these, as well as similar suspensions of European and endemic typhus and American "Q" fever rickettsiae, can be used for diagnostic skin tests.

The method of thus preparing practically pure suspensions of rickettsiae by relatively simple procedures opens up many additional possibilities of study along immunological, serological and chemical lines.

OBSERVATIONS RELATIVE TO A *Dermacentor variabilis* STRAIN OF ROCKY MOUNTAIN SPOTTED FEVER MODIFIED DURING YOLK SAC PASSAGE

In conclusion I would like to report observations relative to a *Dermacentor variabilis* strain of spotted fever that has been maintained in eggs for 240 serial transfers since April, 1938. This strain was originally isolated in guinea pigs by inoculating them with a suspension of tissues from *Dermacentor variabilis* ticks collected in Iowa. Several transfers with spleen tissue were successfully made in guinea pigs, but the infection was very mild and a number of animals showed only inapparent infections or failed to react. The strain in guinea pigs was finally lost, but fortunately had already been established in eggs. Tests carried out with yolk sac suspensions of the eleventh and fifteenth egg passages revealed that a marked change, characterized by much greater virulence for guinea pigs, had taken place. Thirty-six guinea pigs were inoculated intraperitoneally with 1 cc each of a 10 per cent. yolk sac suspension. All had high fevers, prolonged temperature curves, erythema and swelling of the scrotum. Of 19 that showed scrotal necrosis and sloughing, 10 died. Titration tests of this same suspension resulted in frank infections, typical of spotted fever in dilutions up to and including one to a million. No inapparent immunizing infections occurred in those animals inoculated with higher dilutions. This enhanced virulence was maintained through about 50 passages. Tests made at random between the fiftieth and one hundred and twenty-fifth egg passages revealed the yolk sac suspensions were becoming markedly less virulent and that a great number of inapparent, immunizing infections were being induced in inoculated guinea pigs. For the subsequent 100 and more passages this strain has regularly killed chick embryos on the third day after inoculation and stained yolk sac preparations have shown just as many rickettsiae as any of our highly virulent strains, yet guinea pigs inoculated intraperitoneally with as much as 1 cc of a 10 per cent. yolk sac suspension have either failed to show any febrile reaction or at most exhibit a slight temperature rise lasting not more than 1 or 2 days. Animals injected subcutaneously with similar suspensions seldom show any reaction. In fact, we have titrated yolk sac suspensions of this avirulent, *variabilis* strain on numerous occasions and found that inapparent, immunizing infections resulted in guinea pigs receiving dilutions as high as 1 to 100,000. However, *the important finding* is that these animals, even when completely afebrile, are later solidly immune to massive doses of highly virulent strains. Furthermore, identical results have been obtained in rhesus monkeys. Attempts to reestablish this strain in guinea pig passage by transfers of blood, testicular washings and spleen suspensions have thus far failed.

Long-term tests are now under way to determine if the degree of protection afforded by this avirulent strain is as solid and lasting as that produced by killed vaccines. Theoretically, we believe it should be even more so. If this proves true, we may eventually be able to immunize man with modified, living strains of spotted fever virus in much the same way as we now immunize against yellow fever. We already have evidence that European typhus, endemic typhus and American and Australian "Q" fever as well as certain other rickettsial strains may similarly be modified in virulence for mammalian hosts by prolonged maintenance in eggs.

RAFINESQUE'S INTERESTS—A CENTURY LATER: MEDICINAL PLANTS[1]

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To have been selected to participate in this Centennial Memorial to Constantine Rafinesque brings to me feelings of profound humility, on the one hand, those of great satisfaction on the other; humility because the mental stature and achievements of Rafinesque so dwarf those of ordinary men as to make him almost legendary; satisfaction because of the honor so deeply felt in being allowed to become affiliated with this magnificent occasion and because, secondly, it gives me an opportunity of expressing thoughts concerning plant drugs which I have entertained for some time silently. I was indeed happy when Dr. Brown assigned me the subject dealing with some of the problems within the field of medicinal plants.

[1] Part of a symposium during the Rafinesque Centennial Memorial, Transylvania College, Wednesday, October 30, 1940, Lexington, Ky.

