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Alkaloid Biology and Metabolism in Plants

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Preface

This book is designed for the use of the advanced student and professional worker interested in the international scientific community, particularly those in the fields of agronomy, agricultural sciences, botany, biological sciences, natural products chemistry, pharmaceutical chemistry and biochemistry. The purpose is to inform the reader about significant advances in the biology and metabolism of alkaloids in plants. Since alkaloids are generally referred to as "secondary metabolites," the reactions discussed are not, for the most part, involved with the main metabolic pathways. The reactions that we are interested in are pathways that have been developed for the formation of these secondary metabolites, using as their starting molecules one of the compounds produced via a main or primary metabolic pathway. The primary metabolic pathways are common to all plants, indeed to most living organisms, whereas the highly specialized branches leading to alkaloid formation are found in only about 10 to 20% of the known plants. The reason for these diversities in plant metabolism is not clear; however, it seems likely that the formation of highly individualized and specialized pathways resulted as a response to the pressure of natural selection. Nevertheless, the genetic peculiarity that controls alkaloid production has provided many extremely interesting problems for scientists and constitutes convincing evidence of nature's superior ability in biochemistry.

This attempt to pull together in one book most pertinent information is a result of a desire by both authors to present an authoritative, up-to-date treatise. Frequent references are made to the outstanding series *The Alkaloids*, edited by R. H. F. Manske, *Biosynthese der Alkaloide* by K. Mothes and H. R. Schuette, *Secondary Metabolism in Plants and Animals* by M. Luckner, and *The Biochemistry of Alkaloids* by T. Robinson. The authors recognize the contributions of the series *The Alkaloids—Specialist Periodical Reports* edited by J. E. Saxton; of *Chemistry of the Alkaloids* by S. W. Pelletier; and those of the early very authoritative volumes

The Plant Alkaloids (4 volumes) by T. E. Henry, *Die Alkaloide* by Georg Trier, and *The Vegetable Alkaloids* by Amé Pictet (translated into English by H. C. Biddle). This list is not all-inclusive. In presenting this material for *Alkaloid Biology and Metabolism in Plants* we have adopted the view that biosynthesis (which is such a large field that it requires a separate book), catabolism, genetic, chemotaxonomic, environmental influences, sites of alkaloid formation, and the role of alkaloids in plant physiology must be considered. Many of the studies presented have been carried out on whole plants, with results understood poorly, i.e., in terms of genetic control, chemotaxonomic relationships, environmental influences, and sites of alkaloid formation. It would be preferable to rely on the results of isotopic labeling studies, such as have developed over the past 25 years, and some are reported in this book. The study of alkaloid metabolism has not reached a level of sophistication as high as that of some other areas of intermediary plant or animal metabolism.

Writing a book of this type presents many difficulties when the coauthors live more than five thousand miles apart. This book was originally drafted in 1968–69 in Stillwater, where we could work on it together. Recently we met and worked on some of the problems; the others have been settled by correspondence. The coverage of the literature has been completed through 1975. We would appreciate that any errors of commission or omission are called to our attention.

We are indebted to those who reviewed the individual chapters: Dr. Robert M. Ahring, Dr. Donald F. Banks, Dr. Eddie Basler, Dr. B. R. Clay, Dr. Margaret Essenberg, Dr. Robert K. Gholson, Dr. Wilfred E. McMurphy, Dr. Jay C. Murray, Dr. E. C. Nelson, Dr. Jimmy F. Stritzke, Dr. Glenn W. Todd, and Dr. Ronald J. Tyrl (all faculty members of Oklahoma State University), Dr. H. J. Floss (faculty member of Purdue University), Dr. W. W. Weeks (faculty member, North Carolina State University), Dr. Ian Forbes, Jr. (Research Agronomist, USDA, Tifton, Georgia) and also Dr. Otis C. Dermer, who read the entire book. We express our sincere appreciation to Mr. Jack I. Fryrear, who did the drawings in this book.

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Introduction

Twenty years ago the number of known alkaloids was about 800. At present it is estimated that in excess of 6000 compounds with alkaloid-like properties have been described. Most of them are found in the *Angiospermeae* and only a few in the *Gymnospermeae* (including the *Taxus* and *Pinus* pseudoalkaloids). The *Lycopodiales* and *Equisetales* do contain some alkaloids, but the ferns and the mosses have none.

