The 'Thiosulphate Method' of Measuring the Rate of Oxidation of Iodides: Mr. J. M. Bell.

The method was introduced by Harcourt, using sodium peroxide as oxidizing agent; it is not applicable when chloric acid, chromic acid, or ferric salts are employed. Schükarew's assumptions (*Zeit. Phys. Chem.*, XXXVIII., 357) are not justifiable.

W. Lash Miller,
Secretary pro tem.

PROBLEMS IN THE CHEMISTRY AND TOXICOLOGY OF PLANT SUBSTANCES.*

The organic chemistry of to-day is the chemistry of the approximately 50,000 carbon compounds, enumerated in the recent edition of Beilstein's 'Handbuch der Organischen Chemie.' Most of these compounds are the fruit of research in purely synthetic chemistry, enormously stimulated, as it has been of late, by the growth of new, far-reaching conceptions in physical chemistry, and, especially, by the substantial rewards of the chemical industries which have arisen as a result of these investigations; a considerable number of the compounds enumerated have, however, been isolated from plants. Some of this work of plant investigation has been adequately rewarded, but as a rule it has only awakened a greater esteem for the investigator. The larger returns of synthetic chemistry are still enticing most of our best organic chemists into its fold, but its phenomenal success in producing substances such as urea, sugar and several plant alkaloids and glucosides hitherto known only as the products or educts of life, has stimulated inquiry not only into the chemical nature of cell life, but also into the chemistry of the dead principles that may be isolated from these cells. Mother Nature is, however, a very cunning and crafty chemist, with a keen understanding of all of the requirements of cell growth under astonishingly varied conditions of environment, and especially with an eye for the protection and perpetuation of her multitudinous progeny against the ravages of parasites, or of man and beast, she has built up a very great variety of compounds, the properties and methods of formation of many of which she still holds secret. Many of these compounds, especially those primarily designed for the protection of the plant, react physiologically on diverse forms of animal life, and are, therefore, recognized by the medical fraternity and by chemists as 'active principles.' All which produce disturbances of the normal functions of an animal when introduced into its economy are, according to Hermann's well-known textbook on pharmacology, called poisons.

It is a sad commentary on the present state of our knowledge of plant chemistry that all we know chemically about the active principles of many plants is that the plants themselves are poisonous. Chemistry might be excused for her lack of interest in examining such physiologically-inert bodies as cellulose and chlorophyll, but it would seem that the plant poisons should at once challenge attention simply on account of their great tendency to react chemically, as they do with some one or more of the essential constituents of the animal organism. The dreaded effects upon man of such plants as the 'deadly upas,' the 'deadly manchineel,' or the common 'poison ivy,' deter many chemists from handling them, and, as shown above, there is little inducement financially for one to enter into such investigations, but the chemist's lack of a knowledge of botany is more frequently the controlling factor in this neglect. Many of the most interesting problems of plant poisoning cannot be conceived either by the chemist or by the botanist alone, but one who is

* Address of the retiring president of the Chemical Society of Washington, April 10, 1902.

constantly looking at these problems from both points of view could not well be thrown into intimate touch with the subject long before many interesting problems would be presented to him for solution. When once conceived these problems are readily susceptible of treatment, either by the chemist or the physiologist alone, or by one or both of them in conjunction with the botanist, the biologist or the pharmacologist. It was with the object of interesting you, as chemists, in this line of work that I was induced to select it as the subject of my discourse on this occasion. No more interesting and self-sufficient life-work could possibly be suggested to a young student starting on his college career than the investigation of plant poisons. As fascinating as a game of chess, the work calls forth, for its most successful treatment, the widest activities of mind and the most skillful handling of finely adjusted instruments. Art and literature lend a peculiar charm to the work, while the warm plaudits of men await him who solves any of the important chemical problems of immunity. This inviting field comes, I maintain, as properly within the scope of plant chemistry as within that of medicine, for disease is simply a disturbance of the natural functions of the animal economy, caused by poisons, many of which are excreted within the affected animal by such low plant organisms as bacteria and perhaps molds. Indeed it has been shown that all of the lesions supposed to be caused by certain living bacteria can be produced by the administration of sterilized filtrates, obtained by passing extracts made from the bacteria through a Pasteur filter.

Plant poisons divide themselves most naturally and most comprehensively according to their plant origin; all attempts at a chemical classification have been incomplete because of our ignorance of the composition and structure of many of the compounds, while the physiological classification is unsatisfactory on account of our ignorance of the chemical composition of the compounds and of their exact mode of action on animal life. Let us inquire into the nature of the parallelism which exists in the grouping of plant poisons, and the grouping of the plants which contain them!