It might be of interest first to discuss the status of medicinal plants at about the time Rafinesque was teaching medical botany here in the medical department of Transylvania College, and to mention some of the factors which were then beginning to make their effects felt on the popularity of vegetable drugs. In the early nineteenth century our national conscience, medically, was awakened to the need of standardizing in some fashion the quality of the medicinals then in vogue. This led the New York Medical Society, through the initiative of Dr. Lyman Spalding, on March 4, 1818, to circularize the several medical bodies with the view of calling together representative district assemblages in 1819. These gatherings were to inaugurate the formation of a convention, the fruits of which were eventually to be our first national Pharmacopoeia; our first authority on drug standards. It is pleasing to note that the Medical School of Transylvania College was among those institutions which approved this movement. In April of 1819 the college administrators appointed Dr. B. W. Dudley and Dr. W. H. Richardson as their official delegates.

The Pharmacopoeia which resulted from these and other deliberations came into being in 1820, and its decennial revisions have come down to us, the present one being unquestionably the world's best Pharmacopoeia. In its preface this first national drug authority states: "It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage."

Approximately 650 drugs and preparations were listed in this first book, of which about 70 per cent. were of vegetable origin. Of these, the usefulness of slightly more than 100 is still recognized by their incorporation in the present eleventh revision of the Pharmacopoeia. These include such important drugs as digitalis, hyoscyamus, belladonna, opium, cinchona and, of course, castor oil. Among those that have fallen by the wayside are "Cornu cervi (Stag's horn)," "Dracontium (Skunk cabbage)," "Dolichos (Cowhage)," "Magnolia" and "Tobacco." Whisky, now official, was absent from the first Pharmacopoeia. There have been some few dozen other additions as exemplified by chaulmoogra oil, aspidium, cascara, strophanthus and various plant derivatives such as cocaine, ephedrine, physostigmine and the caffeine group.

The isolation of morphine from opium in 1804 not only stirred interest in similar chemical studies of the active principles of other vegetable drugs, but seems to have led to a more profound study of organic chemistry generally. This eventuated in the synthesizing of alcohol by Henry Huenel in 1826 and of urea by Wöhler in 1828. The beginning of synthetic chemistry marked the first major deviation from the interest in vegetable drugs since the time of Paracelsus in the fifteenth century. But another force was to be felt. The study of physiology was simultaneously developing and gathering momentum under such masters as Magendie, Flourens, Johannes Mueller and DuBois-Reymond. This study of function naturally led to study of the various chemicals which might influence function—the beginning of pharmacology. The early workers in pharmacology soon showed that many of the vegetable drugs then in clinical use were devoid of any beneficial action. So informed, the already therapeutically exasperated physician, swinging to a point of juxtaposition, felt that possibly little of therapeutic merit was to be found in any drug, particularly those of vegetable origin. As a result it was not unnatural for a period of therapeutic nihilism to ensue as the nineteenth century reached its three-quarter mark. To further the unfortunate plight of vegetable drugs, physiologists and pharmacologists devoted more and more of their time to synthetic compounds, usually organic ones and to drugs of animal origin. The desertion of the study of vegetable drugs soon became almost complete; at the present time researches dealing with plant medicinals are relatively rare and are becoming more so. To-day is the heyday for organic synthetic chemicals. Present-day medical scientists only too frequently are apt to look askance at those who would investigate the therapeutic possibilities of the vegetable kingdom.

In spite of this loss of dignity, out of a total of approximately 570 drugs and preparations in the present Pharmacopoeia, there are still about 260 (or 45 per cent.) of vegetable origin. These figures must not be too encouraging; many of these drugs are included, not so much because of any belief as to their inherent therapeutic value, but because of their usefulness as pleasant vehicles for the more popular nonvegetable remedies. And further, the indications are that the next pharmacopoeia will contain still fewer drugs of vegetable origin.

In face of such observations, is it justifiable to assume that we have exhausted the medicinal value of plant drugs? The answer is a most emphatic No!

