NATURAL RELATIONSHIP AND MEDICINAL ACTIONS OF VEGETABLE DRUGS

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Since Hahnemann inaugurated Homœopathy 160 years ago, a comprehensive knowledge and detailed description of the actions of drugs *on man* is the indispensable basis for our medical work. Now, as ever, we are convinced that we must first know, as precisely as possible, the signs and symptoms of the human organism when acted upon by a particular substance, before we use it to the best advantage, in a suitable preparation, as a calculated stimulus on a patient.

Apprenhensive lest they might lose this solid foundation, many homœopathic doctors were, and still are, distrustful of any attempt to bring our Materia Medica in line with natural science. It is still quie usual to present the symptoms of each remedy topographically, according to parts of the body from head to feet, at best to separate organ systems and to set apart as "generals" those symptoms which do not fit into such an arrangement. True, in doing so they follow the example set by Hahnemann's *Pure Materia Medica.* All the same such topographical arrangements of symptom after symptom do not conform to the spirit of Homœopathy. Our method actually demands to supersede these old ways of listing ill-connected data; it demands to see the individual organism, undivided and undivisible into body and soul, as a dynamic, self-regulatory whole and to treat it as such. The significance of drug-symptoms can be conceived properly only in relation to this complex unity of functions, the living organism. This then is the supreme viewpoint from which the actions of a drug are adequately seen as a "picture", to be elucidated more and more, and arranged accordingly, in its proper biological setting.

A similar mistrust of science is shown by the text-books when they arrange the subject material in alphabetical order of

the names of drugs. Here again the example of Hahnemann can be adduced; but while it may have been justified for his new enterprise more than a hundred years ago, it is no longer so today; unless one is content to leave homœopathic materia medica at a pre-scientific stage, of collecting and listing unconnected observations. Meanwhile natural science has made great strides in its main task: to obtain ordered knowledge out of the otherwise unmanageable accumulation of observed facts, and thereby an increasingly clearer insight into the relations of events and things in nature. Those who shut their eyes to this development should not be surprised if their cause is left more and more behind.

Homœopathy is thoroughly misunderstood, if such scientific backwardness is thought to be inherent in the method itself. On the contrary, the homœopathic extension of pharmacology is much more suited to fit in with natural science than the orthodox brand which limits itself almost exclusively to experiments on animals. For, properly understood, Homœopathy implies not just some sort of supplement, but an essential and scientifically progressive extension of pharmacological and toxicological knowledge. Our method demands to relate all the available data to the human organism, it sees a drug *sub specie hominis;* any manifestations of drug action, even those observed on animals, are seen in relation to that systemic unit which is evolutionally the highest and, by the same token, the best known to us. This reactive system is the most appropriate to manifest not only the changes in behaviour, but also those in subjective experience, in so far as it can be expressed in speech. By focusing our observation and thinking on this system of inter-related processes, the great diversity of facts can be arranged in its proper order. It hardly needs to be said that we can only approximate but never achieve the ideal of a complete order in knowing the *actual* processes and events.

When the homœopathic knowledge of drug actions is claimed to be scientifically superior to the orthodox, it should reveal more clearly the natural relationship of the drugs by their pharmacological actions; our teaching and learning can indeed be in closer contact with the "natural order" of our

subject matter. The potential actions of a substance from the mineral, plant, or animal kingdom characterize the nature of that substance and can, like other "properties", be made the basis of comparison with regard to similarity and dissimilarity, closer or more distant relationship. Provided, of course, that the actions are ascertained correctly, and orientated on the same reactive system—in this case the human organism. Indeed, if the drug pictures of substances which are of a related nature are similar to each other in their symptoms, or in the trend of their action, this by itself supports the inference that the experimental observations, and especially those from provings on healthy persons, are true and reliable characteristics of the actions of that particular substance.

The mineral remedies have been discussed before, in accordance with the natural groups of the series of chemical elements. To give even an approximate description of the natural relations of the much more numerous vegetable drugs would go far beyond the scope of a journal. In the next few pages only some general viewpoints can be discussed, and illustrated by examples.

