Metabolism and Function of Alkaloids in Plants

Alkaloids appear to be active metabolites, but their usefulness to plants remains obscure.

Trevor Robinson

Even to a scientifically sophisticated group alkaloids are unfamiliar compounds, so it seems worthwhile at the start to attempt a definition. An alkaloid, first of all, is a nitrogen-containing organic compound. Beyond this prerequisite the definition becomes more difficult. Simple amines are not included with the alkaloids by most authorities, but some make a borderline class called "protoalkaloids" to include amines like mescaline, reserving the name "alkaloids" for compounds with nitrogen in a ring. Alkaloids are then classed according to the simple heterocyclic ring systems present in their structures—for example, indole alkaloids, pyridine alkaloids, benzylisoquinoline, and alkaloids. It is no longer possible to include in the definition that alkaloids are made by plants, since several very interesting animal products must certainly be recognized as having all the necessary characteristics of alkaloids.

Probably the first interest in alkaloids was medical because many plants used as drugs for thousands of years owe their effects to the presence of alkaloids. This line of interest is still a major one in that pharmacologists explore the mechanisms by which certain alkaloids exercise their powerful effects on animals. Second, organic chemists became interested in alkaloids because of the complex problems in structure determination and synthesis that they present. Third, with the advent of isotopic tracer techniques in the early 1950's biochemists began to trace the metabolic pathways by which plants synthesized their alkaloids from common substrates.

All three of the approaches to alkaloids continue to be active areas of research presenting many unsolved problems as well as a considerable body of knowledge. However, the subject is none of these. Rather, I want to take more of a botanical or plant physiological look at the alkaloids, to raise questions such as: What control mechanisms operate in the pathways of alkaloid biosynthesis? What are the rate-limiting steps? What fraction of a plant's synthetic effort is directed toward these pathways? What are the effects of light schedules and hormone balances? Are alkaloids inert end products or do they reenter metabolism? A second group of questions verges on teleology—why plants make alkaloids. Is the significance of an alkaloid to be sought in terms of a plant's internal economy or in terms of its relations with competitors and predators?

Metabolism and Accumulation

Studies on the metabolism of alkaloids have focused on the pathways by which alkaloids are synthesized; and many of these pathways are now known in great detail, almost to each intermediate compound. Large groups of alkaloids can be related to amino acids. Thus, indole alkaloids come from tryptophan, benzylisoquinoline alkaloids from tyrosine, pyrrolidine alkaloids come from glutamic acid, and some piperidine alkaloids come from lysine. I do not propose to go into the details of any of these pathways here. The great attention that has been paid to elucidation of these pathways reinforces the long-held concept of alkaloids as end products, like urea in mammals. There has been a tendency to regard the problem of alkaloid metabolism as solved when routes of biosynthesis have been described; but as any student of elementary biochemistry should know, for most metabolites that is only half of the problem.

It is becoming clear that in many cases alkaloids are not inert end products, but are in a dynamic state fluctuating in both total concentration and in rate of turnover. To some extent this has been empirically realized for hundreds, if not thousands, of years in the case of alkaloids that are valued as drugs. Plants containing such drugs have an optimum time for harvest, and this is seldom if ever when the plant is senescent. The clear implication is that alkaloid content must reach a maximum and then decline. The observed variations in content often correlate well with developmental stages, rather than following a simple time course. Many cases could be cited where unfertilized ovules have alkaloids that disappear after fertilization or of seeds that are rich in alkaloids which decline during germination (*1*). A striking case was reported by Mothes *et al.* (*2*) for the periwinkle, *Catharanthus roseus*, from which several dozen indole alkaloids have been isolated. Virtually no alkaloids are present in the seeds. They then appear during germination and by 3 weeks are present throughout the plant. They then disappear almost completely and finally reappear at about 8 weeks.

Flowering correlates with an increase in alkaloid concentration in some species but a decrease in others. A decline of alkaloid content in leaves of belladonna is shown graphically in Fig. 1 (*1*). A graph of the pattern for two alkaloids of the poison hemlock, *Conium maculatum*, is shown in Fig. 2. Here coniine, the major alkaloid, reaches a peak in amount and then falls off while the minor alkaloid, γ-coniceine, remains nearly constant (*3*).

