which, when first met, will ordinarily demand a philosophic solution. With the increase of this circle as science advances goes an increase in the periphery. I neither hope nor look for a decrease in philosophy as science advances, but just the reverse.

We shall need more and above all better philosophy. It seems to me that the most adequate philosopher will have the following characteristics. He will be a man of wide culture, familiar with the arts and sciences, with the psychology of man and with the values of life. He will be an accurate thinker—a sound logician—and have an extensive acquaintance with the facts and the methods of science. There is a peculiar necessity that he be aware of the scientific method. This method aims to secure more permanent solutions to its problems than does any other. It accepts the fact that time and investigation are necessary to this end. Though philosophy acts where these things are impossible the philosopher should attempt to parallel in his thinking what the experimentalist does in fact—only so can there be a tolerably promising philosophic solution of the problem.

Let me illustrate this by a problem which arose during the war. It was necessary to select men for training as officers. It seemed evident that the best selection would depend upon possession by the men of certain traits such as mental ability, physical stamina, moral courage, cooperativeness, leadership, etc. Ratings upon these traits by superior officers of men in camps could be gotten. The problem was how to combine them into single gross ratings which could be used in the actual selection of men. Time prevented an experimental investigation, so philosophizing had to be appealed to. An experimental investigation in which these various trait measures were used to estimate demonstrated success as officers would have yielded the weights that should be attached to the measures separately in order to get the most reliable aggregate measures of fitness as officer material. In short, the experimental treatment would have analyzed the data and then combined the separate trait scores into the most meaningful total ability scores. The concepts of total correlation and of partial correlation (not of course assuming any limited type of relationship, as that of linearity, between measures) here operate and they alone do operate. No logical treatment not paralleling this can be as adequate as one which does parallel it. The more completely the philosopher parallels in his thinking the analysis and synthesis which the experimental treatment would yield the better is his philosophical solution. The great endeavor of the philosopher here should be to ape mentally the steps of science. He can not have a technique which is better (omitting the time factor) than the scientific technique. Just the moment that he demonstrably did have science would claim it as its own, for true science has no fetishes that it clings to in the face of evidence.

CONTRIBUTIONS TO PHYTOPHARMACOLOGY OR THE APPLICATIONS OF PLANT PHYSIOLOGY TO MEDICAL PROBLEMS[1]

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INTRODUCTORY

As early as 1921, while studying general laws underlying physiological and pharmacological reactions, the author conceived the idea of making a comparative study of the action of various drugs on living plant protoplasm in contrast to animal protoplasm. The study of pharmacology, as carried on in our medical schools and research institutions, concerns itself almost exclusively with the effects of drugs and poisons on animals and, strictly speaking, is zoopharmacology, just as the study of physiology in the same institutions is confined exclusively to the physiological functions of animals, or zoophysiology. There is, however, a very important department of biology dealing with plant physiology, to which the name of phytophysiology is sometimes applied, and the writer was curious to inquire into the effects of drugs and poisons on living plants and in this way developed a new department of biology, to which the term *phytopharmacology* might be applied. These studies were begun with an examination of a number of alkaloids, the most interesting of which happened to be cocaine, and the findings in connection with a study of this substance were of such importance that they were followed by other studies along novel and unexpected lines of experimentation, resulting in important discoveries not only of purely scientific value but also of practical worth to pathology, medical diagnosis and therapeutics.

[1] Read before Section N—Medical Sciences, of the American Association for the Advancement of Science, at the Des Moines meeting, January 1, 1930.

The effects of drugs and poisons on plant tissues may be studied in various ways. The author and his associates have investigated the effects of various substances on the germination of seeds, on the growth of roots and stems, on the influence exerted on flowers, the effects on geotropism, on transpiration and respiration, the effect on yeast and fungi, on chloroblasts, on protoplasmic streaming, etc. It was soon found that a most useful and profitable method of making such phytopharmacological studies was the employment of seedlings of *Lupinus albus* and observations on the growth of their roots and stems in normal plant-physiological solutions, on the one hand, and on solutions of various drugs and poisons in the same kind of plant-physiological solutions, on the other hand. In this way the author has developed a quantitative method of studying the phytopharmacological and phytotoxic effects of various chemicals which proved to be of great usefulness.

