ALKALOIDS

This ill-defined group of plant compounds includes many that are both useful and toxic. Though most of them strongly affect human physiology, their functions in plants are still obscure

by Trevor Robinson

The alkaloids are a class of compounds that are synthesized by plants and are distinguished by the fact that many of them have powerful effects on the physiology of animals. Since earliest times they have served man as medicines, poisons and the stuff that dreams are made of.

The alkaloid morphine, the principal extract of the opium poppy, remains even today "the one indispensable drug." It has also had an illicit and largely clandestine history in arts and letters, politics and crime. Quinine, from cinchona bark, cures or alleviates malaria; colchicine, from the seeds and roots of the meadow saffron, banishes the pangs of gout; reserpine, from snake root, tranquilizes the anxieties of the neurotic and psychotic. The coca-leaf alkaloid cocaine, like morphine, plays Jekyll and Hyde as a useful drug and sinister narcotic. In tubocurarine, the South American arrow poison, physicians have found a powerful muscle relaxant; atropine, said to have been a favorite among medieval poisoners, is now used to dilate the pupils of the eyes and (in minute doses!) to relieve intestinal spasms; physostigmine, employed by West African tribes in trials by ordeal, has come into use as a specific for the muscular disease myasthenia gravis. Aconitine is catalogued as too toxic to use except in ineffective doses. On the other hand, caffeine and nicotine, the most familiar of all alkaloids, are imbibed and inhaled daily by a substantial fraction of the human species.

Our self-centered view of the world leads us to expect that the alkaloids must play some comparably significant role in the plants that make them. It comes as something of a surprise, therefore, to discover that many of them have no identifiable function whatever. By and large they seem to be incidental or accidental products of the metabolism of plant tissues. But this conclusion somehow fails to satisfy our anthropocentric concern. The pharmacological potency of alkaloids keeps us asking: What are they doing in plants, anyway? Investigators have found that a few alkaloids actually function in the life processes of certain plants. But this research has served principally to illuminate the subtlety of such processes.

The pharmacology of alkaloids has inspired parallel inquiry in organic chemistry. Some of the greatest figures in the field first exercised their talents on these substances. But nothing in the composition of alkaloids has been found to give them unity or identity as a group. The family name, conferred in an earlier time, literally means "alkali-like." Many alkaloids are indeed mildly alkaline and form salts with acids. Yet some perfectly respectable alkaloids, such as ricinine (found in the castor bean), have no alkaline properties at all. Alkaloids are often described as having complex structures. The unraveling of the intricate molecules of strychnine and morphine has taught us much about chemical architecture in general. Yet coniine, the alkaloid poison in the draught of hemlock that killed Socrates, has a quite simple structure. Nor is there much distinction in the characterization of alkaloids as "nitrogen-containing compounds found in plants." Proteins and the amino acids from which they are made also fit this definition.

From the chemical point of view it begins to seem that alkaloids are in a class of compounds only because we do not know enough about them to file them under any other heading. Consider the vitamin nicotinamide, the plant hormone indoleacetonitrile and the animal hormone serotonin. All these compounds occur in plants, and all contain nitrogen. We would call them alkaloids except that we have learned to classify them in more descriptive ways. As we come to know the alkaloids better, we may select other substances from this formless group and assign them to more significantly defined categories.

Though all alkaloids come from plants, not all plants produce alkaloids. Some plant families are entirely innocent of them. Every species of the poppy family, on the other hand, produces alkaloids; the opium poppy alone yields some 20 of them. The Solanaceae present a mixed picture: tobacco and deadly nightshade contain quantities of alkaloids; eggplant, almost none; the potato accumulates alkaloids in its foliage and fruits but not in its tubers. Some structurally interrelated alkaloids, such as the morphine group, occur only in plants of a single family. Nicotine, by contrast, is found not only in tobacco but in many quite unrelated plants, including the primitive horsetails. Alkaloids are often said to be uncommon in fungi, yet the ergot fungus produces alkaloids, and we might classify penicillin as an alkaloid had we not decided to call it an antibiotic. However, alkaloids do seem to be somewhat commoner among higher plants than among primitive ones.

Some 50 years ago the Swiss chemist Amé Pictet suggested that alkaloids in plants, like urea and uric acid in animals, are simply wastes—end products of the metabolism of nitrogenous compounds. But the nitrogen economy of most plants is such that they husband the element, reprocessing nitrogenous compounds of all sorts, including substances such as ammonia which are poisonous to animals. Indeed, many plants have evolved elaborate symbiotic arrangements with bacteria to secure additional nitrogen from the air. From the evolutionary standpoint the tying-up of valuable nitrogen in alkaloids seems an inefficient arrangement.