Diurnal Fluctuations

A second way to show that plants have an active metabolism of alkaloids is to measure fluctuations occurring during a single day. Such fluctuations have been observed by Fairbairn and co-workers for atropine (*4*), hemlock alkaloids (*3*), and opium alkaloids

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(*5*); and their data are reproduced in Figs. 3 to 5. For the hemlock alkaloids it is to be especially noted that coniine and γ-coniceine vary in a complementary way; but since the coniine content is always much higher than γ-coniceine, all of the coniine that appears in one of its peaks cannot be accounted for by the γ-coniceine that disappears concurrently. Since coniine is more reduced than γ-coniceine, the reciprocal changes might reflect changes in the redox potential of the system. For the morphine alkaloids there is also some suggestion of complementary variations, with codeine and thebaine dropping just before the morning rise in morphine. This pattern could be a reflection of the biosynthetic pathway which is known to go:

Thebaine → codeine → morphine

However, analogously to the hemlock alkaloids, morphine is always predominant; so that more morphine is made than can be accounted for by conversion of the thebaine and codeine that disappear.

Diurnal fluctuation of the kind documented above may account for some of the ancient rules of drug plant harvesting, usually regarded as mere superstitions. Theophrastos (*6*) mentions that the herb gatherers of his time (4th century B.C.) prescribed that "some roots should be gathered at night, others by day, and some before the sun strikes on them." Looking at the graph for morphine (Fig. 5) it is seen that the yield at 9 a.m. could be four times the yield at 9 p.m. The old herbalists may have known what they were doing!

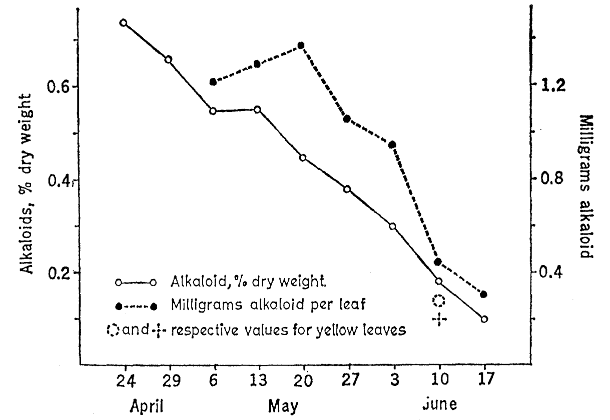
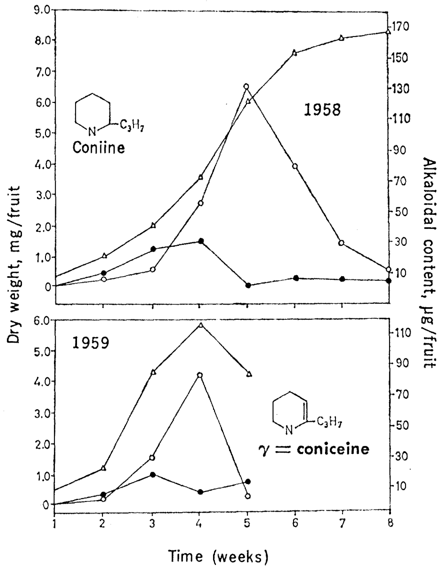


Fig. 1. Total alkaloids in the basal leaves of belladonna throughout their development (*1*). [Courtesy of Academic Press]

Turnover Rates

A third measure of the activity of alkaloid metabolism is made possible through the use of isotopically labeled molecules. By this technique the turnover rate of a compound can be measured even in cases where the total amount remains constant while some molecules are continually being degraded and replaced. Using data from the literature, I have assumed first-order reactions and complete mixing of pools to calculate half-times for the disappearance of several alkaloids. Sander (*7*) injected labeled tomatine into young tomato fruits and found that it disappeared as the fruits ripened. The calculated half-life was 6 days. Data of Frank and Marion (*8*) show a half-life of 42 hours for hordenine in barley. For morphine in poppies I find a half-life of only 7.5 hours from data of Fairbairn and Paterson (*9*). For nicotine in tobacco plants there are data from Leete and Bell (*10*) and Il'in and Lovkova (*11*) that agree in giving a half-life of about 22 hours. When Leete (*12*) fed nicotine to *Nicotiana glauca*, a plant that normally has nicotine as only a minor alkaloid, it was degraded with a half-life of 15 hours. For ricinine in castor bean plants Waller and co-workers (*13, 14*) found at first a very rapid decline extrapolating to a half-life of only 4 hours; but calculated over a longer period the half-life was 160 hours (6.7 days). This change in rate is suggestive of two, nonequilibrating pools.