STUDIES ON COCAINE

It is well known that the cocaine molecule can be easily split by hydrolysis into three components, a complicated nitrogenous base known as ecgonin, a molecule of benzoic acid and a molecule of methyl alcohol. In previous studies, carried on by Macht and various collaborators, the pharmacological effects of cocaine, as such, and other products of decomposition on various animal and animal tissues have been investigated, and it was found that the alkaloid cocaine is very much more toxic for animal protoplasm than the products of its decomposition are.[2,3] A study, by Macht and Marguerite Livingston, of cocaine and of ecgonin, sodium benzoate and methyl alcohol, individually and in combinations, on living plant protoplasm revealed that whereas the alkaloid cocaine is extremely toxic for animal protoplasm, it is comparatively little toxic for plant protoplasm, as much as 2 per cent. cocaine or more being required to inhibit the growth of *Lupinus albus* roots completely. On the other hand, while sodium benzoate, one of the products of cocaine hydrolysis, is practically non-toxic for animal tissues, it was found to be extremely toxic for living plant protoplasm, as little as 0.007 per cent. completely killing the seedlings of the same plant.[4]

These findings, interesting in themselves, revealed that plants may be much more sensitive to certain drugs than animal protoplasm may be to the same drugs, and suggested the idea of employing plant-physiological methods for the detection and study of certain toxic substances not demonstrable by ordinary zoopharmacological or zoophysiological methods. The first extensive study on this subject was carried on by Macht and Lubin in connection with the poison of menstruation.

STUDIES ON MENOTOXIN

The authors undertook to investigate scientifically by experimental methods, accurately controlled, the old belief in regard to contagion of menstruating women. Studies were made with the serum of women during menstrual and intermenstrual periods, and it was clearly demonstrated by phytopharmacological methods that such blood serum contained a toxic substance—"menotoxin"—demonstrable immediately before the onset of catamenia and during its course, which toxin was extremely poisonous for living plant protoplasm. The presence of the same menotoxin was demonstrated by the authors to be not only in the blood serum but also in the saliva, sweat, milk, urine, tears and other secretions during the menstrual period. By means of phytopharmacological experiments, some idea has also been gained in regard to the chemical nature of menotoxin, it being found that it is probably in the nature of an oxycholesterin.[5] Later studies by one of the authors, carried on along the lines of experimental psychology with albino rats in the circular maze, showed that menotoxin affected the behavior of such animals, thus throwing some light on various psychological disturbances frequently encountered in patients at the time of menstruation.[6]

These studies on the poison or toxin of menstruation, while interesting in themselves, from the ethnological, physiological, pharmacological and chemical points of view, led to a still more important discovery, namely, the first demonstration of a toxin in the blood in pernicious anemia.

STUDIES ON PERNICIOUS ANEMIA

While making a routine examination of bloods obtained from clinical laboratories in Johns Hopkins Hospital and elsewhere in connection with his studies on menotoxin, Macht had an opportunity of examining a specimen of blood from a man suffering with pernicious anemia. The serum of this patient was found to be extremely toxic for plants as compared with normal blood serum. Further studies revealed that such a toxic reaction was exhibited by blood specimens from every case of pernicious anemia examined by the author, and furthermore, that such a toxicity was not exhibited by specimens of blood from other blood diseases such as secondary anemias

[2] Macht and Bloom, *Arch. Internat. Pharmacodynamie et Thérapie*, 25: 379–390, 1920.

[3] Kubota and Macht, *Jour. Pharmacol. and Exper. Therap.*, 13, No. 1: 31–44, 1919.

[4] Macht and Livingston, *Jour. Gen. Physiol.*, 4, No. 5: 573–584, 1922.

[5] Macht and Lubin, *Jour. Pharmacol. and Exper. Therap.*, 22, No. 6: 413–466, 1924.

[6] Macht and Hyndman, *Proc. Soc. Exper. Biol. and Med.*, 22: 208–209, 1925.

from various causes, carcinoma, Hodgkin's disease, hemolytic jaundice, myelogenous and lymphatic leukemias, etc. As a result of such phytopharmacological studies, a contribution was therefore made simultaneously to the etiology of pernicious anemia as well as to the differential diagnosis of that dreadful disease.[7] For a number of years, the author has been carrying on such diagnostic studies in doubtful cases submitted to him by clinicians from various parts of the United States.