There has always been a close connection between botany and the pharmacology of plants; witness the many herbals of earlier centuries. It appeared obvious that similar plants should be considered to be similar also in their therapeuttc actions. At first, of course, one relief on similarities in the external appearance, and this was often misleading. Jak. Camerarius (1665-1721) seems to have been the first to take the sexual organs of the plants as the criterion for their classification, and to ascribe similar therapeutic virtues to related plants. Linnaeus (1707-1778), the actual originator of the plant and animal systematization, says: "Plants of the same species have the same therapeutic virtues, plants of the same natural order have related properties, and even plants of the same class have some correspondence in their actions." (Amoen. acad.). Murray, to whose natural system of plants Hahnemann referred in his "Versuch über ein neues Prinzip etc." because he thought it the most perfect—he probably did not yet know the one by De Jussieu (1789)—attempted to place the vegetable drugs ac-

cording to their natural relationship. Of course, Murray's classification is still very far from what today would be called a "natural" systematic arrangement.

Hahnemann (l.c., pp. 405 ff.) disputes that the botanical relationship permits a definite inference as to the similarity of actions. He gives a number of examples which show that plants of the same family have completely different actions, that some are harmless and edible, others, however, poisonous. Although—following Murray—he often places plants in one family which according to our present-day knowledge do not at all belong together, it would be easy to give more and other examples in support of his statement. (In view of a point of controversy which is to be discussed later, it is interesting that in those days the *Rubiaceae* and the *Loganiaceae* were combined in one family of "Stellariae"; in Hahnemann's example: *Galium aparine* and *Spigelia marylandica.*) One can also agree with Hahnemann when he says that even plants of one and the same genus sometimes have different medical actions (l.c., p. 411). In 1796 he still spoke of the actions of plants in the pre-homœopathic sense, i.e. with regard to the empirical effects on the various organs, such as purging, vomiting, etc.; but that does not detract from the validity of his assertion. In those days, when organic chemistry did not exist, he could not take into account the chemical structures of active principles. On the one hand, the same or similar special (secondary) products of the metabolism of various species emphasize their relationship, and on the other hand, they are responsible for a similar trend in their respective actions. The following quotations (ic., p. 410 and p. 412) may show, however, that Hahnemann held by no means a one-sided opinion on this problem. "I am far from under-rating the many important hints the natural system can give to the philosophical pharmacologist, and to him who feels called upon to discover new remedies; but these hints either serve only to confirm facts which are already known and to comment on them, or, if they refer to drugs, give rise to hypothetical assumptions which are too uncertain to be relied upon." And: "Although I readily admit that, on the whole, similarity of action is found much more frequently in species

of one genus than between large groups in the natural system, and that an interference in respect of the former may have far more probability to it, yet from my conviction I must give the warning that, even if there were many genera whose species show great similarity in their actions, the smaller number of those acting dissimilar should still make us very wary of this mode of inference." We can only endorse this warning, that drug actions should not be inferred from the relationships of plants in a speculative way, but have to be proven by observation. On the other hand, this does not justify us to neglect the valuable help we may derive from taking into account the natural relationship of drugs, to bring order into and better understanding of the symptoms, *when* and insofar as these are known from and after observation. Least of all would this neglect be excusable in the case of Homœopathy because by its very method it can claim to have a broader observational basis, perfected by the distinctive reactions of human provers.