A 60-day-old tobacco plant contains about 250 milligrams of nicotine. From the turnover data, 92 mg must be degraded and replaced in a 10-hour day; this is about 0.6 millimole. Since there are ten carbon atoms in nicotine, 6 mmole of fixed carbon dioxide would have to be used to replace that amount of degraded nicotine. It is instructive to compare this with the total rate of CO_2 assimilation in a 60-day tobacco plant. Calculation from several sources of data (*15*) suggests a probable figure of about 35 mmole of net CO_2 fixation per plant per day. If 30 percent of the gross CO_2 is lost by photorespiration (a reasonable estimate for tobacco), about 50 mmole of CO_2 is metabolized. This is a startling result for anyone who believes that alkaloid metabolism is a trivial part of a plant's total effort. Figure 6 summarizes the foregoing considerations, but with considerable ambiguity since the 0.6 mmole of nicotine only replaces another 0.6 mmole that disappears. What disappears may contribute to the expired CO_2, and it may con-



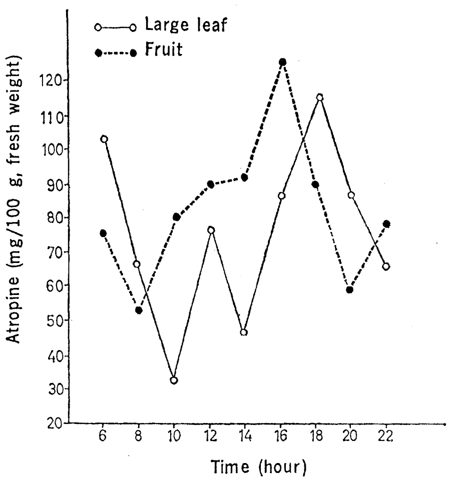
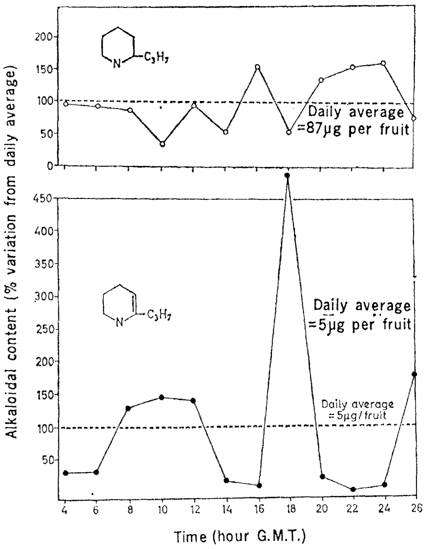


Fig. 2 (left). Alkaloidal content and dry weight for weekly samples of *Conium maculatum* (*3*). Dry weight, △; coiine, ○; γ-coniceine, ●. [Courtesy of Microform International Marketing Corporation, exclusive copyright licensee of Pergamon Press journal back files] Fig. 3 (right). Diurnal changes in atropine content of *Atropa belladonna* (*4*). [Courtesy of *Journal of Chemistry of the United Arab Republic*, Cairo]



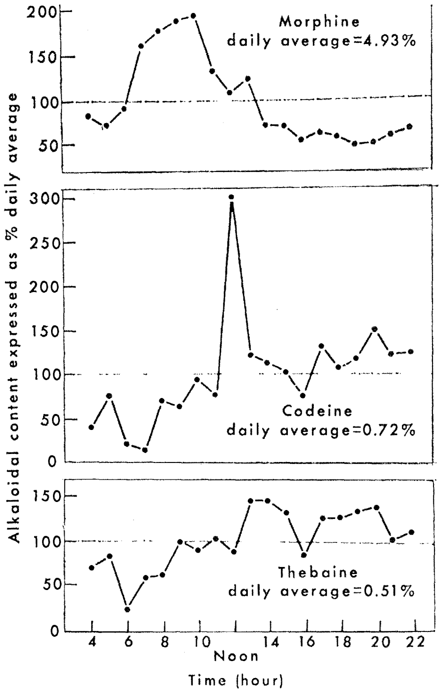


Fig. 4 (left). Diurnal changes in content of alkaloids of *Conium maculatum* in week 4, 1959 (*3*). Coniine, ○; γ-coniceine, ●. [Courtesy of Microform International Marketing Corporation, exclusive copyright licensee of Pergamon Press journal back files]

