observed under the low power of the compound microscope. It will, however, be found that the procedure invariably kills the muscle tissue even before the preparations are ready for observation.

NORTH PACIFIC COLLEGE OF OREGON,
PORTLAND, OREGON.
June 1926.

SOME COLLOIDAL CHEMICAL ASPECTS OF PHARMACOGNOSY.*

BY ANTON HOGSTAD, JR.

Several years ago there appeared in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION an article by one of the younger generation of American pharmacognosists, namely Prof. E. Wirth, which dealt with the subject of Pharmacognosy, Past, Present and Future.

The author at that time called attention to the fact that the phase of chemical Pharmacognosy was being sadly neglected for that of histological work in our colleges of Pharmacy, and that the chemical side of Pharmacognosy was being riddled by others than pharmacognosists.

Let us ask ourselves the question "Wherein lies the value of pharmacognostical training?" Before same can be answered we must bear the thought in mind that those boys and girls who matriculate in our colleges of Pharmacy do so with the thought in mind that some day they hope to become retail pharmacists. The question would then read as follows "Wherein lies the value of a training in Pharmacognosy for the retail pharmacist?"

Pharmacognosy, if separated from the work in Materia Medica proper, should be considered a preparatory course for that phase of Pharmacy that deals with the action and therapeutics of drugs. Therefore, if our colleges of Pharmacy are devoting some 80 per cent of the time allotted to Pharmacognosy in histological work, I feel that we, as pharmacognosists, have failed in our interpretation of the subject as well as in the fulfilment of the obligations placed upon us as pharmacognosists.

There is a great deal more in chemical Pharmacognosy than the mere definition of a constituent, perhaps with mention of its percentage. Over and beyond this type of Pharmacognosy, to which many attach an overabundance of histological work, lies the application of a pharmacognostical knowledge in later life. It is no easy matter to say how much to leave out in the way of this routine phase of Pharmacognosy, but it certainly is apparent that there is more to Pharmacognosy than this 80 per cent of histological work and a mere mention of the constituents of a drug.

Now what has colloidal chemistry to do with this type of discussion and Pharmacognosy in general? To the one who has followed the trend of thought in the realm of colloidal chemistry in relation to medicine, there is a very close relationship as I shall try and point out in the course of this paper.

Before entering upon the discussion of this relationship, I wish hastily to review a few of the underlying principles in colloidal chemistry, which have materially changed my viewpoint of pharmacognosy.

* Read before Chicago Branch A. PH. A., at the 167th meeting, May 17, 1927.

I presume that the majority of those present are fully acquainted with the underlying principles of colloidal chemistry and I shall merely make mention of same from a personal interpretation angle.

The other year it was my privilege to return to the class room and laboratory as a student, entering upon this work with the thought in mind "What have Colloids to do with drug plant constituents?" The work as entered upon was colloidal chemistry from a biochemical viewpoint which is essentially Pharmacognosy, for both deal with the question of the cell and its varied lot of constituents.

Within a short period of time after entering upon this course, we were introduced to the phrase "State of Matter" rather than the "Kind of Matter." The significance of this statement did not make itself apparent to me at first and it was not for some time that I fully comprehended the vast significance of "State of Matter" as compared with "Kind of Matter."

As a pharmacognosist or a pharmaceutical chemist, or whatever I might be termed, my work in the past had dealt entirely with the "Kind of Matter" and not the "State of Matter" so it was quite a difficult problem to shake loose from hide-bound principles and to see the self-same problem in a different light. To-day as I look back over this work in colloidal chemistry, I believe that the interpretation of "State of Matter" has had a greater influence on my present viewpoint of Pharmacognosy than any other one thing as learned throughout that year. To-day the living cell has assumed another aspect—it is still the same old cell but instead of dealing with the cell contents from the routine methods of the past in which "Kind of Matter" played the only and important rôle, there is to-day the interpretation of "State of Matter" as well.