In 1804 (and in a second edition in 1815) the distinguished Geneva botanist A. P. de Candolle published a book: *Versuch über die Arzneikräfte der Pflanzen verglichen mit den äusseren Formen under natürlichen Klasseneinteilung derselben* (An Attempt to Compare the Medicinal Actions of Plants with their External Forms and their Natural Classification). In this book he discusses the problem in respect of 150 plant families. De Candolle's Classification shows a considerable advance over the earlier ones, but by applying only morphological and anatomical criteria, it is by no means "natural" in the sense the term is used nowadays. The plants are classified according to the similarity or dissimilarity of their reproductive organs. This has obvious advantages for, from the morphological point of view, reproductive organs are the most suitable to mark the stage of evolution reached by a species, genus, or family. From our present point of view, however, which sees the organization of each plant as the result of inherited tendencies and of adaptation to the particular environment, a "natural order" should give each species its place in the process of evolution. That, of course, is an ideal at which science aims only since Darwin; though much

has become known much more has to be learnt, before a natural system can be firmly established on evolutionary grounds. The approach of present-day science is on diverse, though convergent paths: the morphology and anatomy not only of the reproductive organs, but also of the assimilative and eliminatory organs and tissues, bio-chemistry and serology, genetics and ecology make their contributions, and many gaps are filled in by palaeontological discoveries. The present systematization of plants may not yet be a natural one in the sense that it adequately expresses the genetic relations between the existing species, but it does, on the whole, give reliable information on the degrees of relationship between families, or the genera of one family, and the species of one genus. In isolated cases there may still be uncertainty about the position of a whole family, e.g. that of the *Rubiaceæ*; the family poses many questions of pharmacological interest, too, and we shall revert to it later.

DE CANDOLLE'S book deserves mention in the historical context of our problem, not so much because its classification represents a great advance towards a natural system, as compared with older ones, for instance Murray's; and not because, in contrast to Hahnemann, it emphasizes the positive aspect of the problem; nor for the reason that De Condolle might have known more of the drug actions than Hahnemann did in 1796. The progress made by De Candolle is that he clearly saw the chemical composition of the plants as a link apt to connect relationship with similar actions. In this respect he could already make some use of new knowledge on chemistry gained since 1796. He saw that the metabolic products of the various plants, on which depends their use as foodstuffs, condiments, or drugs, are by the same token distinctive of the species, genera, and families. De Candolle was, of course, not yet able to give biochemical explanations as to why some plants serve as food, others as spices, and others as drugs.

The carbohydrates, fatty oils, and proteins of plants are food for animals and human beings insofar as the latter possess the enzyme-outfit suited for the degradation and re-organization of the complex plant products. Those organic compounds

which the animal organisms cannot themselves build, and therefore must take from the plants, we call "essential". Among them are certain amino-acids, and a number of organic compounds, the so-called vitamins, which are chemically heterogeneous, i.e. are of diverse structural types. They are products of the plant (partly bacterial) metabolism, essential to the animal organism which builds them into certain co-enzymes. Hence these by-products of plant metabolism may be counted among the food-substances for animals and man.

The choice of plants suitable as food for any animal species and man is more specially determined by accessory flavouring and scent substances. Among the flavouring substances we must count even some of the lower organic acids, such as malic, tartaric, and citric acid. These do, of course, also occur as intermediary products in the animal metabolism, but are concentrated in certain plants, especially in their fruits. Oxalic acid, large amounts of which occur almost universally in plants (with the characteristic exception of the *Cruciferae*), is no longer indifferent for animal organisms if it is in the soluble form, i.e. the animal organism cannot adapt itself to such oxalic acid-containing plants without signs of disorder. The main scent and flavouring substances, however, are the etheric oils contained in the glandular secretions of many plants. In their chemical structure these are conjugates of the terpene- and the phenylpropanetype. The simpler structures, such as are characteristic mainly of the *Umbelliferae* and *Labiatae,* act chiefly, but not exclusively, on the chemical senses. Other forms, like those found in the *Coniferae,* for instance, can cause a much more profound disturbance of the metabolic processes in the animal organism. But we cannot now go into this extensive subject, however fruitful a study of the distribution of compounds of this group in the various plant families may be for their biochemical characterization. An example of this would be the large family (about 3,000 species) of *Labiatae.* This is a "good" natural family, of uniform characteristics in many respects; it shows a close relationship only to the *Verbenaceae.* The construction of the oil-reservoirs under the cuticle from glandular scales and glandular hairs is

one characteristic, but so are also the comparatively simple terpene-bodies, of the p-cymol-type, which constitute their oily secretion. (The same structure of glands, and the same terpene-types in a different composition do, however, also occur in other etheric oils that there are among the *Labiatae* so many "aromatic" herbs (*Salvia, Melissa, Origanum, Thymus, Mentha, Satureia*). On the other hand, this large family has few medicinal plants, although a number of them are popular as "medicinal herbs" because of their mildly stimulating action. The few plants (*Teucrium marum, Scutellaria, Lycopus, Collinsonia, Plectranthus*), which have a very limited use in Homœopathy, probably owe this to components other than the terpene-derivatives common to his family.

