suggest at once a multitude of gums and resins of more or less interest medicinally, but which we will pass by.

In that limitless domain to which we refer in general as "organic chemistry," including therein those things particularly connected with physiological and biological chemistry, there exists a tremendous number of substances of great interest to the pharmaceutical chemist and there lie before him untouched fields for investigation that almost stagger the imagination. In this category appear substances of natural origin and of synthetic production—the alkaloids of aconite, opium, belladonna, stramonium, ergot, nux vomica; the comparatively innocuous glucosides of cascara or the highly toxic ones from strophanthus and digitalis; the digestive ferments such as pepsin, diastase, pancreatin; the endocrine glands and their derivatives, such as the suprarenal whence comes adrenalin, so marvelously potent in its effects on the blood pressure that one-twentieth of a milligram will show pronounced effects on a man; the thyroid, from which but recently an active iodine-bearing substance has been isolated; the pituitary gland of inestimable value in obstetrical practice and in the treatment of surgical shock; and others still less understood. Then we have that formidable and continually increasing array of synthetic substances, some of which, like acetylsalicylic acid (aspirin), or acetphenetidin (phenacetin), are part of the equipment of almost every household medicine cabinet, and others that you and I never heard of and probably never will.

These brief citations give some idea of the infinite variety of work presented to the chemist who deals with medicinal products but do not give any adequate conception of the great number of unsolved and abstruse problems which still lie before us and to which I will refer presently. You can at least see that the chemical knowledge of the man who has to do with pharmaceutical problems in their fullness must be extensive and that he will certainly have no monotonous existence.

Specific examples of some of the interesting questions that arise, which in some instances are very easy of solution and in other cases give us problems that promise to remain unsolved for an indefinite time in the future, will serve to give a more concrete conception of the requirements of the man who has to do with the development and production of medicinal substances in their widest scope.

Remember also that sometimes the solution of the simplest problems may involve the saving of hundreds or even thousands of dollars to the manufacturer who is producing medicinal substances on a very large scale. A question that may be of no particular moment when the quantity involved is only a few

ounces becomes of intensest interest when it may mean the difference between entire loss or the satisfactory distribution of hundreds of pounds or thousands of pints of medicinal compounds of properly high quality.

Take so simple a thing as the almost universally used mild tonic, Beef, Iron, and Wine. Why should continual trouble be experienced with the development of pressure in the bottles, the evolution apparently of carbon dioxide, and continual breaking of packages and consequent loss? "Fermentation, of course," will be your first answer, and the fact that carbon dioxide is evolved seems excellent evidence that this supposition is correct, but fermentation is not likely to occur in a product that contains 18 per cent alcohol, and furthermore, this explanation is impossible when the trouble continues after the product has been thoroughly sterilized in an autoclave and proven sterile by bacteriological tests. The solution when found is very simple and is that due to the action of the actinic rays of light the ferric citrate in the slightly acid solution is reduced to a ferrous salt with liberation of carbon dioxide. If a ferrous salt is originally used, there is no such trouble, and if the ferric salt is employed, the product must be carefully protected from bright light, especially direct sunlight.

Take another case: Why should breakage in ampoules containing cacodylates be very much greater than with any other of the solutions usually prepared in this form? There was no pressure developed and no decomposition of the solutions could be detected. The fact that the breakage occurred largely at the extreme end of the capillary tip, where the ampoule is finally sealed in a blowpipe flame, gave a clue, and the solution of the problem was that traces of the cacodylate solution adhering to the glass were decomposed just at the tip where the flame is used for sealing; the arsenic combined with the glass, forming a ring of arsenical glass, which is entirely different in coefficient of expansion from the remainder of the ampoule and very brittle, hence comparatively slight changes in temperature frequently caused the tip to snap off. On putting into effect means for carefully washing out the tip of the ampoule with distilled water before sealing, the trouble disappeared.

Again, in the manufacture of antiseptic tablets containing corrosive sublimate, some suitable diluent is used that will be completely soluble in water and if possible aid in the solution of the mercuric chloride without reacting with it chemically; for this purpose ammonium chloride or citric acid is commonly used. In some few instances both together have been employed. To prevent the material sticking to the dies on a tablet machine, some lubricant is necessary, and as a comparatively soluble substance, antiseptic in itself, boric acid is often employed in a case of this kind. A quantity of tablets began to evolve considerable amounts of hydrochloric acid gas, sufficient to rapidly attack tinned-iron containers shortly after they were made. It was found that the boric acid used as a lubricant, in the presence of citric acid, reacted upon the ammonium chloride with the evolution of hydrochloric acid. The omission of either the boric or citric acid immediately remedied the trouble.