Fig. 5 (right). Diurnal changes in content of alkaloids of *Papaver somniferum* (*5*). [Courtesy of Microform International Marketing Corporation, exclusive copyright licensee of Pergamon Press journal back files]

tribute additional carbon to the "other products." The point, though, is that the rate of nicotine turnover is appreciable in comparison to what is usually considered to be the main business of the plant, fixing carbon dioxide.

Fate of Alkaloid Molecules

The evidence considered so far is convincing that alkaloids can no longer be regarded as inert end products. The next question is, What happens to the alkaloid molecules that are degraded? or specifically, What happens to the 92 mg of nicotine that is turned over daily in a tobacco plant?

Very little information is available to answer such questions. When isotopically labeled alkaloids are fed to plants, labeled products can be found, but most of them have not been rigorously identified. In both hemlock and poppy so-called "bound forms" have been identified by Fairbairn *et al.* (*16, 17*). These are evidently large molecules or complexes that release alkaloids on hydrolysis. Nucleotide-like derivatives have been suggested. It has been shown that isotopic carbon from nicotine finds its way into protein and many other metabolites in tobacco plants (*11, 18*). Methyl groups from nicotine can be transferred intact to choline (*10*). Tritium from tritiated ricinine is incorporated into nicotinic acid in castor bean plants (*19*). Some carbon from ricinine also appears as CO_2 (*13*) as does some carbon of morphine in poppy plants (*18*). The quantitative significance of all these conversions, though, remains in doubt.

In the case of *Genista* alkaloids certain transformations have been inferred from the observation that the level of one alkaloid goes down while that of another goes up, but such an observation does not require that the first is converted directly to the second. Pathways proposed by Steinegger and Bernasconi (*20*) on the basis of such observations are sketched in Fig. 7. Unlike the γ-coniceine–coniine example described earlier, the concentrations involved are compatible with the conversions that are postulated.

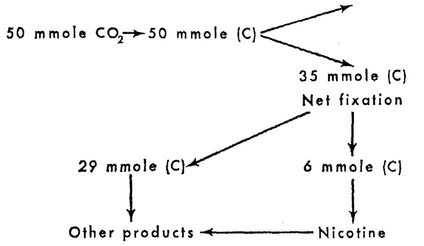


Fig. 6. Quantitative aspects of carbon dioxide and nicotine metabolism in tobacco plants: carbon dioxide assimilation by one tobacco plant per day.

One of the best cases for the metabolism of an alkaloid has been developed by Waller and his co-workers (*21, 22*) for ricinine in castor bean plants, following their observation that this alkaloid disappears completely from leaves that become senescent. A cyclic process of metabolism and translocation has been established by these workers (Fig. 8).

A similar but less studied case of demethylation has been shown to occur in the opium poppy by Miller *et al.* (*23*). They found that morphine was demethylated to normorphine at a rapid rate. Normorphine, however, was never converted back to morphine. It disappeared, going to unknown products, with a complete turnover in 4 hours. Miller *et al.* proposed that the morphine is functionally important as a methylating agent, but transfer of intact methyl groups to other compounds has not been shown.

It seems well at this point to recall the frequently stated teaching of Mothes (*24*) that the presence of an alkaloid in a plant means not only that the ability to synthesize is present. It means also that the rate of degradation is slow enough to permit some accumulation, and that the plant can tolerate the alkaloid. Some plants that lack alkaloids may, in fact, only degrade them faster than they synthesize them. Evidence that this is so is clearly hard to find, but it is known in a few cases that certain reactions of alkaloid biosynthetic pathways are present in plants that do not normally contain the alkaloids. Nonalkaloid legumes, if fed certain lupine alkaloids, will transform them into other lupine alkaloids (*25*). Tobacco fed thebaine will convert it to codeine and morphine (*26*). Cell suspension cultures from the common bean, *Phaseolus vulgaris*, will synthesize harman-type alkaloids if the medium is enriched with tryptophan (*27*). Thus, it is not far-fetched to suggest that certain steps in the pathways of alkaloid metabolism may be commonly occurring in plants and that only a small aberration may be sufficient to convert a plant that does not contain alkaloids into one that does. Such a change could reside in decreased degradative ability as well as in increased synthetic ability.