A similar situation is encountered in the *Cruciferae*, a family nearly as large and also of a well-defined type, but at a simpler level of organization. (The *Cruciferae* come within the *Chroipetalae* or *Archichlamydeae*, whereas the higher developed *Labiatae* are *Sympetalae*, or *Metachlamydeae*.) Chemical characteristics of the *Cruciferae* are the mustard-oil glycosides whose -N=C=S group indicates their probable origin from the sulphur-containing amino acids. These glycosides are responsible for the flavouring qualities of the species of this family which serve as foodstuffs and spices (e.g. *Lepidium, Cochlearia, Brassica, Sinapis*, and *Raphanus*). Again there are remarkably few useful drugs in this large natural family; and the few (*Iberis, Thlaspi, Cheiranthus*) which have found a very limited use in Homœopathy apparently owe this to products which are different from the ordinary mustard-oils.

One can only speak of food, aromatic, and medicinal plants in relation to specified organisms. Even with regard to man such a division cannot be made unequivocally; for what is spice to one, may be pharmacon to another. The adaptation or adaptability of a species or even of the individual decides which is food, spice, or drug for the particular organism. Although such broad divisions in respect of the symbiosis of plants and animals are of some value for practical purposes, they do not correspond to the actual relations. Wherever the reactivity of the individual, as in the case of man, can be applied

as a criterion, it is the decisive one; thus terms like poison, drug, or remedy can be applied only with this reservation. The definition "pharmacon" implies that the organism upon which such a substance acts can adapt itself to it only with (structural or functional) manifestations of disorder. In the same way, food- or aromatic substances cannot be defined without the criterion of adaptation. With regard to vegetable food for animals, primary and secondary plant products are, as we have seen, fitting substrates for the enzymatic equipment and the chemical senses of animals; the outcome of past adaptation of species to their environment. Combinations of peculiar substances are typical of whole plant families, others (also the very highly developed selectivity for host-organisms in the case of certain fungi and bacteria). Cattle, for instance, prefer as food species of *Gramineae, Leguminosae,* and *Compositae* which are rich in coumarin, but generally leave herbs of the *Labiatae, Scrophulariaceae,* and *Solanaceae* untouched. Sometimes the life of an animal species depends on a single plant genus, as for istance that of the silk-worms on mulberry trees. Man, as *homo faber,* has considerably extended the range of his food-supply, but it is well known that in the selection of remedies he has, as *homo sapiens,* still much to learn.

The etheric oils and the closely related, but because of their complexity not so well-defined resins are widely distributed as excreta in the plant-kingdom (and only there); hence their absence rather than their presence can serve as a characteristic of families. Only when specialized, and particularly more complex derivatives of the above-mentioned structural types, terpenes and phenyl-propanes, occur in the plant-sap, do they become chemical characteristics of families, genera, or species. In many cases, however, the chemical structure of just the more complex derivatives of these types (sesquiterpenes to polyterpens) is not yet known, so that one has to be content with mere names, such as ledol, for instance.