Plants are commonly divided into species, genera and families, and these are grouped into two series—the flowering and the non-flowering plants—the latter being the more simple morphologically. Each of these in turn is grouped into smaller classes. Proceeding from the more simple to the more complex, we have in the non-flowering plants such groups as the bacteria, the diatoms, the molds, the fleshy fungi, the mosses and the ferns, while in the flowering plants we have the monocotyledons with parallel-veined leaves and the dicotyledons with net-veined leaves. This classification is, in general, based on the general morphology of the plant, but in the lower orders, especially in the bacteria, the chemical composition or at least the chemical and physiological reactions which the plant is able to induce are taken into consideration in the differentiation of the species. In many of the subdivisions in the higher groups, however, there is often an apparent chemical basis for classification. It seems just as reasonable to suppose, as van Rijn has shown in his book entitled 'Die Glykoside,' that there should be genetic relationships between the chemical substances represented in any one group of plants, as that there should be morphological relationships. Both results are brought about entirely by the energy of the living cell, a process which is undoubtedly largely chemical in its character, and would seem almost as necessary for a plant to gradually evolve new and therefore closely related chemicals for slight changes in environment, as that it should evolve new and closely related forms for the same purpose. The relationship between the chemical constituents of certain groups of plants cannot, of course, be so apparent as is the morphological relationship, simply because it cannot be determined by inspection alone, as the latter can. If, therefore, our knowledge of plant constituents were sufficiently complete we could perhaps write monographs classifying the different species of plants according to their chemical constituents, as well as we now write monographs based solely on morphology. The same alkaloid is often found exclusively in certain families of plants, but the same family, and even the same species, often contains one or more alkaloids which differ from each other by a few atoms of hydrogen or a few simple organic radicals, or they may differ only in being isomers or polymers. In many of these cases one compound can often be transformed into another by a few simple reactions.

Of the two great classes of plants—the non-flowering and the flowering—the former contain very few active principles, and those which do exist are far more simple than those which are found in the flowering plants. In the bacteria, to be sure, we have highly developed poisonous compounds, the toxalbumins, but aside from these there are few active principles in them. The simpler group of poisonous acids is here more abundant; there are few glucosides and still fewer alkaloids. The most prominent of the latter are ergotine from ergot, and muscarine from the fly fungus (*Amanita muscaria*). There has been an immense amount of study done on the former but its chemical composition is still in a most unsatisfactory condition. Trimethylamine, one of the simplest of the so-called alkaloids of the aliphatic series, is also present in ergot at certain stages of its growth. According to the definition of alkaloids now commonly accepted, however, neither trimethylamine nor muscarine is an alkaloid, this class being restricted to the benzol or aromatic series of compounds. Proceeding still higher in our grouping of plants we find that there are but two conspicuous alkaloids, toxine and ephedrine, in the lowest group of flowering plants, and that, in the many families of the next higher group, the monocotyledons, there is but one family, the Melanthaceæ, which contains more than one or two important alkaloids. In the highest group, however, there is a long list of alkaloids, arranged often in groups, characteristic of the family to which the plants belong. The atropine-like alkaloids of the Solanaceæ; the strychnine-like alkaloids of the Loganiaceæ; the morphine-like alkaloids of the Papaveraceæ; and the quinine-like alkaloids of the Rubiaceæ are the best well-known groups. There is a similar distribution of the glucosides throughout the plant kingdom, but these compounds, being simpler than the alkaloids, are found lower down in the plant scale. It is interesting to note, however, that throughout the whole list of the tremendously abundant family of grasses, one of the lowest families of flowering plants, there are but two glucosides, neither of which is at all well known. One of these is loliin, from the poison darnel, *Lolium temulentum,* while the other, setarian, was isolated from millet so recently as in 1899 by Professor E. F. Ladd, chemist of the Agricultural Experiment Station at Fargo, North Dakota. The grouping of all plant constituents in accordance with their plant classification offers a tempting field of work, but this cannot well be undertaken to advantage until the identity and nature of a great many more plant substances have been determined.

Sohn's 'Dictionary of the Active Principles of Plants' enumerates about 600 substances, all of which are included under the three commonly recognized classes of these bodies, viz., the glucosides, the amaroids or so-called bitter principles, and the alkaloids. These three classes do not, however, include all of the groups of toxic substances which are represented in plants. In addition there are mineral substances, which under certain conditions may be taken up by plants, acids, oils, enzymes and their closely related congeners—the toxalbumins.

Mineral substances very rarely cause poisoning on account of their occurrence in plants, but it has been shown that the presence of lead in a certain grass has led to distinct symptoms of lead poisoning in cows that ate it. An exceedingly important problem suggests itself in this connection and that is the possibility of poisoning from the gradually increasing use of insecticides on fruit trees and on vegetables. It has already been pointed out that plants which have been manured with superphosphates, which frequently contain arsenic, may absorb arsenic into their tissues to such an extent that arsenic poisoning may result from eating them.