These studies on pernicious anemia furnished a quantitative method of evaluating the results of various therapeutic procedures employed in its treatment and have led to the discovery of certain very valuable therapeutic procedures.[8] Thus it was found that transfusion of blood in pernicious anemia patients is of very little value, the toxin being regenerated in a few days. Again, it was found by Macht and his coworkers that the liver treatment of pernicious anemia, while being of great usefulness in restoring the normal blood picture of the patients, does not affect much the quantity of pernicious anemia toxin present in their blood, so that such patients invariably have relapses. To use an expression of a German author, the liver treatment improves the "anemia" but does not destroy, or affect to any great extent, the toxic agent producing the disease.[9] On the other hand, studies carried on by the author, at first in the laboratory with blood sera in quartz tubes and later on patients, have revealed that certain ultra-violet rays greatly diminish and even completely destroy the toxin of pernicious anemia and, as a result of these experiments performed by Macht and Anderson, it was suggested that heliotherapy with ultra-violet rays of wavelengths 3130 and 2967 Ångström units be employed in the treatment of pernicious anemia, either alone or supplemented by the administration of certain photosensitizing agents and, particularly, of the sodium salt of tetra-bromfluorescein, or eosin. A series of clinical cases carefully studied in this connection has demonstrated the undoubted value of such treatment.[10] Furthermore, the author's findings concerning the toxin of pernicious anemia and the effects of liver treatment have been confirmed by various investigators in Europe.[11,12]

[7] Macht, *Jour. Pharmacol. and Exper. Therap.*, 19, No. 1: 461–469, 1926.

[8] Macht, *Jour. Amer. Med. Assoc.*, 89: 753–759, 1927.

[9] Jungmann, *Klinische Wochenschrift*, 7: 441–445, 1928.

[10] Macht and Anderson, *Jour. Pharmacol. and Exper. Therap.*, 34, No. 4: 365–389, 1928.

[11] Tscherkes, *Proc. Soc. Exper. Biol. and Med.*, 26: 869–871, 1929.

[12] Adler, Sinek and Reimann, *Zeitschrift f. Klin. Med.*, 110, No. 3: 309–333, 1929.

The author wishes to announce, on the present occasion, a new set of experiments conducted by him in connection with pernicious anemia, namely, on the phytopharmacological effects of spinal fluid. A large number of specimens of human spinal fluid have been examined in order to determine the normal toxicity of such fluids. Study is now being made of spinal fluids from cases of pernicious anemia. Such specimens are rather difficult to obtain, but the observations so far in hand reveal that spinal fluid of pernicious anemia patients is definitely more toxic than normal spinal fluid, and this finding may throw light on the origin of the spinal lesions and symptoms so often encountered in such patients.

STUDIES ON LEPROSY

The author wishes to announce some interesting studies which he has been conducting on the blood sera obtained from leprosy patients. Phytopharmacological examination of such sera, by Macht's methods, on the growth of *Lupinus albus,* has revealed for the first time that such blood sera contain a very powerful toxin, a toxin of even greater potency than that of pernicious anemia. This toxin is quite different from that of pernicious anemia in respect to the effects of ultra-violet rays. Whereas ultra-violet rays destroy the toxin of pernicious anemia, they do not affect, to any appreciable extent, the toxin of leprosy. A comparative study has been carried on by the author on the blood serum of leprosy, on the one hand, and two diseases which simulate it in certain respects, on the other. These diseases are tuberculosis and syphilis. The author wishes to announce in this place the results of these studies. A large series of experiments reveals that the sera of tuberculosis and syphilis are both even less toxic than normal blood serum, whereas the serum of leprosy exhibits an extreme toxicity. Thus, by means of a phytotoxic or phytopharmacological test, it has been our good fortune to contribute to some extent not only to the question of the etiology of leprosy but also to its differential diagnosis from syphilis and tuberculosis (Table I).