A similar situation is met in the case of the derivatives of the sterol-type. These are formed by almost all living beings (very rarely only by bacteria). According to their occurrence in fungi, higher plants, and animals, they are distinguished as

mycosterines, phytosterines, and zoosterines. Their basic structure which is common to all (of three six-membered rings arranged in phenanthrene-type, condensed with one five-membered ring) is well-known from cholesterol, the bile acids, vitamin D, the sexual and adrenal hormones; another such derivative is found in the venom of the toad. There is one type among the phytosterines which is pharmacologically of great importance, the so-called steroid glycosides. Glycosides, i.e. sugars linked with other plant metabolites, are, of course, a common occurrence. Many genera form and use special kinds of sugars in such glycoside linkages; so do the so-called cardiac glycosides, but these sugars are not decisive for the heart-affinity. The special effect on the heart seems to depend rather on the presence of a lacton-group in a particular position (on the 17-c-atom). (Lacton designates an inner anhydride of certain carbonic acids). Such steroid glycosides (which are also called digitalis-glycosides, or digitaloids) occur sporadically in various, though only in a few plant families. They are particularly frequent in the *Apocynaceae* and the closely related *Asclepidaceae*. The latter contain steroid glycosides, as far as is known, in four or five genera; but species of this family have not yet been used (or at least very rarely). Three genera of the *Apocynaceae* (*Apocynum, Nerium,* and *Strophanthus*) comprise important cardiac drugs, but although their active principles are closely the indications for the use of *Apocynum cannabinum, Nerium oldeander,* and *Strophanthus hispidus* are not identical. So far no use has been made of a further five *Apocynaceae*-species which also contain steroid-glycosides. The frequent occurrence of this type of steroids (with a lacton side-group) in those two neighbouring and closely related families is by itself remarkable, though such steroids are not exclusive to the two families. Similar metabolic products are found in the *Scrophulariaceae* (*Digitalis, Gratiolo*), the *Cactaceae* (*Cereus—grandiflorus*) the *Ranunculaceae* (*Adonis, Helleborus*), the *Liliaceae* (*Convallaria, Scilla*), and in a few species of other families. Much more common in the *Apocynaceae* and *Asclepiadaceae* than steroid-glycosides are polyterpenes; a great many species of the two families are

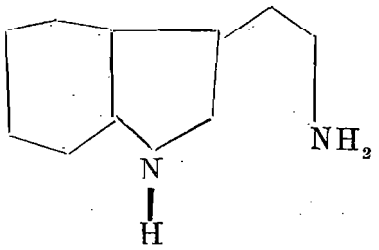
rubber-suppliers. Polyterpenes, however, are a class of substances which occur in many families. Until more is known of the diverse structures of these macromolecules, they are not distinct enough to permit inferences as to the relationships of plants producing polyterpenes. By contrast, the formation of structurally well defined steroid-glycosides in one tribe of the *Apocynaceae* is one, but only one biochemical characteristic. This is all the more apparent when for other genera of this family alkaloids of a certain type (tryptamine derivatives) are characteristic principles; and once more these genera (*Aspidospermia, Alstonia,* and *Rauwolfia*) belong together morphologically, namely to one tribe of the same sub-family (*Plumieroideae*).

The term "alkaloids" as alkaline heterocyclic nitrogen-compounds is much too wide to permit inferences as to the pharmacological actions of such plant products. Biogenetically they are connected with the metabolism of amoni-acids; these are of course ubiquitous in plants and animals, being primary products. Amino acids such as tyrosine, histidine, and tryptophane are themselves heterocyclic nitrogen compounds, and their amines, tyramine, histamine, and tryptamine, being chemical bases, come near to alkaloids as defined above. The transformation of amines into alkaloids in plant metabolism is marked by the formation of amines into alkaloids in plant metabolism is marked by the formation of a further heterocyclic ring; in the case of the named amines the ethyl-amine side-chain is closed by combining with other plant metabolites. Each further complication of structure implies potentially a greater specialization of physiological function and/or pharmacological action.

Alkaloids of this stricter definition are still so widely distributed in the plant kingdom that their presence in families and genera is unsuitable for characterizing vegetable drugs and their natural relationships. The position is different, however, if the alkaloids are subdivided according to types of chemical structure; and such an arrangement is a "natural" one in so far as it represents biogenic diversities in the metabolism of the pertinent plants. Since the structural formulae of many

alkaloids have not yet been determined, such an arrangement, and the pharmacological study based on it, are bound to be incomplete; yet where it is feasible at the present stage of knowledge, it proves extremely fruitful for an orderly arrangement and better understand of pharmacological facts.