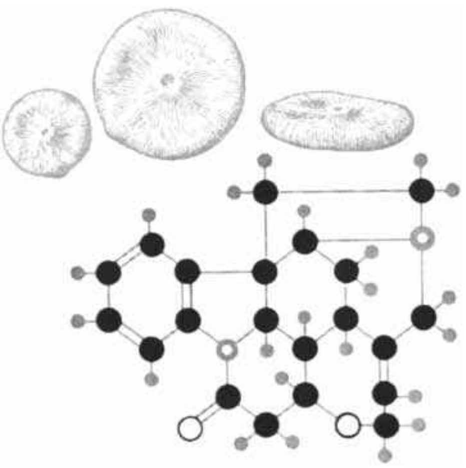
More recently investigators have come to regard alkaloids not as end products but as by-products thrown off at various points along metabolic pathways, much as substandard parts are rejected on an assembly line. That is to say, alkaloids arise when certain substances in the plant cell cross signals and make an alkaloid instead of their normal product. This idea is certainly plausible when it is applied to the alkaloids formed by the action of the commonest enzymes on the commonest metabolites. The alkaloid trigonelline, for example, is found not only in many plant seeds but also in some species of sea urchins and jellyfish. It is merely nicotinic acid with a methyl group (CH_3) added to it. Now nicotinic acid is one of the commonest components of plant cells. Compounds that can donate methyl groups are also common, as are the enzymes that catalyze such donations. A "confused" enzyme, transferring a methyl group to nicotinic acid instead of to some other substance, could thus form trigonelline by mistake [*see illustration at top of page 121*]. Nicotine, which has an equally wide distribution, may likewise be produced by everyday biochemical processes.

The more frequent occurrence of alkaloids in higher plants suggests another idea. More highly evolved organisms have obviously made more experiments in metabolism. Some alkaloids may represent experiments that never quite worked. Others may have originated as intermediates in once-useful processes that are no longer carried to completion. Since most alkaloids seem neither to help nor to hurt the plant, natural selection has not operated for or against them. Thus the modern plant that produces alkaloids may do so for no other reason than the persistent pattern of its genes.

Such explanations for the presence of alkaloids in plant tissues find support in what we know about the synthesis of these substances. In 1917 the noted British chemist Sir Robert Robinson showed that the structures of scores of alkaloid molecules could be built up from amino acids by postulating reactions of a few simple types: dehydration, oxidation and so on. For example, he showed that the amino acid tyrosine could easily be transformed into the alkaloid hordenine. Even the complex molecule of reserpine could be built up, according to his scheme, from tyrosine and the amino acid tryptophan, plus a methylene group [*see illustrations on pages 118 and 119*]. More recently Robert B. Woodward of Harvard University has proposed that the same three substances, through another series of reactions, may yield the extremely complex molecule of strychnine.

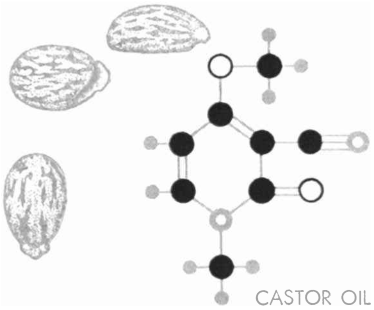
During the past 40 years considerable experimental evidence has accumulated to show that these reactions are not just paper-and-pencil chemistry, but actually occur in nature. Robinson himself correctly predicted the structures of several highly complex alkaloids before these structures were worked out. Later experimenters have shown that enzyme-containing plant extracts can promote amino acid-alkaloid transformations such as the tyrosine-hordenine synthesis. Other investigators, by simply mixing together the postulated precursors of certain alkaloids, have obtained compounds of approximately the correct structure even in the absence of enzymes. Tracer experiments have furnished additional support for Robinson's scheme. If labeled amino acids are injected into alkaloid-producing plants, the plants produce labeled alkaloids. Moreover, the alkaloids contain labeled atoms at just the points that theory predicts.