Another problem that seemed on the face of it so simple that it was really no problem at all was the obtaining of material such as sodium chloride, milk sugar, and alkaloidal salts of such purity that they would give a solution in distilled water *completely free* from insoluble floating particles. I would not go so far as to say that it cannot be done; I think that conditions are conceivable under which it might be accomplished; but I have never seen it done, and upon a commercial scale it has, so far as I know, never been accomplished. You must remember, of course, that the floating particles thus referred to are minute, though easily visible to the naked eye. Some years ago it was desired to prepare C. P. sodium chloride in crystalline form suitable for redissolving in distilled water for intravenous injection. No sodium chloride of sufficient purity was obtainable

on the market, and in attempting to make a quantity, it was found that during evaporation of a carefully purified solution, the sodium chloride would attack tinned copper, aluminum, and several grades of special enameled iron to such an extent that the crystals when redissolved in water would show a weighable amount of insoluble matter. The best thing available was one particular grade of resistant enamel, though had it been available on a commercial scale, a pure silver pan would probably have been just as effective.

When it comes to milk sugar or alkaloidal salts, it would seem that all that is necessary is to carefully filter the solution and evaporate, to obtain a product that will redissolve in distilled water without showing any signs of floating particles. When you come, however, to critically examining such solutions, you will discover that the first thing is to get distilled water which under the most rigid tests will show no tiny particles floating in it. So far I have never seen any of the above mentioned substances or distilled water that would show absolutely no signs of tiny floating particles when viewed by the naked eye against a dark background under an electric light. Remember, though, that one liter or even five liters of such a solution will leave no weighable residue on a filter paper; in fact, unless the filter is hard and smooth it is very likely to make the solution worse.

After problems connected with the manufacture are solved, there come up also numerous questions in regard to containers used. For example, glass that contains any trace of alkali soluble in water (and this is the rule rather than the exception) cannot be used in making ampoules containing very delicate substances, for strychnine alkaloid will be precipitated from its salts and a delicate organic preparation like adrenalin will be quite rapidly destroyed. Containers made from coke tin plate cannot be used to hold materials that might slowly attack iron, whereas charcoal tin plate is satisfactory, the difference being that the former has occasional exceedingly minute holes through the tin, while in the latter the tin coating is uniform and unbroken.

When we come to the consideration of the more difficult problems connected with medicinal substances and their development we reach a vast unknown region that has been but most imperfectly explored. We speak glibly oftentimes of relationship between chemical constitution and physiological action, but our actual and definite knowledge of the relationship is at the best extremely limited. We have acquired what seems like a considerable amount of empirical understanding that certain effects are in some way associated with certain combinations of elements or radicals, but we may draw a hasty conclusion merely to find that there are numerous exceptions to our supposed "law." For example, pyrocatechol (ortho-dihydroxy-benzene) is more poisonous than its monomethyl derivative, guaiacol, which in turn is more potent than the dimethyl derivative, veratrol. Apparently we are on the road to prove that alkylation of a hydroxy group in aromatic compounds decreases the toxicity, but presently we find that from resorcinol, which is meta-dihydroxy-benzene, we obtain a dimethyl derivative that is very much more toxic than the parent substance and our interesting theory suffers a rude shock.

If now we cautiously advance along some of the blazed trails in the jungle of organic compounds, hoping fervently that harsh and unrelenting facts will not pounce upon and tear to pieces some of our nicely domesticated pet theories, we discover some rather astonishing things. Take adrenalin, which, as derived from its natural source, is levorotatory. When prepared synthetically it is racemic and much less active than the naturally occurring form. Further investigation shows that the dextro-rotatory form is only about one-twelfth as powerful in increasing the blood pressure as the levorotatory form. The peculiar effect of the atropine group of alkaloids in dilating the pupil of the eye is about fifteen times as great in levohyoscyamine as in its

stereoisomer. Atropine and cocaine are not widely different chemically, both being derivatives of the nucleus tropine, but while some points of likeness may be found in their physiological action, there are many and pronounced differences, for instance, cocaine is a powerful local anesthetic, while atropine is devoid of this effect. Again, cocaine is methyl-benzoyl-ecgonine and ecgonine has no local anesthetic properties, while neither benzoyl-ecgonine nor ecgonine-methyl ester have more than a very slight effect of this kind. And so we go, gradually accumulating a great store of isolated facts and laboriously fitting them together. We are very like the child with a jig-saw picture puzzle: we fit together a few facts here and a few more over there and occasionally have to take apart some which do not fit perfectly, hoping that some day we will get enough of this picture together to find out what it really looks like.

Turning for a moment to other questions, how shall we determine the medicinal activity of aconite preparations? The drug contains one important and highly toxic alkaloid, aconitine, but also varying amounts of related alkaloids which are not only much less toxic but in some cases actually antagonistic in their action to the aconitine. The aconitine itself is very easily affected by heat, especially in the presence of moisture, and decomposes into various other bodies which possess quite different physiological action. One can obtain concordant results on repeated chemical assays, and find that they fail entirely to agree with the physiological activity as determined by tests on animals. Both the physiological test and the chemical assay seem to be affected by the presence of secondary alkaloids. The present situation as regards the determination of the activity of aconitine preparations is in a very unsatisfactory state.