A comment on the definition of alkaloids is appropriate. The term "alkaloid" is applied to nitrogen-containing compounds, produced primarily in higher plants but also in lower organisms and in some animals, that have significant pharmacological activity. They are grouped together because of the presence of a basic nitrogen atom in their structures rather than by ring size or type. They represent one of the largest and most diverse families of natural compounds, and they contain some of the most complicated molecular structures.

Alkaloids were considered for a long time as specialized products solely of plant metabolism. Yet in recent times alkaloids have been isolated from both vertebrate and invertebrate animals. Some of the animal alkaloids can clearly be traced to a food plant ingested. As an example, the alkaloid castoramine, isolated from the beaver (*Castor canadense*), resembles the alkaloids of the water lilies, *Nuphar* spp., which serve as food for the beavers. Some caterpillars accumulate alkaloids from the plants on which they feed. Other alkaloids, however, such as the ones found in toads, salamanders, and some fishes, are true products of animal metabolism.

Alkaloids can be recognized as resulting from aberrations of metabolic pathways in both plants and animals. Most alkaloids have a disturbing effect on the animal nervous system; therefore, it is unlikely that a mutation (followed by hybridization) in metabolism causing the synthesis of an alkaloid can be established because it would be self-destructive (lethal). Only in instances where the mutation occurs in a tolerant (preadapted?)

system can the mutant survive. In many laboratories alkaloids are considered merely offshoots of normal metabolism, so-called aberrant forms. Then, what is the reason for a scientist to spend time and resources to investigate these metabolic curiosities—the alkaloids—particularly when our knowledge of the basic metabolism of higher plants is negligible? We shall address ourselves to answering this question. Over 90% of the biological compounds on the earth's surface are produced by higher plants, yet we only have a fragmentary knowledge of the metabolic pathways that operate in these plants. If our knowledge of higher plant basic metabolism is so limited, why bother with alkaloid research?

Alkaloids are the oldest drugs. Since the times of Hippocrates, extracts of plants have been known to serve as medicine for a number of diseases. Later on, many of the respective active principles of those plant extracts have been identified as alkaloids. Even with the dramatic progress of organic chemistry which has resulted in an enormous production of synthetic drugs, some of the most powerful remedies are still of plant origin. Whereas organic synthesis of complicated molecules is often extremely costly, *plants produce them with apparent ease and at little cost; so plants will remain important sources of some*. In the last 40 years, the attention of the pharmaceutical industry has been directed to the lower plants, predominantly to fungi, as sources of antibiotics. There are no reasons to believe that higher plants are entirely void of antibiotics since they do survive in a world infested with bacteria and fungi. The search for alkaloids with anticancer activity has revealed a number of compounds which can retard the development of tumors. A surprise for many scientists was the finding that a common ornamental plant, the periwinkle (*Vinca rosea*), produces such alkaloidal compounds. Other plants such as *Tylophora crebiflora*, *Ochrosia elliptica*, *Acronychia baueri*, and *Camptotheca acuminata* have yielded still other substances of this type. Moreover, some steroid alkaloids are important to the pharmaceutical industry. While the price for some synthetic steroids is prohibitive, certain plants accumulate compounds which after a simple chemical modification become steroid hormones, just like those regulating metabolism in animal and human bodies. With millions of women throughout the world taking "the pill," the demand for steroid alkaloids is increasing. Our knowledge of the distribution of those alkaloids in the plant kingdom has increased considerably. The best sources are in tropical flora, but some countries in temperate zones want to limit import of raw materials. Thus a search for indigenous plants containing steroid alkaloids is going on continuously, and experiments leading to the highest production of these compounds in plants are being performed.

The *Thallophyta* were, for a long time, regarded as alkaloidless, but

recently a number of compounds of alkaloid character have been isolated from various lower plants. These new alkaloids may represent new alkaloid families according to their structure, and it is hard at present to estimate their significance both for plant metabolism and for chemotaxonomy. The metabolism of lower plants is still mostly unknown; however, heterotrophic organisms such as the fungi have been helpful in some areas of biological research, e.g., *Neurospora*, *Aspergillus*, *Claviceps*, and *Saccharomyces*. The concept of "lower plants" is an artificial one since it refers to a conglomerate of taxonomic units which can have common ancestors as far back in time as the pre-Cambrian era. Extended research on the lower plants would be likely to yield more new compounds that show some alkaloid-like character. Indeed some such compounds have been isolated, and in some instances they (the peptide-like compounds) are of value for their bacteriostatic properties. A number of antibiotics have been shown to be alkaloidal in nature.