Let us immediately recognize that even at the present time some of our most valuable drugs spring from vegetable sources. Such old drugs as opium, digitalis, cinchona, belladonna and ergot still remain almost unchallenged by synthetic opponents. As studies have been made in more recent times the value

of other plant drugs and preparations has been definitely established. Such studies have led to the introduction of ephedrine, picrotoxin, curare, and others. Again, renewed attention to the older vegetable drugs has led not only to new uses, such as the successful use of belladonna in the treatment of certain diseased conditions of the central nervous system, but also to the discovery of new, therapeutically valuable principles, as exemplified by the recent isolation of the alkaloid ergonovine from ergot. This alkaloid, incidentally, was discovered years after it was supposed that all the active principles of ergot had been detected. That more has not been done is undoubtedly due to the lagging interest in drugs from this natural source. In addition to the reasons previously mentioned, this neglect is further explained because of the intense research activity shown by the chemical industries seeking new drugs in the synthetic field, which can be fairly readily protected from competition by suitable patents. Protection is more difficult in the case of studies concerning vegetable drugs. The field for exploitation is far greater in the case of synthetics than it is for that of the later group. This is not stated to disparage those responsible for the destinies of our chemical and pharmaceutical houses; these concerns have made many excellent contributions. They must look after their own interests, however, and they, as is natural, also tend to follow the custom of the day.

We have but scratched the surface in our study of medicinal plants. We have fairly well classified botanically the plants which inhabit our world; relatively their chemistry and particularly their pharmacology have been ignored. If only for purely scientific reasons this should not be so.

Now during this period of national emergency, it would be most important to know more about our national resources from the point of view of plant medicinals. Forgetting the possibilities offered by unstudied plants, it would be comforting if we had in cultivation in our country the vegetable drugs on which we lean so heavily. Of the five drugs mentioned above (opium, digitalis, cinchona, belladonna and ergot) we raise appreciable quantities of digitalis alone. Had we but found it possible to follow seriously Rafinesque's example in sponsoring a drug farm at Transylvania College, the picture would be different. It should be stated that this deficiency is due largely to economic factors. To those who are interested in following the rise and decline in medicinal plant culture in this country, I would recommend the excellent article by A. F. Sievers published in the *Journal of the American Pharmaceutical Association* for September, 1940.

It is interesting and instructive to follow the developments, often dramatic, which so frequently characterize the course of thorough observations on vegetable drugs. The leaf of the tree Erythroxylon Coca will serve as one good example. The early explorers of the Andes noted that the natives chewed an alkaline cud made of these leaves and, presumably as a result, they were enabled to work prodigiously without fatigue and to go unfed for days without hunger. The Shamans, the priest-doctors of old Peru, were observed to follow a similar custom but for a different purpose. They treated with their spittle the wounds of the patients on whom they had operated, and by so doing gave to their patients surcease from pain. This crude procedure represents the first practice of local anesthesia. Centuries pass. In 1855 and again in 1860 chemical studies in Germany revealed the presence of an alkaloid in extracts of the leaves. It was variously called erythroxyline and cocaine. That the alkaloid produced anesthesia when applied to the tongue led to no suggestion as to its use in man. This awaited the advices of the pharmacologist Anrep, who in 1879 subjected the active compound to a careful study of its action, and as a result he recommended its use to produce local anesthesia in humans. But more was needed to convince the contemporary medical opinion. As evidence of the still degraded station of cocaine in the therapeutic armamentarium of the day, it is to be noted that in 1880 a distinguished medical commission in Great Britain designated it as of little therapeutic importance: at best only a poor substitute for caffeine as a stimulant. Four years later two young scientists in Vienna began anew studies on the action of cocaine. One was to distinguish himself later in a different field—he was Sigmund Freud. The other was to become the father of modern local anesthesia, Carl Koller. Because of pressure from other duties Freud soon left Koller to carry through the studies that they began jointly. After noting that a water solution of cocaine produced deep anesthesia, in the eye of the animal into which it was dropped, Koller tried it on himself and on his friends. Then, being an ophthalmologist, he tried it as an anesthetic in operations on the human eye. Other investigators soon showed that when brought into contact with any sensory nerve it could temporarily block the passage of impulses. It was soon used in dentistry to block those nerves carrying painful impulses from the teeth. Surgeons, among them notably Dr. William S. Halsted in this country, proposed it not only for such use but for other types of so-called "conduction anesthesia." Soon, however, it was found that cocaine has two great disadvantages. It belonged to that group known as "habit-forming" drugs; and, because of self-experimentation for the