For over 100 years we have known that the most important alkaloid of opium is morphine, but only within the past 10 years have we come to a definite understanding of its chemical constitution, and though at present morphine is worth \$200 per pound, there is no commercially available process for producing it synthetically.

Then there is that class of substances known as enzymes, typified among medicinal agents by pepsin, pancreatin, and diastase. We have for years used these products, particularly pepsin, as an aid to imperfect digestive activity, but do not yet know their exact constitution. Most extensive investigations have been pursued regarding the nature of pepsin, and it has been possible to produce a material under this name of such strength that one part will digest 50,000 parts of coagulated egg albumin, showing a tremendous power of protein digestion. Even here apparently the limit is not reached, and we have not succeeded in isolating any definite substance whose chemical identity we can establish.

Pancreatin is known to be a mixture of several different enzymes, but we are no better acquainted with the constitution of any of them than we are with that of pepsin. Besides these substances there are numerous other enzymes of more or less importance that occur either in vegetable or animal life, and many of which undoubtedly have important rôles to play in connection with vital processes, and as we come to understand them better we may find some of them of great service in dealing with diseases that are now but imperfectly understood.

In investigating enzymes we are struck with the similarity in many respects between catalytic action of these organic substances and those inorganic colloidal solutions of metals that are quite extensively advocated as remedial agents. For instance, both are rendered inactive by boiling and are affected by the reaction of the medium in which they act. The decomposition of hydrogen peroxide by catalase, which reaction may be used for the quantitative determination of this enzyme in the blood or liver, or the similar decomposition by colloidal solution of platinum, both proceed more rapidly in a slightly alkaline medium. The presence of a trace of hydrocyanic acid

acts as a distinct poison, and inhibits the activity both of enzymes and colloidal solutions, though there are some exceptions to this rule. What is the chemical reason back of these resemblances between substances that seem otherwise so dissimilar?

One of the scourges of humanity in Eastern Asia, the Philippines, Borneo, Sumatra, and the Straits Settlement has been a disease known as beri-beri. This through long and laborious investigations was found to be connected with the type of food used, being especially prevalent where polished rice was the main article of diet. It was found that a very remarkable and rapid improvement in the condition of those afflicted with this disease could be produced by extracts from the husks and polishings removed from rice. Continued investigation has led to recognition of certain bodies called "vitamines" present not only in the pericarp of rice but also in other grains, in yeast, and in a number of different plants. The name has been given because it is known that these substances are related to the amines and are so intimately associated with vital processes. They are present in only exceedingly minute amounts and yet their effect is very great. To the presence or absence of the same compounds has been traced the disease quite prevalent in our own southern states, known as "pellagra."

We are just beginning to understand that these vitamins, which all these years we have taken into our systems with our daily food, have in some way a tremendous effect upon our health, but how widely they are distributed or what their chemical constitution is and how they may differ as derived from different sources, and why they are so necessary to our healthful existence, still remains almost a complete mystery. Few, if any, greater fields for chemical investigation of medicinal substances exist at present than that of the vitamins.

Some 400 years ago Paracelsus founded what came to be known as the School of Iatrochemistry, on the assumption that the human body was made up of chemical substances and that illness was caused by chemical changes in the organs and juices of the body, and that to cure these ills chemical compounds must be found that would restore the original healthy condition. This fundamental principle was so obscured by fantastic ideas and was carried to such extremes by overzealous followers that it fell into disrepute and finally disappeared entirely, giving place to a chemistry founded on careful experimentation rather than fanciful theories. Strangely enough we are now returning, but under very different auspices, to something of that older idea. We have come to understand better the limitations of our knowledge and the fact that we must not be too eager to draw conclusions from the isolated facts we know, but as in former days the practice of pharmacy and the art of healing did much to develop chemical knowledge, so to-day must chemistry in its fullest application go far toward improving our means of treatment and control over disease.

PARKE, DAVIS AND COMPANY
DETROIT, MICHIGAN

THE DEOXIDATION OF STEEL BY FERROMANGANESE¹

By ALBX. L. FEILD

In spite of the recent advances in the field of high temperature research, the precise nature of the function which ferromanganese performs in steel manufacture is not yet known with certainty. Owing its discovery to accidental circumstances in the early days of the industry, the addition of a manganese ferro-alloy to molten steel for the purposes of producing a sound product, free from undesirable "blowholes," still remains one of the basic practices in modern steel metallurgy. The question of an adequate supply of manganese ore has been one of the most critical problems of the present war, so that, search where he may, the chemist

¹ Presented before the Division of Industrial Chemists and Chemical Engineers at the 56th Meeting of the American Chemical Society, Cleveland, September 10 to 13, 1918.