The second underlying factor in colloidal chemistry that also materially aided in the change of thought was that of "Particle Size." It is true as a pharmacist particle size had previously been considered, wherein the question of powdered drugs enter as to whether the powder was a No. 60, 80 or 100 etc. This, however, is far different from particle size in colloidal chemistry, where one deals with particles ranging from 0.001 of a micron to 0.1 of a micron. It is to be readily understood that particle size also played a very important rôle in the proper interpretation of "State of Matter," for the former is but a part of the latter.

The third important underlying principle, and the last one that I shall discuss at this time, concerned itself with that of electrical charges and the word "Adsorption."

As a pharmacognosist of a few years ago, adsorption played a very minor rôle in my studies and research work, but to-day I find myself face to face with the question of adsorption on every hand. No matter what the problem may be, adsorption looms up and must be duly considered at all times, whether it be that of staining of histological sections, study of plant constituents, action of drugs or what not.

There are many other underlying principles which have influenced my work in Pharmacognosy, but these three will suffice for the present. Now let us look into some practical applications of what colloidal chemistry has to offer Pharmacognosy both from the angle of Pharmacognosy as such and from the angle of "Wherein lies the value of a pharmacognostical training for retail pharmacists?"

As previously stated the work of the past dealing with pharmaco-chemistry

dealt chiefly with "Kind of Matter," in which routine methods or modified routine methods of analysis, etc., were conducted upon the drug in question. Let us consider for a moment the question of alkaloids. During my college days I was taught that alkaloids occur in plants associated with some acid, organic or inorganic, or as was told me that narcotine occurs free. Since those days I have taught the same thing that I received in the way of instruction during my college days. But let us pause for a moment and consider whether or not this statement is entirely correct.

What do we actually know about the "State of Matter" within a plant cell? What has literature to offer one in regard to this question as reported at the Colloid Symposiums of which the fifth is about to be held at Ann Arbor, Michigan? Has Pharmacognosy been duly represented at these symposiums through the agency of outstanding papers? To the one who has been in attendance as well as to the one who has attempted to follow colloidal literature, the pharmacognosist as such has fallen far short in representation, in fact it may be said that he has been absent in the entirety. Yet on the other hand we see investigators from all other phases of Science representing textiles, leather, glue, photography, insects and what not, and yet the pharmacognosist possessing one of the most fertile fields of colloidal research has failed to make his appearance. I shall not enter upon a discussion of why this condition exists for it is self-apparent.

Coming back to the question of alkaloids the question comes to mind, "Does morphine represent the action of opium?" From our present knowledge of the constituents of opium we know that it does not, for other alkaloids, such as thebaine, are present which will modify the action of morphine. However, the story does not end there, for our knowledge of the therapeutic action of opium is far from complete and this not only applies to opium but to belladonna, hyoscyamus, in fact, to most of our vegetable Materia Medica.

This question is but one problem for the colloidal chemist working in conjunction with the colloidal medical research worker of the near future. Colloidal chemistry is rapidly changing our viewpoint of medicine, for here again adsorption is playing a very important rôle, as well as "State of Matter" and the other underlying principles of what has been termed "The Twilight Zone."

Colloidal chemistry has a number of working tools to offer the pharmacognosist in the way of colloidal mills, homogenizers, dialyzers, electro-dialyzers, ultramicroscopes, etc.

The four walls surrounding our present work in Pharmacognosy must be removed and in their places we must substitute bonds of applicatorial relationships, not only with the other departments of our own profession but with allied professions as well.

The pharmacognosist should work hand in hand with the colloidal medical man on the question of arterio-sclerosis, which is after all an excellent case of "State of Matter." Digitalis therapy of the future must needs call in both the colloidal pharmacognosist and the colloidal medical man. The sum total of our present knowledge concerning this valuable cardiac stimulant and tonic is, I feel, but a drop in the bucket as compared with that which will be brought to light in the future, through the agency of colloidal applications.

The question of the existence of alkaloids in plants is a problem for the in-

vestigator who is dealing not alone with the "Kind of Matter" but the "State of Matter" as well. Professor Tschirch has offered the suggestion that alkaloids may occur in the form of gluco-tannoid combinations, which would seem to be within all reason considering the general makeup of a cell as we now know it to be.