We know, however, that many steps intervene between the introduction of a labeled precursor and the production of a labeled alkaloid. Moreover, a compound that yields an alkaloid when it is injected in high concentration may not be the normal precursor. Some intermediates go to form all sorts of things, and may only get to alkaloids by quite devious routes. The problem of alkaloid biosynthesis resolves itself into the task of establishing the point at which the alkaloid-producing process diverges from the other metabolic processes of the plant. In principle we might feed various labeled compounds to a plant and ascertain whether the labeled material shows up only in alkaloids or in other substances as well. But we must decide which intermediate compounds we are going to feed. It is fruitless to test a versatile intermediate like glucose, which enters into many processes. In a sense, therefore, we must know our intermediate before conducting the experiment that will identify it. One way of breaking out of this impasse may be to work backward by feeding the alkaloid itself to the plant. By building up high concentrations of alkaloid in the plant's tissues we can perhaps block the alkaloid "production line" and thus cause the im-



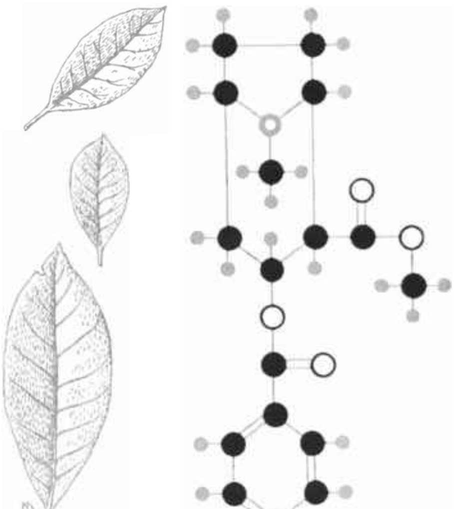
STRYCHNOS NUX-VOMICA

STRYCHNINE



CASTOR OIL BEANS

RICININE

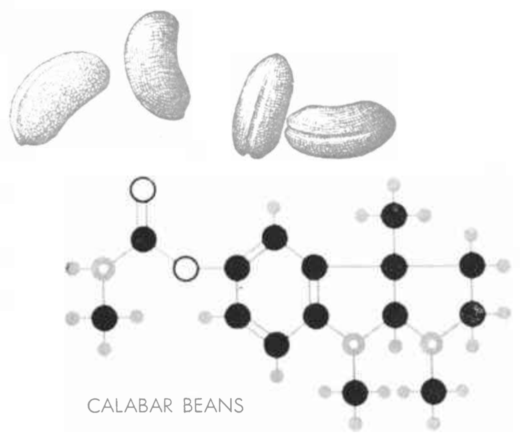


COCA LEAVES

COCAINE

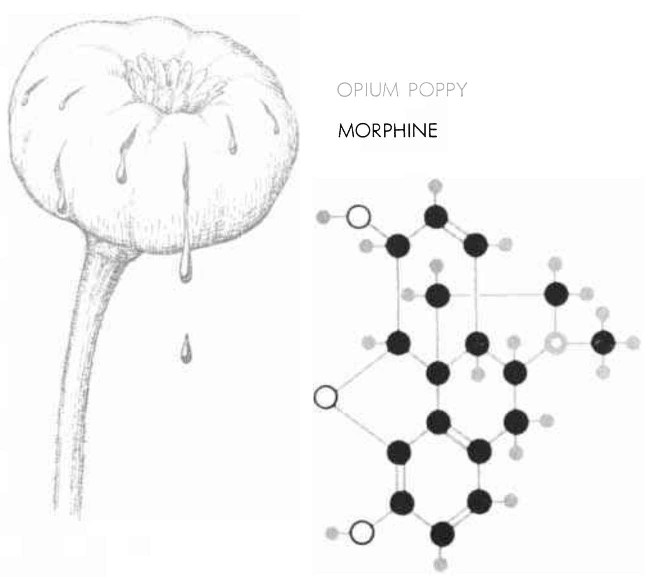
● CARBON
○ OXYGEN
◎ NITROGEN
• HYDROGEN

ALKALOIDS show great structural variety. Depicted in this chart are molecules of nine typical alkaloids together with