In view of the interesting findings obtained by the author in connection with the liver treatment on the blood of pernicious anemia, it was deemed of interest to study phytopharmacologically the effects of certain chemotherapeutic agents on the toxin of leprosy. All these studies were carried on in the author's laboratory on sera of leprosy patients sent to him through the courtesy of medical men in the field, to whom grateful acknowledgment is due. In this connection, the author wishes to make an announcement of certain very interesting findings. Studies were

TABLE I

COMPARATIVE TABLE OF BLOOD SERA

Kind of blood serum	Average of no. of cases	Phytotoxic index	Effect of ultra-violet irradiation
		Per cent.	
Normal human	100	72	no effect
Menstrual	50	51	more toxic
Pernicious anemia	48	44	detoxification
Pemphigus	18	54	slightly less toxic
Leprosy	22	47	not detoxified
Tuberculosis	27	78	no change
Syphilis	20	81	no change

made on leprosy sera with and without the admixture of dilute solutions of extracts of chaulmoogra oil or its esters, care being taken to make all conceivable controls and checks in regard to the effect of chaulmoogra oil and its esters alone on living plant protoplasm. It was found that chaulmoogra oil and its esters exerted a truly chemotherapeutic detoxifying effect on the toxin of leprosy, whatever it may be. The author is happy to announce, furthermore, that through the courtesy of Professor R. N. Chopra, of the School of Tropical Medicine, Calcutta, India, he examined a series of blood sera from both treated and untreated leprosy patients, and the findings in toxicity in these cases agreed with the laboratory findings in Baltimore. The untreated cases showed the greatest toxicity; the cases treated with chaulmoogra showed a definite decrease in the amount of toxin in their blood, thus clinically confirming the findings made in the author's laboratory. These studies, of course, are of a limited nature but it is hoped that they will lead to further work on the subject (Table II).

TABLE II

CHAULMOOGRA EXPERIMENTS

	Phytotoxic index
I. Leprosy Blood A (India)	Per cent.
1. Serum, 1 per cent., alone in Shive	49
2. Serum, 1 per cent., alone in Shive, irradiated with quartz lamp	45
3. Chaulmoogra ester alone in Shive	73
4. Serum, 1 per cent., plus chaulmoogra ester in Shive	71
II. Leprosy Blood B (America)	
1. Serum, 1 per cent., alone in Shive	58
2. Serum, 1 per cent., alone in Shive, irradiated with quartz lamp	58
3. Chaulmoogra oil alone in Shive	78
4. Serum, 1 per cent., plus chaulmoogra oil in Shive	80
III. Pernicious Anemia Blood	
1. Serum, 1 per cent., alone in Shive	25
2. Serum, 1 per cent., plus chaulmoogra ester in Shive	24
3. Serum, 1 per cent., irradiated with quartz lamp	60

STUDIES IN DERMATOLOGY

The author, in collaboration with Dr. Isaac Pels, a dermatologist, has been examining the phytopharmacological reactions on sera from all kinds of skin diseases, and such a routine study has led to the discovery of another toxin in connection with one more baffling disease, namely, the very grave condition known as pemphigus. Macht and Pels have succeeded in demonstrating the presence of a toxic substance in the blood, as well as in the contents of the bullae, of pemphigus patients, which is a contribution to the etiology of this hitherto entirely obscure and misunderstood pathological condition.[13] Studies on other dermatoses are in progress.

STUDIES ON ECLAMPSIA

Eclampsia is one of the gravest pathological complications of pregnancy and puerperium. Various theories concerning its causation have been advanced, the most popular being that which regards it as a toxemia. This theory, however, is not generally accepted because no toxin has hitherto been demonstrable in all the clinical and chemical studies of eclamptic patients that have been made. Even transfusions of eclamptic blood into other animals fail to produce the disease. A new conception regarding eclampsia, which differs from the old toxemia theory, has recently been advanced by Zanggemeister.[14] It was interesting, therefore, to inquire whether a toxin could be demonstrated in eclamptic blood by the newer phytopharmacological methods. Such an investigation has been undertaken by Macht and Losee, and it may be announced in this place that their findings corroborate the newer views concerning the etiology of eclampsia. No toxic substance in the blood serum of eclamptics could be detected by phytopharmacological methods.

ZOOGENIC *versus* PHYTOGENIC POISONS

The experimental investigations described above definitely reveal that certain poisons, or toxins, which could not hitherto be detected by chemical, physical or by zoophysiological and zoopharmacological methods, could be demonstrated by phytopharmacological

[13] Macht and Pels, *Arch. Dermatol. and Syphilol.*, 19: 640–647, 1929.