The great toxicity of prussic acid is well known. It occurs free in certain plants and in the form of a glucoside in several others, especially in those belonging to the rose and apple families. Oxalic acid is also present in the form of an acid oxalate in many plants. It is extremely poisonous. Crotonoleic acid, from *Croton tiglium*, is still more poisonous, the fatal dose being represented by only .38 of a milligram per kilogram of body weight. Poisonous acids are not so generally looked for in plants as they should be, and it is quite possible that the active principles of some plants, the chemical nature of which is still unknown, are acids. The effect of the common locoweed of the Western States, *Astragalus mollissimus*, has been attributed to loco acid.

The medicinal and therapeutic effects of the vegetable oils are tolerably well known, but it is not commonly recognized that some are poisonous. Among the most powerful of these are the oils of chamomile, cloves, cinnamon, sassafras, savine, rue, hedeoma, and tansy. Many of these are commonly used as flavor and to preserve food, but it is certain that their excessive use might result in serious gastric disorders if not in death. All are useful on account of their being antiseptic, a property which was commonly recognized centuries ago by the Egyptians in embalming bodies. Nutmegs contain a volatile oil which is toxic; two of the nuts proved fatal to a young girl who ate them. The extreme toxicity of toxicodendrol, the non-volatile oil of the common poison ivy, *Rhus radicans*, and poison sumach, *Rhus venenata*, has recently been shown by Dr. Franz Pfaff, of the Harvard Medical School, who proved that the hundredth part of a milligram easily caused a severe dermatitis on many persons, while as little as the thousandth part of a milligram caused severe itching of the skin and half a dozen vesicles on some persons, and localized œdema on others that were more sensitive to its effects.

The glucosides are well known. One of the most poisonous representatives of the group is the active principle antiarin, from the East Indian tree so well known to legendary history as 'the deadly upas.' Its juice has been used in times of war by savage tribes to envenom their arrows. It takes but one to two milligrams of this glucoside to kill a moderate-sized dog in nine minutes. Frogs are killed with a hundredth of a milligram in twenty-four hours. The results of a most interesting investigation on the poisonous constituent of a leguminous plant of Egypt, known botanically as *Lotus arabicus*, have been recently published by two English investigators, Messrs. Dunstan and Henry. Its seeds when ripe are commonly used as fodder, but the growing plant is quite poisonous to horses, sheep and goats. It was noted that when the dry leaves were crushed and moistened with water they gave off an odor of hydrocyanic acid. An investigation revealed the presence of a glucoside, lotusin, which was hitherto unknown. Under the influence of an enzyme, also present in the plant, the lotusin was transformed into prussic acid, sugar and a new coloring matter called lotoflavine. It will thus be seen that this glucoside is very similar in its properties to amygdalin and also to linamarin from common flax. These glucosides may cause poisoning when taken into the stomach but are innocuous when administered hypodermically, for in the latter case they are excreted unchanged, while in the former they are apt to be decomposed by the acids and enzymes of the stomach.

The class of amaroids has not been well investigated chemically, but we know several compounds belonging to the group which are extremely toxic. Cicutoxin is the poisonous constituent of the common water hemlock, *Cicuta maculata,* a plant which probably causes more fatal cases of poisoning in the United States than any other plant. Digitoxin, one of the poisonous constituents of the foxglove, *Digitalis purpurea,* is poisonous to cats in a dose of 0.4 of a milligram per kilogram of body weight, while andromedotoxin, the poisonous constituent of many Ericaceous plants such as the common laurel, *Kalmia latifolia,* and the rhododendrons, is still more toxic, being fatal to frogs and to birds in a dose of 0.1 of a milligram per kilogram when injected subcutaneously. But, as we shall see, it is much less fatal when fed to birds. It is much more fatal to frogs than is atropine or strychnine.

The alkaloids are so well known that they do not need much discussion here. Aconitine is one of the most poisonous, being fatal to birds in the small dose of 0.07 of a milligram per kilogram when injected hypodermically.

The enzymes are not very well known, and in most cases they are not toxic. Some of them are, however, capable of causing disorders when injected under the skin. Very closely related to these are the toxalbumins which embrace the most deadly of all of the poisons, as may be recognized from the fact that they are the poisonous constituents of the venom of snakes and spiders, of many pathogenic bacteria, and of the most poisonous fungi, such as *Amanita phalloides.* We shall have more to say about these substances later.