The above-mentioned alkaloids of the *Apocynaceae* may serve as an example. All of them are derivatives of tryptamine. The further development into alkaloids arises when the ethyl-amine side-chain of the indole nucleus is closed to form a third ring. This produces the so-called carbolin-frame. All the various alkaloids of the *Apocynaceae* have proved to be structural extensions of this carbolin-nucleus. Unfortunately the drug picures of *Quebracho* (*Aspidosperma quebracho*) and the *Alstonia*-species (*Alstonia scholaris* and *Alstonia constricta*)



are, as yet, so inadequate that a comparison with the better known *Rauwolfia serpentina* does not permit definite conclusions as to their relationship as drugs. From the results of provings of *Rauwolfia* one would expect that all these drugs share the tendency to act on the vegetative (and especially the vasomotor) centres and that they interfere with the emotional and mental condition of man. For *Rauwolfia,* the latter tendency has been proved also by clinical observation following the administration of *Rauwolfia*-alkaloids (e.g. reserpine). The following hypothesis has been advanced for the mode of action of the carbolin-alkaloids (5, p. 50): "The carbolin derivatives are structural analogues of 5-oxytryptamine. According to recent observations, this amine has, as Gaddum already suspected, the role of a neuro-hormone in the central nervous system. By virtue of their structural similarity to the physio-

logical oxytryptamine (it is also named serotonin or enteramine), the more complex carbolin-compounds also derived from tryptamine would temporarily take the place of the normal metabolite serotonin and thus set it free. If this anti-metabolite hopothesis for the carbolin-compounds is confirmed experimentally to the same extent as is the case for many other "anti-hormones" and "anti-vitamins", it would explain the affinity of these alkaloids to certain regulatory centres.

Since this hypothesis for the effective mechanism of the *Rauwolfia*-alkaloids was put forward, experimental findings have been published from another side (Brodie *et al.*), which support out assumption. According to their experiments, reserpine does in fact liberate serotonin (5-hydroxytryptamine) from the brain. The serotonin-content of the brain (normally about 0.55 μ/kg.) decreased rapidly after intravenous inspection of 5 mg./kg. reserpine by about 75 per cent. in 30 minutes, by about 90 per cent. in 4 hours. The low level was maintained for about 24 hours, then rose slowly, and the normal value was regained after about 7 days. Even dose of 0.1 mg./kg. of 0.1 mg./kg. of reserpine lowered the serotonin-content of the brain substance perceptibly. Reserpine was no longer detectable in the brain twelve hours after injection. (Both serotonin and reserpine were measured fluoroscopically). The sedative effect and the diminution of serotonin in the brain continued for more than 48 hours. During the phase of low brain-serotonin definite quantities of 5-hydroxindole- acetic acid, a metabolic end-product of serotinin, appeared in the urine. Serotonin apparently continued to be produced in the body, but was not bound or stored in the brain.

As the result of their researches, the authors visualize the action of reserpine as follows: normally serotonin is present in the brain (as also in the intestine and in the blood-platelets) in a bound form, and is thus protected against decompoosition by monoamino-oxidase, a very active enzyme. Through reserpine the brain cells lose their ability to bind serotonin. (The authors do not suggest that reserpine, being a ryptamine-derivative, may act as an anti-metabolite of serotonin, i.e. that the alkaloid, because of its structural similarity, temporarily replaces sero-

tonin at its physiological sites). Although, as the authors state, reserpine disappears quickly from the brain, its effect on the brain's ability to blind serotonin continues for longer. They assume that during this time more serotonine is produced and a large amount of it becomes available in the active form. This serotonin the authors regard as the cause of the continued action of reserpine.