In the last 10–15 years the pathways leading to alkaloid biosynthesis have been partly elucidated by the work of numerous laboratories. In spite of the enormous number of alkaloids only a few pathways leading to alkaloid biosynthesis are known. Several pathways lead from essential amino acids to alkaloids, one from a vitamin, nicotinic acid, and/or its coenzyme form NAD, and one from isoprenoids and certain other small molecules that are active intermediates. Usually it is easier to isolate an alkaloid than an amino acid or a vitamin. The purity of the isolated compound is also much higher. Knowing from recent research that a certain alkaloid is a derivative of an amino acid, we can investigate the biosynthesis of this amino acid, using the alkaloid as a model compound. It is a less cumbersome approach, although less direct. Degradation procedures that were elaborated when the structures of the alkaloids were elucidated were helpful in demonstrating how the precursors were transformed into the amino acid, which in turn served as the substrate for alkaloid biosynthesis. This indirect study of amino acid metabolism is applicable only to the few known amino acids which are intermediates in alkaloid biosynthesis. These very important amino acids are lysine, tryptophan, tyrosine, phenylalanine, and aspartic acid. They are essential for humans and certain animals. We need more knowledge in the near future to be able to manipulate plant metabolism in such a way that the plants will produce more and higher quality proteins. The biosynthesis pathway for nicotinic acid, which proved to be entirely different in plants and in animals, was probably learned only with the help of alkaloid research; specifically, the route of biosynthesis of ricinine and nicotine provided proof of the pyridine nucleotide metabolic cycle in higher plants. It is extremely difficult to examine the biosynthesis of a compound such as

nicotinic acid in plants where the concentration is less than 1 mg/g of dry weight. Yet, in several examples, an alkaloid can accumulate in concentrations up to 10% of the dry weight of the substance. An isolation procedure for a substance that occurs in low concentration is usually cumbersome and expensive; in contrast, the isolation of an alkaloid, once the proper procedure is found, is relatively simple and quick.

Interdependence of individuals is a fundamental characteristic of societies, be they plant, animal, microorganism, or human. Humans today depend more on intellect for survival and an understanding of food problems is essential; some food habits and attitudes toward eating may become quite strong. Some civilizations have died out while others have survived; some alkaloid-containing plants may have been responsible. It is well-known that certain animals have the capability to smell and/or taste the plant which has a high alkaloid content. Thus if given a choice they will avoid the high-alkaloid-containing plant and consume the low-alkaloid-containing plant; but if they have no choice then they will consume the high-alkaloid-containing plant, sometimes to the animals' own demises.

We are living in a world where most plants produce secondary metabolites that are not without significance for our health. Properly used, they can be medicines, but they can also be poisons. Because of progress in processing food, mass poisoning by alkaloids accidentally introduced is much less common today than it was in the past, e.g., with bread made from flour contaminated with the sclerotia of *Claviceps*. Yet new dangers arise. Increased application of synthetic fertilizers can upset the precarious balance of metabolism in some cultivated plants with the result that the plant can start to produce compounds of alkaloid character. Until recently there were only a few known examples, the victims being herbivorous domesticated animals. Edible varieties of cultivated plants bred under certain conditions proved to be poisonous when grown under other conditions. Our knowledge of the processes leading to changes in alkaloid metabolism is still limited, but some clues are already available. Some alkaloids which at first glance seem to be harmless have, after further investigation, been recognized as mutagenic or tumorigenic, e.g., lysergic acid diethylamide (LSD) and some pyrrolizidines. Minute amounts of alkaloids are taken daily by everybody in food. People may be fully conscious of their intake in the case of beverages like coffee, tea, and cocoa (all of which contain caffeine), but they may ingest some unaware, since increased alkaloids may be present as a result of the changes in the environment of the plants.