Nearly all of the active principles which have been isolated from plants have also been studied toxicologically, and have been classified in different ways, but chiefly with regard to the character of their effect and the organ most seriously poisoned. We thus have those which cause marked anatomical changes of tissues, those that principally affect the blood and those that do not cause any marked anatomical lesions. The fatal dose, also, has in many cases been established, so that we can often tell how much of a given substance will kill a given animal in a given time. In this determination it is absolutely necessary, of course, that the animal tested be a healthy one, otherwise a fatal lesion may be produced by the poison simply on account of the previous weakening of the affected tissue by the disease. The time and dose limitations of poisoning are not essential in our accepted definition of a poison, for it considers only derangements of function. If these are produced even by commonly edible substances, such as sodium chloride or sugar, we are obliged to say that under the special conditions of the case in hand these substances are poisonous. Sugar is thus poisonous to a diabetic patient, while pure salt when fed regularly even in normal quantities would undoubtedly prove fatal if all other salts were withheld from the food for a considerable time; half teacupful doses of the saturated solution are said to be sometimes taken by the Chinese to commit suicide. This elimination of the time and dose elements makes it very difficult, sometimes, to distinguish poisonous substances from foods, but it is eminently satisfactory because it calls for subsequent explanation showing in what way and to what extent a substance is toxic. It calls more forcibly to mind, also, the danger in the continued use of drugs and of such narcotics as tobacco and hasheesh, and also to the flagrant and outrageous use of antiseptics in such foods as milk and bread which are consumed daily, sometimes in large quantities. Who can say how much material damage is done to the progress of civilization by this criminal practice? Until proven to the contrary, it ought to be taken for granted that any substance which has antiseptic or germicidal value is also capable of exerting these properties in a deleterious way in the human body, especially when the substance is ingested frequently for a long period of time. The Spanish people are said to be a race of dyspeptics because of their inordinate use of condiments; let us pray that the American people will never become degenerate on account of the use of the antiseptically preserved food which is too often sold in our markets.

There are 16,673 leaf-bearing plants included in Heller's 'Catalogue of North American Plants,' and of these there are nearly 500 which, in one way or another, have been accused of being poisonous. This does not, of course, mean that any one part or all of each of these plants would be fatal if eaten by man or by any one kind of an animal, but simply this, that some part or parts of each, at some period of the plant's growth, contain an active principle which is capable of causing death or some serious derangement of function in one or more forms of animal life when administered in a certain way, not necessarily by way of the mouth. Snake venom is none the less poisonous because it can be swallowed with impunity in considerably more than what would be a fatal dose if injected into the skin in the natural way through the serpent's fangs; neither is the death cup, *Amanita phalloides,* to be considered non-poisonous because it has been eaten after the poison was extracted by chemical methods. Other plants may be eaten with other things which will either enhance their poisonous effect, as in the case of amygdalin when an amygdalin-splitting ferment is also consumed, or counteract it, as might be the case when other medicinal plants are eaten; others again may be considered non-poisonous because the active constituent may be removed or destroyed from the plant by boiling or by drying; and finally others may be declared innocent because the poison is not present in the part consumed, or is present only at certain brief stages of growth; the amount present might also have been increased or diminished according to the conditions of growth or cultivation of the plant, as is most commonly the case in those which are cultivated for their medical value.

We cannot take time to even mention all of the unsolved problems which have arisen in connection with all of these suspected plants, but there are several interesting questions in connection with the variable amount of poison present in a plant, its variable location in the plant, and especially the variable effect upon animals, that should receive special attention.

Few poisonous plants are of sufficient commercial importance to have been investigated chemically with anything like the detail necessary in order for one to draw definite conclusions in regard to the development of their poisons, or of their location in the plant, but all druggists and physicians are aware that the chemical compound by virtue of which a drug is of therapeutic value is almost invariably more abundant in one part of a plant than in another. The same is true of all plant compounds. The variability of cultivated drugs in their contents of active principles was alluded to above. A more satisfactory example of how artificial environment can affect the chemical constituents of plants may be found in a Bulletin recently published by Dr. H. W. Wiley, Chief of the Bureau of Chemistry of the Department of Agriculture, and entitled 'The Influence of Environment upon the Composition of the Sugar Beet.' In this bulletin it is shown that the factors which determine the maximum yield of sugar are as follows: high latitude, free use of fertilizers, and an even distribution of a rainfall of from three to four inches during the months of May, June, July and August, and a reduction of rainfall for September and October.