The thought has often come to mind and no doubt many of you have faced the same query from time to time as to how alkaloids produce their marked physiological actions. Let us follow the course of an alkaloid when administered orally, and ascertain just how little we really do know about those things which came into existence through the work of Derosne, Sertürner and others working in the realm of alkaloidal chemistry.

Quinine on passing to the stomach is, no doubt, changed to the more soluble hydrochloride and possibly some dihydrochloride. But is this all? What effect have foods upon alkaloids? Vegetable matter we know now carries certain electrical charges and in the case of such materials as lettuce, or other greens, there is that of the negative charge. Alkaloids, positive in character, might be quite readily adsorbed by such materials as carry a negative charge. This thought must also be borne in mind in the filtering of alkaloidal materials through filter paper, for filter paper itself carries a negative charge to which would be adsorbed a certain amount of alkaloidal material in the process of filtration. Likewise in the dialysis or electro-dialysis of such materials, the question of the charge of the dialyzing membrane must always be taken into consideration, otherwise negative or erroneous conclusions may be the result of the investigation.

Well we will presume that most of the quinine remains as quinine hydrochloride and is now on the way to the duodenum. But here a noted change must necessarily take place, for as we know the intestinal juices are alkaline in character. Are the alkaloids precipitated from solution? If so, how is it possible for this precipitated alkaloidal material to be absorbed by the intestinal membranes and to find its way into the circulation? Does the electrical charge of the intestinal membranes play any part in the assimilation of such materials as well as in food materials?

Let us pass over this intricate question and note what may or may not happen in the blood stream. Blood as we know is slightly alkaline in character. Is this alkalinity sufficient to throw alkaloids out of solution? Blood cells carry certain electrical charges as can be demonstrated by means of electrophoretic migration. Are alkaloids adsorbed by blood cells? Then there is the question of the serum which no doubt plays a very important rôle when dealing with the question of alkaloids. Beutner and others have shown that certain types of sera will adsorb certain alkaloids while another type of serum will not adsorb the same type of alkaloid. There is then a certain specificity of adsorption of alkaloids by sera, which then would seem to account for the fact that certain animals can tolerate more strychnine or other alkaloids than another type of animal. Wherein does this peculiar adsorption lie? What fraction of the serum adsorbs alkaloids? Colloidal chemistry is beginning to solve many of these intricate problems and another one that needs explanation is how this alkaloidal material produces its action we will say upon the central nervous system. This is again a truly colloidal chemical problem.

You may say that work of this character is not a part of Pharmacognosy and

should not be considered within the sphere of Pharmacognosy. I fail to see how the same can be ignored by the pharmacognosist for he is essentially the one who deals with the constituents of a drug plant and his interpretation ought to prove of great value to the experimental medical man, who does not have the time to devote to this phase of the work.

When discussing a drug in Pharmacognosy, should one stop at a certain point and say that the next phase of the work belongs to another department and thus lose the greatest value of the work for the day, in which the application of the work has been ignored? The value of any type of instruction lies in the application of that knowledge to the daily problems in life and not in the mere facts of the case alone.

From my present particular angle of interest "Origin, Nature, Distribution and Physiological Rôle of Essential Oils" colloidal chemistry has much to offer me as a pharmacognosist, for herein we have an excellent example of "State of Matter" in addition to "Kind of Matter." Take for instance the question of the "Resinogenous Layer" of the morphological doctrine. If essential oils are elaborated through the agency of such a layer, just how is this accomplished? What do we know at present concerning the permeability aspect of this layer as well as of the other membranes concerned? Here again the question of electrical charges no doubt will play a very important rôle and may in part explain many of those things that mystify us at the present time.