With all the above-mentioned data in mind it is understandable that research on alkaloids should and will proceed. In some plants they have acquired the name "a metabolic curiosity," important to study both on its

own merit and because of its contribution to understanding of basic nutrition processes. In this manner even alkaloids can be nutrition research tools. Alkaloids in medicine remain important sources of drugs both for physical illnesses and for increasing numbers of mental diseases. So, there is need for research on alkaloids produced in plants that serve as food and feed; for example, scientists breed a disease-resistant crop variety and then a new destructive strain of the disease develops and the scientists have to start over again. When the superior varieties bred in one country are grown in other countries under new environmental conditions, studies on alkaloids as well as on the nutritionally valuable components should be made.

As the world turns to alternative energy technologies the role of agricultural output will become more important. Of particular interest are those plants which will be able to provide the world with huge amounts of energy (via photosynthesis and nitrogen fixation, the two energy processes of plants and microorganisms) that humans will need during the next century to maintain and/or improve economic growth and the standard of living. We know very little about how the alkaloids and their production interface with the increasing emphasis on energy. *It will be vitally important that the agriculture, biology, medicine and biochemistry of the alkaloids be included in the study of all of the living plants during the next 100 years.*

The future of research in alkaloids will be inextricably tied in with the new scientific effort to boost the food output of the world. The biological and chemical techniques involved in advances in farming may result in producing new types of alkaloids. Scientists have recently succeeded in imparting new qualities to a whole tobacco plant which was generated from fused single cells of two tobacco species. Cells of more than a dozen plants have already been fused in laboratories in several countries. We can expect cell fusion and cell culture to become commercially useful after another several decades of experimental work. This is the most promising way to tap the unused biological potential of plants and animals. The effort is just beginning. Scientists by the hundreds from university, government, and agricultural-industrial laboratories the world over are conducting imaginative experiments to improve the mechanisms of plant growth so that the plants will yield more food. Other researchers are seeking to get more offspring from farm animals and to propagate animals of superior quality. *The production of "secondary metabolites" of these natural species may be both desirable and undesirable; thus the future of alkaloid research will be exceedingly exciting, difficult, and challenging.*



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1 | Alkaloids in Chemotaxonomic Relationships 化学分类学

1.1. Introduction

The idea of utilizing results obtained by chemical analyses for the revision of plant systematics based on morphology is relatively new. James Petiver in the 17th century endeavored to prove that plants with similar morphological aspects "of the same make or class" possess similar forces, which he described as "the like virtue." Subsequently, considerable evidence has been accumulated, and at present chemotaxonomy is well established. Some of the first studies were made on seeds of Leguminosae, subfamily Papilionoideae, which contain much protein, and on cereal grains (wheat, rye, and corn), which are high in starch content. At the beginning of the present century, Gohlke (1913), Mez and Gohlke (1913), and Mez and Ziengenspek (1926) tried to apply serological reactions in an attempt to establish a systematic relationship among these plants (Figure 1.1, Table 1.1). Although only rather primitive procedures were available, they managed from their crude results to construct a phylogenetic tree, the content of which was partially in agreement with modern views on the relationship between classes and families of plants. For example, Mez and Gohlke obtained a precipitation reaction with anti-*Lens* serum (from *Lens esculenta*, the common lentil) using the following dilutions: *Lens* serum and *Vicia faba* proteins 1:25,600; *Pisum* 1:12,800; *Phaseolus* and *Trifolium* 1:6400; while proteins from *Astragalus*, *Lotus*, *Melilotus*, *Laburnum*, *Lupinus*, *Acacia*, and *Mimosa* gave the precipitation reaction in a dilution of 1:3200. Proteins of nonleguminous plants showed no reaction; however, some of the Rosaceae plants showed traces of positive reaction after a very long time. The idea of combining chemical and morphological character was first developed into a systematic approach in