Natural environment affects some poisonous plants in a similar way, but in this case the more southerly plants are apt to have a greater development of the active constituents than those further north. This is particularly noticeable in the Indian hemp, *Cannabis sativa*. The plants of the Southwest contain a larger quantity of the active principles than the more northerly ones do. A striking example of the possible diurnal variation of the amount of poison in the leaves of plants is shown in a very instructive investigation by Dr. J. P. Lotsy of the cinchona plant. The author showed that the quantity of alkaloïds varied greatly in the leaf as taken by day or night and on sunshiny or cloudy days, being most abundant in the first instance in each case. He showed also that these alkaloids are formed in the leaves during the day and are almost wholly deposited in the branches or bark at night. If gathered in the early morning therefore cinchona leaves would be practically inert, while if gathered in the evening, especially on a sunshiny day, they would be in their most active condition. The foliage is, in general, the part of a plant which causes most cases of stock-poisoning. The period of leaf maturity is regarded by some cultivators of medical plants as being the time at which its chlorophyll content is most highly developed, or when the leaves are most intensely green. This is generally soon after the flowering time in the case of herbaceous plants, but with some, such as the aconite, the purple larkspur and the poison camas of Montana, and many bulbiferous plants closely related to the last, it is earlier, the leaves of some of these having commonly dried up before the plants have flowered. In such cases the leaves would naturally be most active physiologically if eaten before the plants blossom, and might be practically inert at other times. Such is probably the case with the purple larkspur and death camas just referred to. The active principles are sometimes found most abundant in the most rapidly growing parts of the plant, as in the white sprouts of potatoes, and again they are to be found in parts which have been fully developed, as in the case of sapotoxin in the corn cockle, *Agrostemma githago*. It has recently been shown that in aconite seeds the central parts contain most of the aconite, while the seed coats are free from it. In the calabar bean the very poisonous alkaloid eserine is found in the cotyledons. In the seeds of the common jimson weed and black henbane the alkaloids are located chiefly in the layer beneath the epidermis; the epidermis itself and the seed covering of each are free from alkaloids. In jimson weed the quantity of alkaloids in unsprouted seeds was found to be fifteen times as great as in sprouted seeds, and in the seedlings of the jequirity bean, *Abrus precatorius*, it has been definitely shown that most of the toxalbumin is retained in the cotyledons. In growing colchicum the percentage of alkaloid is high in the growing tips and comparatively low in the lower part of the bulb. The first year's crop of leaves of foxglove and of henbane is inferior to that of the second on account of the smaller quantity of active principle. The variation in strength of the powerfully poisonous drug known as strophanthin is so well known to physicians that its medical use is being abandoned. Many such instances might be cited, but these show the importance of knowing the entire history of a plant in testing its character as poisonous or non-poisonous.

There are several molds and smuts which often infest corn and fodder. We know that some of these, when eaten or inhaled, sometimes cause death in a mechanical way by clogging up the system by their growth within the body, but there is much reason to believe that some of them contain poisons which are either consumed with the mold or are generated *pari passu* with the growth of the mold in the body. Probably some of these compounds like the sulphocyanic acid of *Aspergillus niger*—a weak poison—are absorbed with difficulty, especially when taken into the stomach, and this may be the reason why the plants are often eaten with comparative impunity. But are there not conditions when a greater quantity of toxic substances may be present in them, or may there not be a condition of the system in which the poison is more easily absorbed? The large number of cases of stock-poisoning said to have been caused by molds and smuts demand an extended investigation.

Another problem which is essentially of the same nature is in connection with the large polymeric group of saponin-like glucosides. These substances are, as a rule, not very poisonous when taken into the stomach, but it is a noticeable fact that few of the many plants which contain them are eaten by animals. Some are, however, eaten both by the lower animals and by man, as is the case with the fruit of the Moreton Bay chestnut or bean tree, *Castanospermum australe*, of Australia. Some persons assert that this fruit is edible, others that it is merely indigestible, while still others are emphatic in regard to their deleterious effect upon man. Nearly all of the saponins are difficult to dialyze, so it is quite probable that when taken into the stomach they are ordinarily excreted before they can accumulate in sufficient quantity in the blood to cause symptoms of poisoning, but in other cases where poisoning has resulted it seems probable that some condition of the digestive tract, perhaps ulceration, has facilitated the absorption of the compound into the system, where it at once exerts the same powerful effect that it does when injected hypodermically.

Some animals are, for various reasons, entirely immune against the effect of certain poisons. This difference in susceptibility is, in general, correlated to the mental development of the animals compared. The brain and nerve poisons, such as morphine and atropine, are much less poisonous to animals than man. Dogs and horses can, in proportion to their weight, endure ten times as much morphine as man, while doves can stand 500 times and frogs even a thousand times as much. In herbivorous animals, especially in those which chew their cud, such as sheep and cattle, the digestive tract is much longer than in the case of omnivorous or carnivorous animals, consequently the food remains in the body for a much longer period. In case of herbivorous animals this period is usually several days, while in carnivorous animals it is about twenty-four hours only. In the former case, therefore, the poison would have much more time to become absorbed into the blood than in the latter. This, according to Fröhner, probably explains why it is that the metallic poisons are much more fatal to herbivorous than to carnivorous animals.

The flesh of an immune animal to which a large dose of poison has been administered is apt to be poisonous to other animals that eat it if they themselves are not immune to its effects. For example, it is asserted that advantage is taken of this fact in our Southern States in feeding strychnine to chickens in order to poison the hawks that prey upon them. Cases of human poisoning may inadvertently occur by thus eating the poisonous principles of plants which are present in the honey, the milk or the meat derived from certain plants.