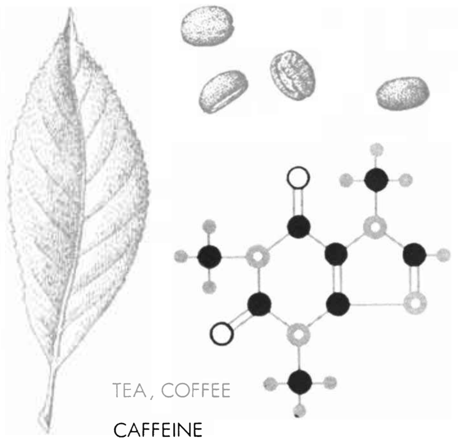
CALABAR BEANS

PHYSOSTIGMINE



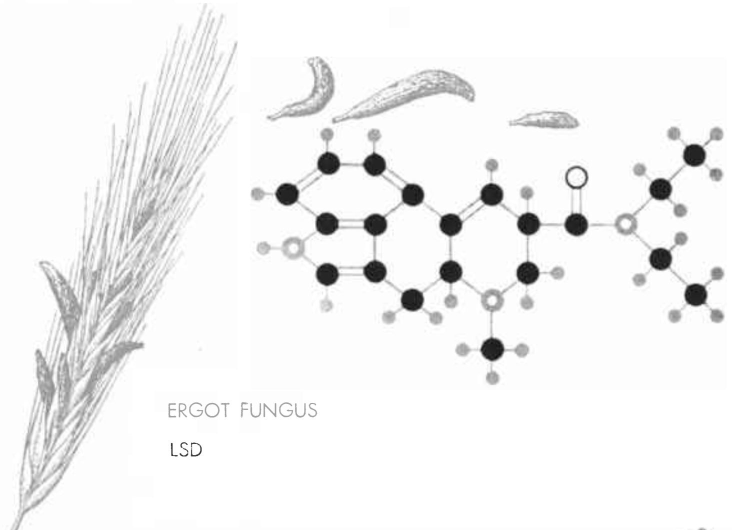
OPIUM POPPY

MORPHINE



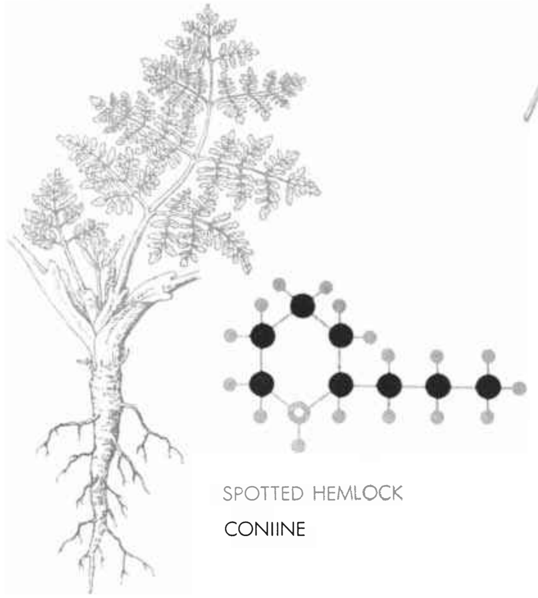
TEA, COFFEE

CAFFEINE



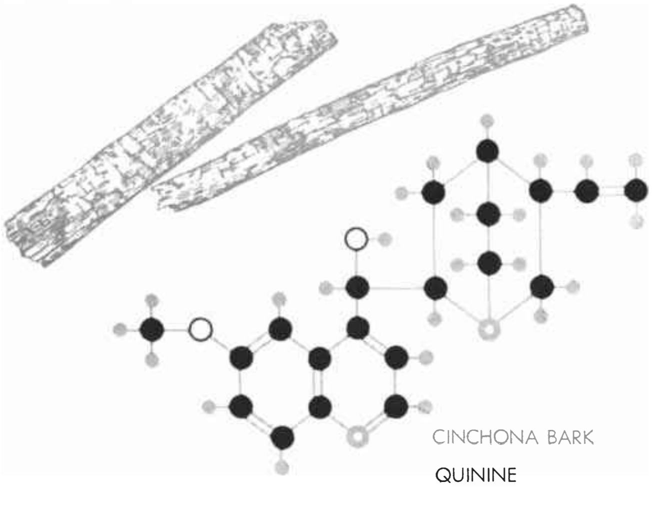
ERGOT FUNGUS

LSD



SPOTTED HEMLOCK

CONIINE



CINCHONA BARK

QUININE

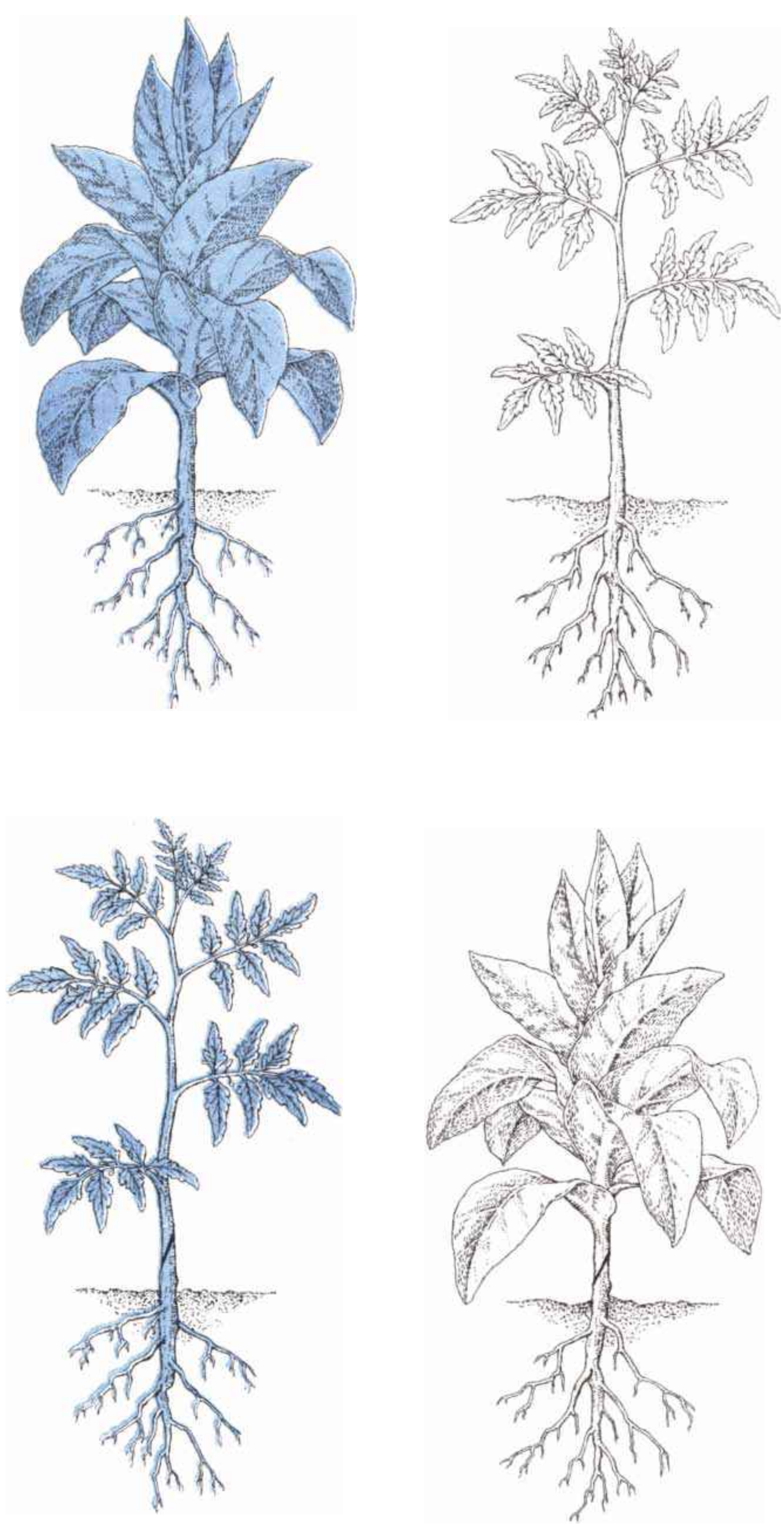
the plants or plant substances from which they derive. At left is the key to these diagrams and those elsewhere in this article. Strychnine, a violent poison, is one of the most complex alkaloids; coniine, the poison which killed Socrates, one of the simplest. Physostigmine, a West African "ordeal poison," is now used to treat the muscular disease myasthenia gravis; LSD (lysergic acid diethylamide) produces delusions resembling those of schizophrenia. Ricinine is one of the few alkaloids that exert little effect on human beings.

mediate precursors of the alkaloid to accumulate to the point where they can be identified.

With this information in hand, we can go on to inquire which enzymes transform these precursors into alkaloids and whether these enzymes function only in alkaloid formation or in other metabolic processes as well. If we find, for example, that a certain enzyme catalyzes the transfer of a methyl group to an alkaloid precursor but does not function in other methylations, we will have to regard this alkaloid synthesis as a definitely programmed process, and not as a mere aberration. Our present sparse knowledge strongly suggests that at least some alkaloids are programmed. Thus ricinine contains a nitrile group (CN), which rarely occurs in living organisms. If the formation of this group is catalyzed by an enzyme that normally does some other job, we have no indication of what the other job might be. From intimate understanding of this kind we may yet help the plant physiologist to discover what there is about different plants that causes one to make reserpine, while another makes strychnine from the same starting materials.

Of course the study of any metabolic process involves not only the synthesis but also the breakdown of the substances involved. If a given alkaloid is just a waste product or by-product, it has no future and there is no breakdown to be considered. In this case it may simply accumulate in the plant's tissues. For example, quinine piles up in the bark of the cinchona tree, and nicotine in the leaves of the tobacco plant. Some ingenious grafting experiments have furnished additional evidence that many alkaloids, once synthesized, become inert and play no further role in the plant's metabolism. The tobacco plant, for example, manufactures nicotine in its roots, whence the alkaloid migrates to the leaves. However, if we graft the top of a tobacco plant to the roots of a tomato plant, which produces no nicotine, the tobacco flourishes despite the absence of the alkaloid. Conversely, a tomato top grafted to a tobacco root becomes impregnated with nicotine with no apparent ill effects.