Turning to the angle of Pharmacognosy that has to do with histological sectioning and subsequent staining, we find that colloidal chemistry explains a great deal as to why certain parts of a cell are stained by one type of stain, and another by still another stain. We must admit that our present methods of studying plant tissues by the use of dehydrating agents, stains, etc., are very, very, crude indeed and do not give us the true picture of that which we desire to see. The ultraviolet light and quartz glass are now being used and through the agency of these two things as now employed in colloidal chemistry we are noting entirely different pictures concerning the "State of Matter" within a cell. "State of Matter" within a cell cannot be truly pictured by means of powerful dehydrating agents, stains or counter stains. To get the true picture we must go to the living cell, tampering with same as little as possible, and note the condition of the "State of Matter" in the living condition.

Many other applications of the use of the tools of colloidal chemistry in relation to the solution of pharmacognostical problems could be cited, but such is not the purpose of this paper.

Now what has all of this to do with "Wherein lies the value of a training in Pharmacognosy for the retail pharmacist?" Simply this, that the future of medicine is in a large measure dependent upon the endeavors of the colloidal medical man of to-day. Rapid advances are being made in medicine utilizing the principles of colloidal chemistry.

Therefore, let us remove the four walls that now surround our departments of Pharmacognosy and make this work a dynamic part of Materia Medica, so as to give the boy or girl the correct interpretation of Pharmacognosy, so that when the day does arrive that they are face to face with the physicians, they can talk in other terms than transverse sections, powdered drug characteristics, length of bast fibers, size of starch grains, etc.

Let us as pharmacognosists prepare now to show the students the way in which to apply the knowledge as obtained in Pharmacognosy and Materia Medica, besides holding them for a grade in the final examination. May I ask, "Are you teaching the correct interpretation of the Digitalis-Therapy Problem or are you merely having your students prepare elaborate drawings of the glandular and non-glandular hairs on the mid rib and leaf of this plant? Do you merely teach the students the names of the glucosides present, from the angle of the textbook, or do you teach same from the angle of the Digitalis-Therapy Problem?

Do we as pharmacognosists embody the thought in our teaching as has been expressed by Glenn Frank, President of Wisconsin University, as follows:

"I should like to see an educational experiment made in which a good daily newspaper was the only textbook used, with widely informed and alert-minded teachers simply reading over the newspaper with the students, and trying each day to induce the students to fill in the background and to find the meaning of the news. I venture that in four years or less we could produce a more thoroughly educated and more broadly informed type of graduate than by the more or less helter-skelter process of an extreme elective system under which the student may learn a great deal about a great many things without ever relating his knowledge to current human affairs or even seeing present-day society."

In the "daily newspaper" of your Pharmacognosy class, do your students merely read the paper, without filling in the background or relating the information as thus secured to the problems of future life as retail pharmacists?

We have seen Pharmacognosy of the past—we are now experiencing Pharmacognosy of the present—but what of Pharmacognosy of the future? That is your problem—that is my problem—that which I have set forth in this paper partly explains some thoughts that I have in mind as to how I am trying to meet up with Pharmacognosy of the present and the future, in which day by day the student is being shown the why and the wherefore as well as the relation of same to the future problems that are bound to arise for pharmacists of to-morrow.

NEW METHODS FOR THE DETERMINATION OF CINCHOPHEN AND THE CHOICE OF INDICATORS FOR ITS TITRATION.*

BY S. PALKIN.

Previously described methods[1,2] for the determination of cinchophen (2 phenylcinchoninic acid) in medicinal preparations depend on the extraction of the dry powdered material with hot alcohol or similar solvent and titration with standard alkali.

The sparing solubility of crystalline cinchophen in organic solvents in general and in solvents immiscible with water in particular has apparently led to the erroneous conclusion that quantitative extraction from aqueous medium cannot be accomplished.

Although it behaves like a fairly strong acid, forming stable salts with alkalies, cinchophen exhibits only weakly basic properties in aqueous solution. These

* Presented before the Section of Chemistry of Medicinal Products at the Richmond meeting, April 1927.

[1] Rabak, "Ann. Reports, Chem. Lab. Am. Med. Assoc.," 11, 73 (1918).

[2] Rabak, *J. Assoc. Offic. Agri. Chem.*, 7, 32 (1923); THIS JOURNAL, 16, 15 (1927).