All grades of merit or flavor are attributed to the honey derived from plants, thus indicating that the chemical constituents which give characteristic odors and tastes to flowers are often transferred directly to the honey derived from them. Some of the undesirable constituents of nectar are probably eliminated by the bee in some little-known way, and other portions are perhaps selectively retained. Formic acid is a poisonous substance which is found as an apparently essential constituent in all honey, but as it is present only to the extent of about three grains per liter it does not produce toxic effects. Gelsemine, the poisonous constituent of the southern jessamine, *Gelsemium sempervirens,* is said to have been found in honey from Branchville, South Carolina, and andromedotoxin has lately been found in honey from *Rhododendron ponticum* of Europe. The most convincing proof that poisonous honey may be derived from rhododendrons and that its toxicity may be due to andromedotoxin has been furnished by Plugge and Thresh. The former has obtained the poison from the nectar of *Rhododendron ponticum;* the latter found it in 1887 in a sample of honey from Trebizond.

Cases of poisoning from milk are more apt to happen nowadays from the use of preservatives and from bacterial toxines rather than from any other causes, but cases arise from milk becoming sour while in metallic containers or from the plants eaten by an animal. The effect of garlic on milk is well known but it is not so well known that cabbage and turnips also give milk a bad taste. Chicory imparts a bitter flavor to milk and Dyer's weed, *Genista tinctoria,* is said to make the butter and even the cheese made from milk derived from it very unpleasant to the taste. Kobert states that children have been killed by the milk of goats that had eaten colchicum or the broom plant. In my 'Preliminary Catalogue of Plants Poisonous to Stock' mention was made of a severe case of poisoning which was due to drinking milk from a cow that had been feeding on mandrake, and investigations made by Dr. E. V. Wilcox and myself in Montana show that lambs are frequently killed by sucking milk from their mothers after these had eaten death camas, *Zygadenus venenosus.* It was a common impression throughout various districts in the South only a few years ago that the disease known as 'milk-sick' was due to milk from cows that had been eating poisonous plants. This problem has never been solved, although the disease is still reported occasionally. Other cases of such poisoning are comparatively rare, but two have recently been reported to the Department of Agriculture, one from Nebraska and another more important one from the Pecos Valley in New Mexico. The butter and cheese were also suspected in the latter case.

The interest in connection with poisonous honey is both theoretical and practical; that with poisonous game is, perhaps, only theoretical, since no cases have been called to public attention for many years and the records of past cases are few in number. To determine whether the flesh of a bird or animal that has eaten a poisonous plant is poisonous or not it is necessary to prove: first, that the birds or animals in question may eat the suspected plants with impunity to such an extent as to render their flesh poisonous; and secondly, that, perhaps under stress, they actually do so. This latter point can be solved only by the close study of actual cases. An attempt was made by the writer a few years ago to examine into the former question, especially in connection with some historic cases of poisoning, supposed to have been due to eating partridges which had fed on mountain laurel, *Kalmia latifolia*. It is true that partridges eat laurel leaves in winter, and that they may not be poisoned thereby. I have seen as much as 14 grams of the leaves taken from the crop of a single partridge, yet this bird was eaten without any ill effect arising therefrom. In this case, however, the leaves were still in large pieces, many of them being over a half inch square. The andromedotoxin was, therefore, not extracted, and, unless the bird's previous meal consisted of the same food, its flesh could not have contained much of the poison. Andromedotoxin was fed for several days in gradually increasing doses to a chicken, which, at the end of the fourth day, had received a very large dose without affecting it at all seriously. The chicken was then killed, cleared of entrails, boiled for a half hour and fed to a cat with the result that it was very badly, but not fatally, poisoned. Similar problems might be suggested in connection with the poisonous plants eaten by game animals, and especially in connection with the edibility of fish caught for food by the use of plants thrown into the water to stupefy and poison them. Some detective work, also, is desirable to determine to what extent poisonous plants are clandestinely added to whiskey and other alcoholic beverages to increase their intoxicating effect. It is reported that in some country districts throughout the South use is thus made of the leaves of mountain laurel and other andromedotoxin-containing plants.