But the alkaloids in plants are not always inactive. Hordenine, for example, is found in high concentrations in young barley plants, and gradually disappears as the plant matures. By the use of tracers Arlen W. Frank and Leo Marion of the National Research Council of Canada have found that the disappearing hordenine is converted into lignin,



GRAFTING EXPERIMENT indicates that nicotine has no effect on plants. Tobacco plant (*top left*) produces nicotine (*color*) in its roots; the alkaloid then migrates to the leaves. Tomato plant (*top right*) produces no nicotine. A tomato top grafted to a tobacco root (*bottom left*) becomes impregnated with nicotine with no apparent ill effects; tobacco top grafted to tomato root (*bottom right*) is unaffected by the absence of alkaloid. Similar grafting experiments with other alkaloid-producing plants have with few exceptions yielded similar results.

the "plastic" that binds the cellulose fibers in the structure of plants. To be sure, not all plants employ hordenine as an intermediate in making lignin [see "Lignin," by F. F. Nord and Walter J. Schubert; Scientific American, October, 1958]. But it is gratifying to find at least one case in which an alkaloid performs an identifiable function. Similarly, Edward Leete of the University of Minnesota has shown that in some plants nicotine serves as a "carrier" for methyl groups which it ultimately donates to other molecules.

Such modest findings are a far cry from the first grand-scale function assigned to alkaloids a century ago by the great German chemist Justus von Liebig. Since most alkaloids are alkaline, he proposed that plants use them to neutralize deleterious organic acids by forming salts with them. Many alkaloids do, in fact, occur in plants as salts of organic acids. But no one could explain why alkaloid-producing plants should elaborate poisonous acids when closely related plants manage to get along without either the acids or their metabolic antagonists. The question "Why?" still persists. Today it stimulates more modest but sometimes quite intriguing proposals.

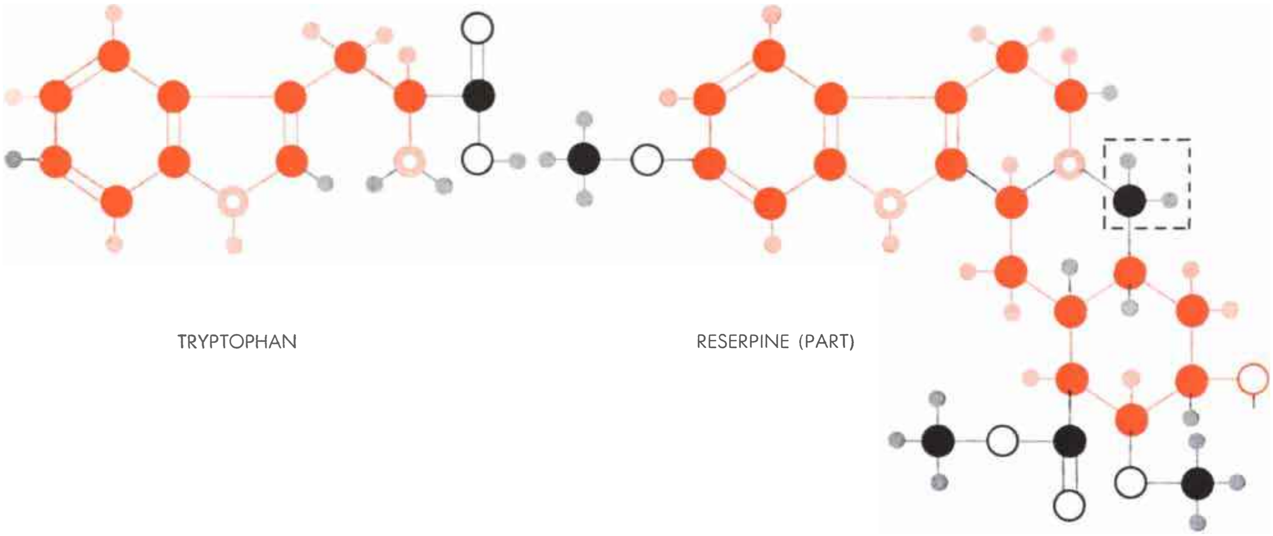
Some experiments by the French physiologist Clément Jacquiot suggest a variant of Liebig's neutralization theory. Jacquiot has shown that the tannin produced in cultures of oak cells inhibits cell growth. The alkaloid caffeine counteracts the effects of the tannin and allows growth to proceed. Unfortunately this suggestion merely replaces one question with another, since the function of tannins in plants is itself unknown. The suggestion has another flaw in that oak cells produce no caffeine of their own. But here, at any rate, is one case in which caffeine is good for something other than providing a pleasant stimulant for coffee-drinkers.