Controls

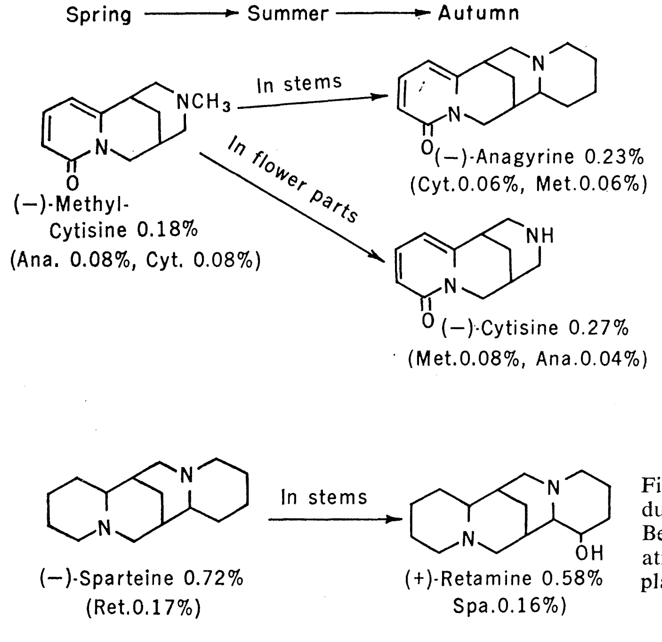
The last-mentioned consideration leads to the question of what controls operate in alkaloid metabolism. Assuming that the genetic potential is present for a plant to synthesize and degrade alkaloids, what can be said about the rates at which these processes may be influenced? Certain general rules have often been repeated and have stood the test of time (*1*, *28*). One of these is that alkaloid formation is greatest in those tissues that are most active in overall metabolism. Thus, one would expect that factors that stimulate metabolism or growth rate might also stimulate alkaloid biosynthesis. Because of the economic importance of certain alkaloids, many such factors have been tested. For example, the influences of mineral nutrition and light intensity are well summarized in a review by James (*1*). Those conditions of light and mineral nutrition that favor increased growth, in general, favor increased alkaloid synthesis, but there are many exceptions to this correlation. Effects of light quality have not been studied very much but are of interest in possibly relating control of alkaloids to particular pigment systems, such as phytochrome or the photosynthetic pigments. The formation of solanine in sunburned potato tubers is a well-known phenomenon accounting for the toxicity of green potatoes. It was shown by Conner (*29*) in 1937 that ultraviolet light is most effective in stimulating solanine formation. Therefore, solanine cannot be regarded as resulting simply from increased photosynthesis. Species of *Lycopersicon* that flower under short days contain five times as much tomatine when they are grown on long days. Species that are less strongly short-day plants show a smaller difference in alkaloid levels between the two day-length regimes (*30*). In *Datura metel* long days favored production of scopolamine and hyoscyamine; but this seems not to be a phytochrome effect since short days plus a half hour of red light in the middle of the nights were not as effective as long days. There may, however, be a low intensity effect on the ratio of scopolamine to hyoscyamine (*31*). Tso and co-workers (*32*) have studied the effect of photoperiod and light quality on tobacco alkaloids and found that long days favored alkaloid production. This is evidently a phytochrome effect since the yield was higher if 5 minutes of red light was given at the end of the light period than if far-red was given. For example, with 18 days of treatment the content in leaf blades was 0.70 percent with 5 minutes of red light at the end of the day and 0.39 percent with 5 minutes of far-red at the end of the day—almost a twofold difference.

Table 1. Some effects of gibberellic acid treatment on alkaloid content of plants.

Plant	Effect	Reference
Atropa belladonna	Increase under some conditions, decrease under others	(*49*, *50*)
Catharanthus roseus	Increase, then decrease	(*51*)
Datura stramonium	Increase reported by some, decrease by others	(*50*, *52*)
Nicotiana spp.	Decrease in all cases	(*53*)

There is some scattered information on effects of plant growth regulators on alkaloid biosynthesis, but no consistent picture emerges. Auxins depress the nicotine content of *Nicotiana tabacum* both in whole plants and in callus tissue cultures (*33*). Some gibberellin effects are summarized in Table 1. All possibilities are observed. The apparent differences may well arise from differences in time or manner of application. The conclusion from all of these experiments is that nothing of fundamental importance has been learned either about the metabolism of alkaloids or the mode of action of growth regulators, both of which remain intriguing mysteries.