The practices above mentioned suggest another subdivision of my paper, and that is the effects of the habitual use of narcotic plants. In the United States this use is confined mainly to tobacco smokers, but it is interesting to note that the use of Indian hemp is spreading throughout the Southwest, where it was most probably introduced from Mexico. The effect of this drug is well known from accounts published in the daily press and elsewhere. The common Mexican name of the plant in '*mariguana*,' but this name is also applied in some parts of Mexico to a native *Datura, D. meteloides*, much like our common jimson weed. Both of these plants and others, such as the tree tobacco, *Nicotina glauca*, are sometimes called locoweeds in Mexico. 'Loco' is a Spanish word which, in its original sense, means mad or crazy. Of late, however, it has been extensively applied, especially in northern Mexico and the United States, to certain plants which so affect the brain of animals that eat them as to cause chronic derangements of the power of thinking and of coordinating movement. It is, however, most popularly applied to several weeds—*Astragalus* and *Aragallus* spp.—of the bean family, which cause a peculiar kind of insanity in animals that eat them. It is not uncommonly asserted by Mexicans that sometimes a single dose of hemp will cause long-lasting insanity. Van Hasselt, a Dutch authority on poisonous plants, also asserts that a single dose of this drug may cause mania for months, but the best pharmacologists are agreed that such might be the case only when the person affected is already badly diseased by the use of drugs or otherwise. There is reason for scepticism here, especially in regard to the crazing effect of single doses, but it is highly desirable that the subject be inquired into to find out how little of any one plant can cause insanity in a short time. With the true locoweeds of our Western prairies I am satisfied that at least several days' feeding is necessary to produce any bad effect. The Department of Agriculture is at present engaged in an investigation of the curious behavior of these weeds.

The question of disease-producing food presents many important problems closely related to those mentioned above. Aside from the study of locoism there are such problems as the relation of ergotism to the ergot of rye; of lathyrism to the seeds of the species of *Lathyrus* and *Vicia*, both commonly represented in our native flora; of the so-called 'bottom disease' of Missouri and the seeds of the rattlebox; of githagism to the seeds of the common corn cockle which is abundant in the wheat fields of the middle Northwest, and also to the spring cockle, *Vaccaria vaccaria,* which is also becoming common in the extreme Northwest, and finally the relation of dry food or of dry moldy foodstuffs to blind staggers or cerebro-spinal meningitis and the so-called cornstalk disease of the middle Western States.

The toxic theory of disease is by no means a new theory, for Albrecht von Haller advanced it about the middle of the eighteenth century in connection with the extracts of putrefying animals, but it has received proper prominence only lately in connection with the toxalbumins, the first of which to be described was 'echidnin' or 'viperin.' This was extracted in 1843 by by Prince Louis L. Bonaparte, from the venom of vipers. Crotalin, the poison of the rattlesnake, was described by Dr. S. Weir Mitchell, an American, in 1860. But it was not until after 1884, when two English chemists, Warden and Wadell, isolated abrin from the seeds of jequirity, *Abrus precatorius,* that these bodies were closely investigated in plants. Since 1884 ricin has been isolated from the castor-oil bean, crotin from a bean of the same family, phallin from the deathcup fungus, *Amanita phalloides;* and robin from the bark of the common locust. From many pathogenic bacteria and from some poisonous spiders similar compounds have been isolated. All resemble ordinary albumen in being coagulable by heat and all are remarkably poisonous, but death often ensues only after several days when the poison has been taken internally. After these substances once get into the blood there is no established method of offsetting their effects. There is, however, a most interesting method of preventing and perhaps offsetting their effect which is bound to come more and more into general use. I refer to the use of blood serum and to the various artificial ways of producing immunity or a high degree of tolerance.

Ehrlich, a German investigator, first showed in 1891 that animals can be made to endure very large doses of two plant toxalbumins, abrin and ricin, and, in 1897, Cornevin showed that by heating ricin to a temperature of 100° C. for two hours a substance is formed which, when injected two or three times under the skin of hogs, ruminants or chickens, will produce immunity against the effects of ricin for several months. The essential factor of success in combating these poisons within the body seems to be the development of an increased number of white blood corpuscles within the body. It has been experimentally proven that these corpuscles are not only capable of attacking the destroying bacteria, but also of destroying toxic substances present in the body, the chemical reaction involved being probably an oxidation. These bodies contain an oxydase or oxidizing ferment, and it is known that such oxidizing bodies as permanganate of potash and chloride of lime easily oxidize most if not all of the toxalbumins and thus render them harmless. Any substance, therefore, which is capable of developing a larger number of white corpuscles in the body would serve as a kind of antitoxine against these poisons and it would not appear to be necessary that each particular toxine should have a separate antitoxine. Indeed, experiments show that antitoxines are not chemical antagonists to toxines, but act simply as stimulants to the body to manufacture its own antidote. Certain chemicals, such as sodium hypochlorite and nuclein, an albuminoid obtained from cæsine or from beer yeast, stimulate the production of these cells, and these substances may, therefore, be looked upon as antitoxines. Whether or not these substances will also stimulate the white corpuscles or the other oxidizing organs of the body so that they will offset the effect of plant poisons is a problem which is yet to be solved. It is not known how many poisons the leucocytes are able to destroy in the body, but if their action is really in the nature of an oxidation we may assume that all poisons which are harmless when oxidized, as plant poisons are apt to be, would be destroyed by them whenever they gained access to the blood, providing, of course, that the leucocytes were in sufficient abundance to do the work. We see then the great importance both from the poisonous-plant point of view and for general prophylactic effect against disease of building up an animal's system so that it will contain a maximum quantity of leucocytes. It is probably impossible to stimulate the formation of leucocytes so rapidly that the process would be available for immediate treatment in cases of acute poisoning, but, since it requires only four or five days to produce immunity to snake venom by repeated injections of a dilute solution of the chloride of lime, it might possibly be useful in chronic cases where the poison concerned is harmless when oxidized.