Botanists and ecologists have speculated that the bitter taste of some alkaloids may discourage animals from eating a plant that contains them, and that poisonous alkaloids may kill off pathogenic organisms that attack the plant. One species of wild tomato does produce an alkaloid that protects it against Fusarium wilt, a common fungus disease of the cultivated tomato. However, the "protection" idea must be handled with

TYROSINE

HORDENINE

LIGNIN MONOMER



TRYPTOPHAN

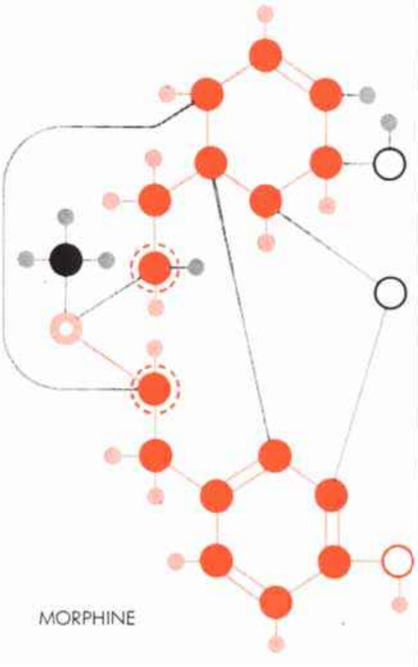
RESERPINE (PART)

AMINO ACIDS appear to be the source of most alkaloids. Thus the skeleton (*color*) of tyrosine, an amino acid, can be easily transformed into hordenine, an alkaloid; broken circles indicate the "labeled" atoms which confirm the synthesis. Two tyrosine skeletons similarly form morphine, as shown at right; the morphine molecule shown here is distorted (*see diagram on page 115*) to emphasize its derivation. Tyrosine and tryptophan, another amino acid, could join with a methylene group (*broken square*) to form part of the molecule of reserpine, an alkaloid tranquilizer. Hordenine is one of the few alkaloids known to undergo further metabo-

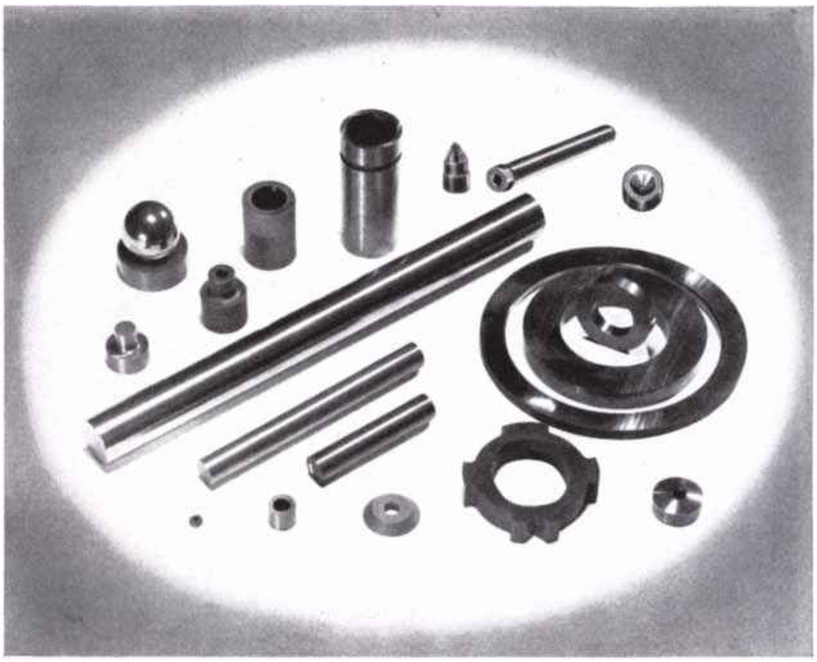
caution because of its anthropocentric bias. What is unpalatable or poisonous to a man may be tasty and nourishing to a rabbit or a cutworm.

More recently the concept of chelation, the process by which certain organic molecules "sequester" the atoms of metals, has suggested another possible alkaloid function. The structures of some alkaloids should permit them to act as chelating agents. The structure of nicotine is temptingly similar to that of dipyridyl, a common chelating agent for iron [*see illustration at bottom of page 121*]. Such alkaloids might help a plant select one metal from the soil and reject others. Alternatively, they might facilitate the transport of the metal from the roots, where it is absorbed, to the leaves, where it is utilized. Quite a few alkaloids, including nicotine, migrate from roots to leaves, but no one has yet determined whether any of them carry metals along with them.