[14] Zanggemeister, "Die Lehre der Eklampsie," Leipzig, 1926.

means and, in general, it has been the experience of Macht and his coworkers that poisons produced by plants, or phytogenic poisons, are more toxic for animals than for plants, while poisons elaborated or produced by animals, or zoogenic poisons, are commonly much more toxic for living plant protoplasm than for living animal tissues. A series of investigations carried on by the writer tends to support this view. Macht has examined a large number of alkaloids, glucosides and other plant products known to be extremely poisonous for animals and found them to be comparatively very little toxic for living plants. On the other hand, he has made studies of various drugs and poisons of animal origin and found them to be extremely toxic for living plants. Thus it has been found that nicotine, atropine, morphine, aconitin, gelsemine, homatropine, lobelin, scopolamin and ouabain, all very powerful poisons for animals, are very little toxic indeed for living seedlings of *Lupinus albus*. On the other hand, studies made with the poison of toads, scorpions, spiders and other animals were found to be extremely toxic for such living seedlings.

STRIKING EXAMPLES

To illustrate the difference in phytopharmacological reactions between the poisons derived from the plant and animal kingdoms, the following may be appropriately cited. A comparative study of the active principle of the suprarenal gland, known as epinephrine, on the one hand, and the alkaloid ephedrine, in many respects resembling the action of epinephrine on animals, revealed that, whereas epinephrine was very toxic for living plant protoplasm, ephedrine, or "vegetable epinephrine," was practically non-toxic for it.[15] The drug cantharidin, obtained from the Spanish beetle and used to some extent in medicine, was compared with a most powerful and deadly poison known as ricin, obtained from the shells of the castor-oil seed. It was found that ricin was not at all toxic for growth of *Lupinus albus* in Shive solution, whereas cantharidin, in concentration of 1:50,000, killed it.[16]

Applying phytopharmacological methods to the study of bee virus and extracts of red ants, the author succeeded in demonstrating conclusively that these substances are not irritant by virtue of their content in formic acid but that they contain small quantities of unknown animal toxins.

[15] Macht, *Arch. f. exper. Path. u. Pharmacol.*, 143: 329–336, 1929.

[16] Macht, *Proc. Soc. Exper. Biol. and Med.*, 25: 592–593, 1928.

SNAKE VENOMS

One of the most interesting studies carried on at present by the author is that on snake venoms. The venoms of cobra, rattlesnake, moccasin and other reptiles are being investigated. These poisons, of course, are well known to be extremely deadly for man and other animals. A phytopharmacological study of such poisons, made by dissolving the dried venom in plant-physiological solutions and growing various plants in them, reveals that, if anything, snake venoms are even more poisonous for living plant protoplasm than for animal protoplasm. The author is developing a method of quantitatively expressing the toxicity of these venoms and purposes to use it in connection with the study of various antidotes and therapeutic agents employed for snake-bite.

CONCLUSION

Thus it will be seen that, starting with a purely abstract objective, namely, the comparative study of animal and plant protoplasm in respect to their reaction to various poisons and chemicals, a number of interesting discoveries have been made. These studies are of interest not only to the medical man but also to the biologist, including the botanist and zoologist, on the one hand, and to the chemist, pharmacologist and pharmacist, on the other. The same methods have also been employed by the author for comparative studies of all kinds of chemicals, such as organic mercurials, preparations of digitalis, etc., and have been found very useful. In view of the fact that in all such experimental observations, made not on one or two individuals but generally on ten living plants and sometimes more, an average reading of all the measurements is taken, the results obtained are certainly just as reliable as those gathered from animal test objects, if not more so.

The author is quite aware that the subject of phytopharmacology is only in its infancy, that many additions and modifications in regard to the methods of study and even some of the data adduced will certainly be made, but this is true of all scientific investigation. The results reaped already from his studies on menotoxin, pernicious anemia, leprosy, pemphigus, eclampsia, snake venoms and various animal poisons, however, have fully demonstrated a definite value for this new line of work and, if these discoveries will serve to direct the attention for other investigators to the field, he will be more than grateful for having had the privilege of contributing what little lay in his power to the advancement of experimental science and benefit of humanity. It may be well to conclude with a quotation from an ancient sage:

'Tis not incumbent on thee to complete the whole,
Yet art thou not absolved from doing what thou canst.