A particularly interesting phase of oxidation in relation to germicidal action has recently been investigated by Professors Freer and Novy at the University of Michigan. Their preliminary paper shows an interesting comparison of the germicidal effect of:

Hydrogen peroxide......	H—O—O—H.
Benzoyl peroxide.......	$C_6H_5CO—O—O—COC_6H_5$.
Acetyl peroxide.........	$CH_3CO—O—O—COCH_3$.
Benzoyl acetyl peroxide.	$C_6H_5CO—O—O—COCH_3$

It will be noticed that the three organic compounds are symmetrical like that of hydrogen peroxide. The amount of available oxygen in each compound is the same but the germicidal action of each varies greatly. The use of hydrogen peroxide as a germicidal agent, especially in strong solution, is well known. Benzoyl peroxide is almost insoluble in water and is not hydrolyzed; it is therefore of no value as a germicide. The last two compounds have no germicidal value of themselves, but they are readily hydrolyzed in the presence of water yielding benzo peracid $C_6H_5CO—O—OH$, and aceto peracid $CH_3CO—O—OH$, both of which have a very marked germicidal value. These organic peracids or peroxides are, according to the authors, at least several hundred times more active than is hydrogen peroxide. The active oxygen content is the same in each, so that the difference in effect cannot be due to nascent oxygen. Hydrogen peroxide loses its available oxygen readily and even violently on contact with enzymes, but these organic peroxides do not. The authors were, therefore, forced to the conclusion that the difference in action is due to the behavior of the acid ions. In this case, therefore, it is the benzoyl and the acetyl ions and not the oxygen which does the germicidal work.

In close connection with this investigation there is another recent piece of work suggestive of important problems in connection with the chemistry and physiology of plant poisons which I wish to allude to before closing, and that is the paper by Dr. A. P. Mathews entitled 'The Nature of the Nerve Impulse,' published in the March *Century*. This treats of nerve stimulation and nerve paralysis on the basis of our modern theories on the nature of solution, a trend of investigation now being carried on at the Hull Physiological Laboratory of the University of Chicago under the direction of Dr. Jacques Loeb, Professor of Physiology at the institution. The author's conclusions are as follows:

"It has been shown: first, that the chemical stimulation of protoplasm is really an electrical stimulation; second, that the poisonous action of inorganic salts is due to the electrical charges of the salts and probably to the movements of these charges: third, that the negative charges stimulate protoplasm, while the positive prevent stimulation, and if not counteracted by the negative will destroy life; fourth, that muscle contraction is probably in its essence an electrical phenomenon and that the conduction of a nerve impulse is almost certainly an electrical phenomenon; fifth, for the first time we have a physical explanation which agrees with all the main known facts of the nerve impulse and changes in irritability; sixth, we have secured a physical explanation of the way in which an anesthetic produces its effect; seventh, we are led to the hypothesis of the identity of stimulation by light and by chemicals."

The author does not, in this paper, discuss the possible effect of the ions of plant poisons, but it is difficult to see if his theory really holds good for organic compounds, why the complex cathion of so many alkaloids should be so extremely poisonous, and one is forced to wonder how any acid ion could be found which could be powerful enough to offset the toxic effect. One is also tempted to wonder if death can be the complete physiological opposite of life, for is there not a tremendous difference between the automatically reversible character of the cell protoplasm which enables it alternately and in rapid succession to solidify and redissolve, and the simple irreversible solid or liquid state which is the result of death?

In the foregoing paper I have attempted briefly to discuss some of the practical, as well as some of the theoretical, features of plant poisons, throwing out suggestive hints rather than concrete problems here and there, and although I feel that the ground has not been adequately covered, I trust that at least some of you have been interested in the discussion, and I venture to express the hope that some of the suggestions have fallen on good ground and will result some day in a rich harvest of facts giving solutions to some of the problems suggested.

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SCIENTIFIC BOOKS.

Reports on Plans for the Extermination of Mosquitoes on the North Shore of Long Island, between Hempstead Harbor and Cold Spring Harbor. Published by the North Shore Improvement Association. 1902. Pp. 125.

This is an extremely interesting and in some ways a most remarkable publication. It is a sign of the times that a number of men interested in a given territory should form themselves into an improvement association whose principal aim seems to be to do away with the