In a few cases alkaloid synthesis is



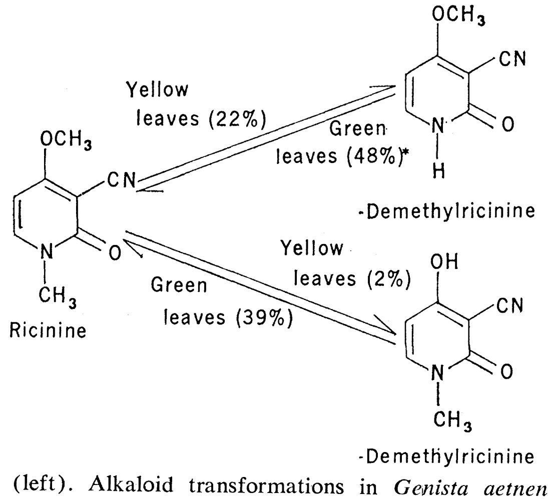


Fig. 7 (left). Alkaloid transformations in *Genista aetnensis* during a growing season. [From the data of Steinegger and Bernasconi (*20*)] Fig. 8 (right). Methylation and demethylation reactions involving the alkaloid ricinine in castor bean plant leaves (*22*). [Courtesy of Pergamon Press]

Table 2. Some biochemical effects of alkaloids; ATPase, adenosine triphosphatase.

Alkaloid tested	Primary action	Later effect	System used	Reference
Theophylline	Inhibits 3′,5′-phosphodiesterases	α-Amylase released	Barley endosperm	(*54*)
Quinine	Intercalates in DNA helix	Phenylalanine–ammonia lyase induced	Pea pods	(*55*)
Caffeine	Binds to part of operon	Adenylsuccinate lyase activity increased	*Bacillus subtilis*	(*56*)
Diaminosteroid alkaloids	Complex with DNA	Inhibit replication	Bacteriophage	(*57*)
Tubulosine	Hinders transfer of amino acids from tRNA	Inhibits protein synthesis	HeLa cells	(*58*)
Quinidine	Inhibits ATPase, pyruvate kinase, lactic dehydrogenase	Slows glycolysis	Rat heart	(*59*)
Cryptocaria alkaloids	Inhibit peptide bond formation	Inhibit protein synthesis	Ascites cells	(*60*)

apparently limited by lack of a particular precursor of the alkaloid molecule. These observations agree with the hypothesis that alkaloids represent ways of disposing of excess substrates, shunting them out of pathways that could lead to deleterious effects. In tissue cultures of *Scopolia parviflora* and *Datura* spp. tropic acid must be added to obtain good production of the usual alkaloids scopolamine and hyoscyamine (*34*). These alkaloids are esters of tropic acid, and it is proposed that the synthesis of tropic acid from phenylalanine is repressed in cultured cells. Addition of the tropane alkaloid precursors arginine or ornithine also stimulates alkaloid production in cultured belladonna roots (*35*). Barley embryos in culture produce no hordenine unless tyramine and a methyl donor, such as methionine, are added. The endosperm ordinarily supplies these precursors (*28*). Tryptophan acts as an inducer for the synthesis of the indole alkaloids of ergot (*36*). It is, of course, also a precursor for these alkaloids. The stimulation of alkaloid biosynthesis by addition of some compound that then serves as a precursor of the alkaloid must be regarded cautiously. A number of artifactual pathways have turned up in such experiments, pathways that do not occur in normal plants with normal concentrations of metabolic intermediates. One must constantly keep in mind that the only true organic substrate for a green plant is carbon dioxide at 0.03 percent. Introduction of any other organic compound creates an abnormal situation to which the plant may respond in an abnormal way. Several aberrant pathways all leading to normal tobacco alkaloids have been reported (*37*).