sake of science, at least one of the early investigators became a cocaine addict. It is gratifying to know that he subsequently cured himself. The second early recognized disadvantage was that this substance could at times have an alarmingly poisonous effect when used on human beings. A suitable substitute was needed. The time now was at the turn of the present century. The chemical formula for cocaine was by now so well known that pharmacologists could study various degradation products with the view of determining what part of the cocaine molecule was responsible for its benumbing action. Once this was known the chemist synthesized a series of compounds based around this active nucleus. These substances were then studied and compared with cocaine in the medical laboratory as to action, toxicity and, if possible, tendency to habit formation. One result of these observations was the introduction in 1905 of novocaine, or procaine as it is listed in the present Pharmacopoeia. This is a compound low in toxicity, satisfactorily active as a local anesthetic and devoid of the curse of habit formation. In all but its inability to produce anesthesia except when injected in close proximity to nerves, it has most of the advantages of cocaine and none of its disadvantages. To-day many other cocaine substitutes are available. Most of them, however, depend on the presence of the active cocaine nucleus for their therapeutic efficacy. And so it goes with other drugs. From the vegetable drug we learn a fundamental action, a definite clue, and then set about to improve that which gives to the natural drug its beneficial effect.

The story of opium is equally fascinating; unfortunately, the solution of the problems which now restrict its usefulness has not been solved with the same degree of satisfaction as is the case of the leaves of the "coca" tree.

The use of opium is recorded in our earliest medical archives. Mention is made of it in the Egyptian papyrus discovered in 1872 by Georg Ebers, which reveals the more popular medicinals as of the year 1552 B.C.

Collected as the juice from the poppy capsule it was used more or less in this rather crude form until the English physician Sydenham in the seventeenth century refined it into a tincture which he then called "laudanum." Epochal in its significance was the further refinement of opium therapy when Sertürner, the German apothecary, isolated morphine from opium in 1804. By animal experimentation and trial on several of his friends and himself he determined this compound to be the major active constituent of opium.

Although it had long been known that opium is a most notorious habit-forming drug, relatively little attention was paid to this problem until the turn of the present century. Then legal measures were instituted with the hope of controlling, in part at least, this marked disadvantage. But more than legal means was needed, and attempts were then made, primarily by pharmaceutical manufacturers, to find opium substitutes having the desired opium effect but free from addiction tendencies.

While some progress was made much remained to be desired. And so in 1929 a program of research was begun under the auspices of the Committee on Drug Addiction of the National Research Council. Under this cooperative scheme, the synthetic chemist, the pharmacologist and the physician all work together towards a single goal—the discovery of an ideal narcotic which could replace morphine, heroin and other similar drugs without fear of addiction. Scores of synthetic compounds bearing chemical resemblance to the natural alkaloids of opium have been synthesized and tested on animals. Some of the more promising ones have been extensively studied by the clinical component of the research triad here in Lexington under the supervision of Dr. C. K. Himmelsbach in the U. S. Health Service Hospital. While the results have been encouraging the ideal substitute has not yet been found, and so the search goes on. Here again is an example of a natural plant gift which is unrivaled in its therapeutic ability and which, due to the studies to which it serves as a cue, may eventually be the instrument whereby human suffering may be relieved to an extent never before realized and with complete safety.

Now in conclusion, from this brief summary of the chemical and pharmacological status of our knowledge of plants, three facts present themselves boldly: (1) Botanical knowledge abounds while chemical and pharmacological information concerning plants is relatively scarce. (2) Drugs belonging to the vegetable kingdom are to be found among our most important medicaments, and so we have reason to have faith in plants as a source of drugs. (3) The potentialities of the vegetable kingdom as a source of useful drugs have by no means been adequately studied.

The logical deduction is obvious. The time seems propitious for an extensive study of plant medicinals, for earnest consideration of the establishment of an institute to systematically study the chemistry and physiological action of members of the vegetable family. The rewards may be astounding, and at any event they would justify themselves solely on the grounds of scientific inquiry. We might not find another sulfanilamide, but we might find another digitalis, another belladonna, another opium. I believe that Rafinesque would have approved of this idea.