Table 1.1. List of Names Corresponding to the Numbers in Figure 1.1

1. Chroococcus	53. Chiloscyphus	92. (omitted)	142. Lythraceae
2. Nostocaceae	54. Scapania	93. Blechnum	143. Lecythidoideae
3. Scytonemataceae	55. Psidium	94. Aspidium	144. Punicaceae
4. Tetrasporaceae	56. Marsipella	95. Cystopteris	145. Araliaceae
5. Mougeotia	57. Plagiochila	96. (omitted)	146. Nyctaginaceae
6. Protoceae	58. Madotheca	97. (omitted)	147. Lentibulariaceae
7. Hydrodictyaceae	59. Georgia	98. Trichomanes	148. Chenopodiaceae
8. Chrysomonadales	60. (omitted)	99. Aneimia	149. Basellaceae
9. Peridinales	61. Anthoceros	100. Pitularia	150. Proteaceae
10. Siphonocladiales	62. (omitted)	101. Araucaria	151. Julianiaceae
11. Cladophora	63. Hostimella	102. Selaginella	152. Salicaceae
12. Saprolegnia	(fossil group)	103. Walchia	153. Morioideae
13. Saccharomycetes	64. Asteroxylon	(fossil group)	154. Betulaceae
14. Aspergillaceae	(fossil group)	104. (omitted)	155. Berberis
15. Exoascus	65. Hyenia	105. (omitted)	156. Cappariaceae
16. Hypocreaceae	(fossil group)	106. Picea	157. Dilleniaceae
17. Exobasidium	66. Sphenophylla	107. Sciadopitys	158. Hydrastis
18. Stereum	(fossil group)	108. Glyptostrobus	159. Lardizabalaceae
19. Vuilleminia	67. Calamitaceae	109. Pseudolarix	160. Mercuriales
20. Tulostoma	(fossil group)	110. Nilssonniaceae	161. Euphorbia
21. Geaster	68. Equisetum	(fossil group)	162. Aceraceae
22. Melanogaster	69. Pseudobornaeales	111. Caytoniales	163. Rutaceae
23. Hymenogaster	(fossil group)	(fossil group)	164. Simarubaceae
24. Secotium	70. Aneurophytum	112. Cyclothaceae	165. Bursaceae
25. Hysterangium	(fossil group)	113. Nymphaeaceae	166. Empetraceae
26. Dacrymyces	71. Eoflices	114. Trochodendraceae	167. Staphyleaceae

27. Uredineae	(fossil group)	115. Potamogetonaceae	168. Hippocrateaceae
28. Craterellus	72. Callixylon	116. Lauraceae	169. Linaceae
29. Peniophora	(fossil group)	117. Ranunculaceae	170. Erythroxylaceae
30. Tremellaceae	73. Mesoxylon	118. Ceratophyllaceae	171. Tiliaceae
31. Pilacre	(fossil group)	119. Menispermaceae	172. Caricaceae
32. Clavaria	74. Cordatales	120. Cephalotaxus	173. Caryocaraceae
33. Hydnum	(fossil group)	121. Podocarpus	174. Ochnaceae
34. Fistulina	75. Lepidospermae	122. Chamaecyparis	175. Oleaceae
35. Boletus	(fossil group)	123. Butomaceae	176. Gentianaceae
36. Cantharellus	76. Kaulfussia	124. Pontederiaceae	177. Buddleia
37. Schizophyllum	77. Helminthostachys	125. Dioscoreaceae	178. Apocynaceae
38. Lentinus	78. Botrychium	126. Iridaceae	179. Myoporaceae
39. Limacium	79. Baiera (fossil group)	127. Burmanniaceae	180. Selaginaceae
40. Paxillus	80. Stangeria	128. Orchidaceae	181. Acanthaceae
41. Russula	81. Ceratozamia	129. Zingiberaceae	182. Labiatae
42. Clitocybe	82. (omitted)	130. Scirpoidae	183. Plantaginaceae
43. Tricholoma	83. Cycadoidoidea	131. Caricoidae	184. Dipsacaceae
44. Chaetophora	(fossil group)	132. Restionaceae	185. Caprifoliaceae
45. Coleochaete	84. Cycadoflites	133. Eriocaulaceae	186. Boraginaceae
46. Fegatella	(fossil group)	134. Conmaraceae	187. Turneraceae
47. Peltia	85. Marattia	135. Plantanaceae	188. Droseraceae
48. Blasia	86. Angiopteris	136. Pittosporaceae	189. Frankeniaceae
49. Sphagnaceae	87. Todea	137. Crassulaceae	190. Styracaceae
50. Archidiaceae	88. (omitted)	138. Thymelaeaceae	191. Passifloraceae
51. (omitted)	89. Cyathea	139. Elaeagnaceae	192. Cucurbitaceae
52. Fossombronia	90. Alsophila	140. Haloragaceae	193. Campanulaceae
	91. Ceratopteris	141. Saxifragaceae	