Role of Alkaloids

The third aspect of alkaloids that I want to consider is the most treacherous because of the danger of slipping into teleology and anthropocentrism. Nevertheless, it is the aspect that is of the greatest general interest. Why do plants make alkaloids? Or, in more sophisticated language, what selective advantage does the presence of alkaloids confer? A number of the leading writers on this subject have concluded that the production of alkaloids is, in general, of no advantage (*28, 38*). It is to be considered like the human appendix, a relic of a period when cellular metabolism was more varied and inefficient than it is in most of today's surviving organisms. Before looking at some specific instances where the possession of an alkaloid does seem to be advantageous to a plant's survival, it is worth stressing again that perhaps 10 percent of a tobacco plant's carbon metabolism is apparently directed toward nicotine biosynthesis. Such a high degree of diversion into a useless pathway would seem adequate to doom a plant to extinction in competition with plants that avoided such waste. A similar argument can be made against the survival of photorespiration. We need a better understanding of these apparently wasteful processes or we need some change in appreciation of how much selective disadvantage dooms to extinction.

The conversion of alkaloids into metabolites of recognized worth has been mentioned earlier. The complexity of these pathways and the low rate at which they operate seem to preclude any quantitatively important role for them. For the indole alkaloids that are derived from tryptophan, a proposal that crops up from time to time is that the production of an alkaloid saves the plant from converting excess tryptophan into indole-3-acetic acid that would then upset the hormonal balance. This seems to be a painfully contrived argument. Control of the rate of tryptophan synthesis or a system for oxidative degradation of tryptophan would clearly be more efficient ways of achieving such a goal.

The most widespread belief for the function of alkaloids is that they act as poisons or repellents toward predators, parasites, and competitors. Among the thousands of alkaloid-containing plants there may not be a dozen for which there is evidence that this is a valid argument. Nicotine and ryanodine are specifically insecticidal (*39*). The steroidal alkaloids of potato are repellent to potato beetles (*40*). The senita cactus (*Lophocereus schatti*) is toxic to most species of *Drosophila* by virtue of the alkaloids it contains. Interestingly, though, *D. pachea* is resistant to the alkaloids and is the only species that breeds in old stems of the cactus (*41*). As a contrast to these toxic effects on insect predators, it must be mentioned that the attack of aphids on broom (*Sarothamnus scoparius*) is actually stimulated by the presence of the alkaloid sparteine. The aphids adjust their feeding sites to follow gradients of sparteine in the plant. If sparteine is painted on pea plants—abnormal hosts—aphids can be induced to feed on them (*42*).

The best case for alkaloid protection against consumption by higher animals can be found in reports that sheep avoid grazing varieties of lupine that contain high levels of alkaloids. They readily graze on the so-called "sweet" varieties that are not absolutely free of alkaloids but have very low concentrations (*43*).

A few examples can be cited for a possible role of alkaloids in competition between plants. Alkaloids can be toxic to plants in high concentrations, even toxic to the same plants that make them. The powerful effects of colchicine on mitosis are well known because of their practical applications. Other antimitotic alkaloids exist but are less well known (*44*). *Veratrum* alkaloids have been shown to inhibit growth of oats and rye, apparently through a specific effect on DNA stability (*45*). Diterpenoid alkaloids of *Delphinium ajacis* inhibit internode growth in peas, perhaps by some interference in the gibberellin system (*46*). Nicotine has been reported to act as an antiauxin (*47*). It also has a specific inhibitory effect on chlorophyll synthesis (*39*). Other less specific inhibitory effects of a variety of alkaloids can be found. One that probably has real importance in plant competition is the inhibition by barley plants of growth of several other plants. This inhibition has been shown convincingly by Overland (*48*) to be, at least partially, the result of gramine excreted by the barley roots.

A number of other known biochemical effects of alkaloids could have relevance to their functions in plants. A summary of such effects is given in Table 2. The point of this tabulation is that the processes affected are all processes that do occur in plants, and it is, therefore, in the realm of possibility that the alkaloids listed could in their own plants influence these processes. However, in no case is there a shred of evidence that such a thing actually occurs.

Summary

In conclusion, there are three major points to be reemphasized:

1) Never again should anyone say that alkaloids are inert end products of metabolism. Rather, there is a wide range of metabolic rates among them and some of these rates are appreciable.

2) In most cases the products of alkaloid degradation are unknown; and where the products are known, the quantitative significance of the pathways leading to them is unknown.

3) Although alkaloids have been considered as protective substances in plants, there is very little hard evidence that such is the case.

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