The structures of many alkaloids re-



lism in plants; it is converted into one of the units that form the long-chain molecules of lignin, an essential structural material in many plants. The complete structure of the lignin monomer is not known.



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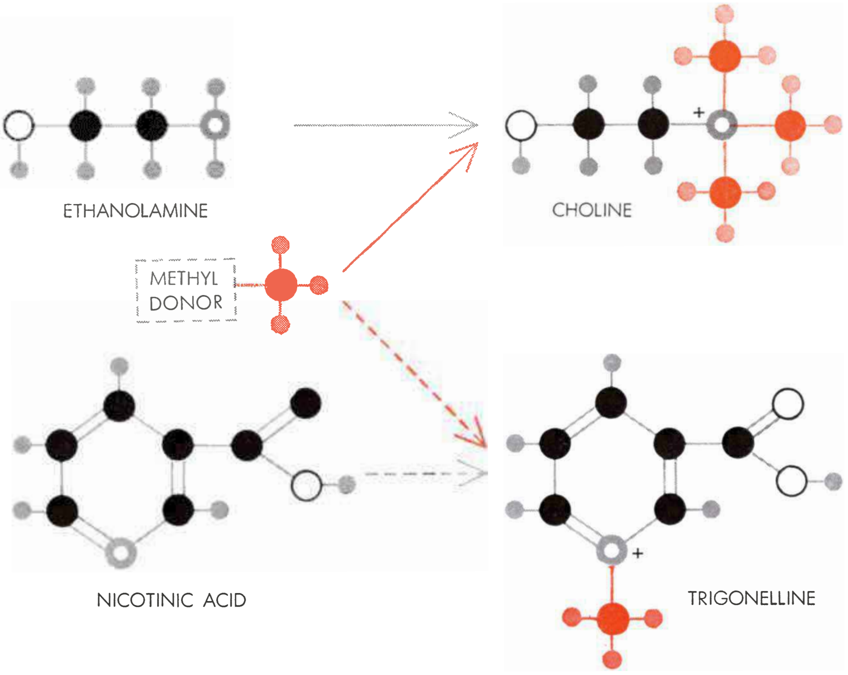
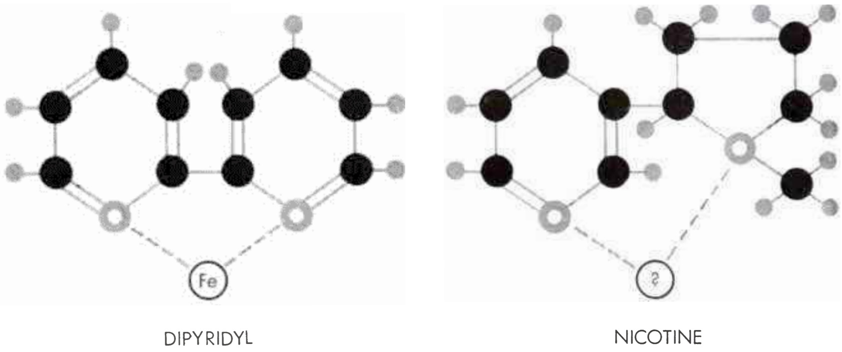


METABOLIC ACCIDENTS may account for the synthesis of some alkaloids. Changing one compound to another by adding methyl groups (*color*), as in the ethanolamine-choline transformation, is a common biochemical process. If a methyl group were added "by mistake" to nicotinic acid, a common plant substance, the alkaloid trigonelline would result.

semble those of hormones, vitamins and other metabolically active substances. This resemblance suggests that such alkaloids may function as growth regulators. In a way this hypothesis fits in with the chelation theory, since certain important growth regulators seem to owe their activity to their chelating capacity. Some alkaloids do affect growth processes: Alkaloids from the seeds of certain lupines can inhibit the germination of seeds of related species that produce no alkaloids. Presumably they help the former species to compete successfully with the latter. Similar alkaloids may function as "chemical rain gauges" which prevent germination until sufficient rain has fallen to leach them away and provide adequate moisture for plant growth. Many plants in arid and semiarid environments depend on such rain gauges for survival [see "Germination," by Dov Koller; Scientific American, April].

No one theory can account for the functions of so heterogeneous a group of compounds. The steroid compounds, a much smaller and structurally a far more homogeneous group, play a wide variety of physiological roles. Future research will probably reveal an even greater functional diversity among the alkaloids. Certainly we must learn a good deal more about the functions of a few alkaloids before we can safely propose generalizations about all of them.



STRUCTURE OF NICOTINE resembles that of dipyridyl, a compound that can "chelate" or bind atoms of iron. This similarity suggests that nicotine, and perhaps other alkaloids, may function as chelating agents in some plants. Whether they actually do so is not yet known.