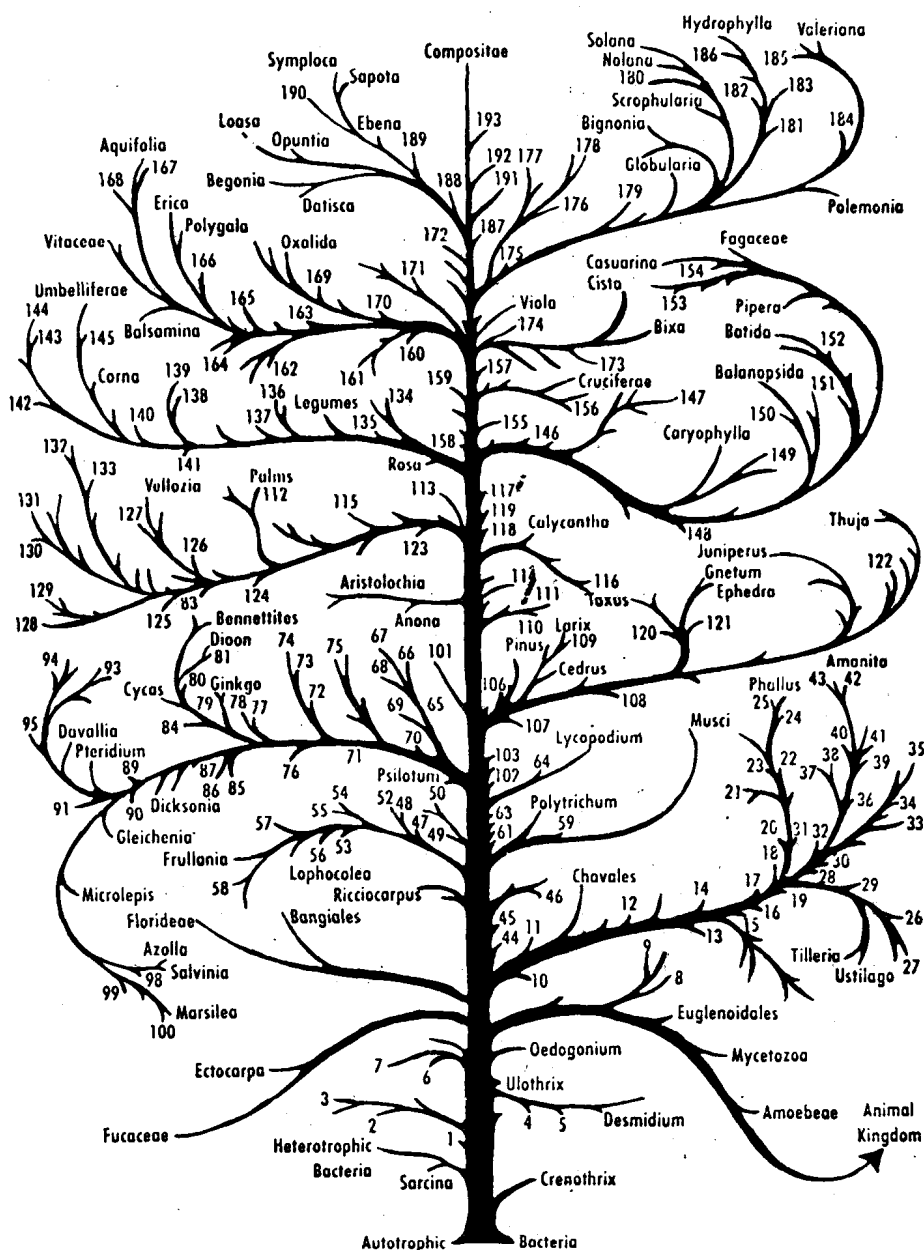


Figure 1.1. The “Stammbaum” of Mez, a phylogenetic tree purportedly constructed, in part, from serological data. The ending “aceae” is omitted from many of the families. For the names of taxa that correspond to the numbers indicated in the figure, see Table 1. Adapted from R. A. Gortner, 1929, *Outlines of Biochemistry*, courtesy of John Wiley & Sons.