Simpler and much more plausible is the assumption that the neurohormone, displaced from its normal bonds, is inactivated (by acetylation) and that its absence from its normal sites of attachment at certain nerve centres is responsible for the functional disorders. We may take this conception as a glimpse into the biochemical mechanism of the action of reserpine; reserpine is, however, only one of a series of (structurally similar) alkaloids of *Rauwolfia serpentina.*

The recognition that substances of a similar structure act in the same direction is of great importance, particularly for understanding the drug pictures in their natural relations. This does, however, by no means imply neglecting and it would be quite wrong to do so, the differentiating characteristics of each particular drug in action, its special symptomatology; for we do not select the remedy for the individual patient from general tendencies of action, but from the precise symptoms of their effects on man.

Two diverse kinds of metabolites occurring among the species of the family of *Apocynaceae* call for our special attention: some of them produce steroid-glycosides, others carbolin-alkaloids. From this bio-chemical divergence in tribes of one family one can infer that the *Apocynaceae* are not a uniform group and that they are not as near to the end of their evolutionary career as f.i. the *Labiate* and *Cruciferae.* The species of one genus, the genera of one family, and the families of one order or class actually are not at the same stage of evolution. Hence the natural relationships within such groups are here closer, there more distant. The necessarily schematic classification cannot do justice to these gradations. Yet the conformity in essentialc characteristics, be they morphological or biochemical, is a valuable gauge of the existing relationships.

(Incidental features conditioned by environment have to be disregarded, of course.) Secondary plant-products as, for instance alkaloids, are the more indicative in this respect the less often they occur in plants; and alkaloids of a type like, say, the carbolin-derivatives occur the less often, the more complicated their structure. Greater complication of structures indicates a higher degree of specialization in organismic processes. The very rarity of such highly complicated metabolites makes it unlikely that they would occur as identical formations in widely distant families, unless there is some genetical connection beween them.

Such a coincidence confronts us in the case of the *Apocynaceae* and *Rubiaceae*. The alkaloids quebrachin from *Aspidosperma quebracho* (*Apocynaceae*), and yohimbin from *Corynanthe* (or *Pausinystalia*) *yohimbe* (*Rubiaceae*) are identical. The structure is fairly complicated, as two further rings are condensed with the three rings of the carbolin-structure. It is unlikely that such a configration is formed sporadically in genera of two families, without there being some genetic relationship. An adaptation to similar conditions of living cannot be assumed for the *Querbracho* from the Argentine and *Yohimbe* from the Cameroons. The position held by the *Rubiaceae* in the system of plants was under dispute for a long time. Murray placed our native genera of that family (*Galium, Asperula, Rubia*) in one family with genera of the *Loganiaceae* (like *Spigelia*). The *Loganiaceae* (genera *Gelsemium, Spigelia,* and *Strychnos*) are fairly closely related to the *Apocynaceae,* and the *Loganiaceae,* too, are distinguished by alkaloids of the carbolin-type (the structure of the *Spigelia*-alkaloids, though, is not yet known). The alkaloid sempervirin, from *Gelsemium sempervirens,* has a structure very similar to quebrachin-yohimbin, whilst other *Gelsemium*-alkaloids appear to be even more complicated and specialized in the direction of strychnine. In strychnine (*Nux vomica, Ignatia*) we encounter the highest development of the carbolin-type. From the biochemical point of view we may therefore bring the *Apocynaceae*—via the *Loganiaceae*—into a relationship with the *Rubiaceae* which is closer than that shown in the present systematic arrangement of plant families.

The *Rubiaceae* are not at all a uniform family. This becomes obvious when one compares our few native genera (all of them herbs) with the tropical, or sub-tropical trees and shrubs, like *Cinchona, Corymbe, Coffea, Uraroga* (*Ipecacuaha*). To judge from the active chemcal substances of the medicinal *Rubiaceae,* the genera and species show extraordinary divergencies. It is a heterogeneous family, apparently still in the full process of evolution. Apart from the carbolin-derivatives in *Yohimbe,* alkaloids of the quinoline type are found in the genus *Cinchona* (and in the closely related *Remijia,* but only in these two!). Recently it has been pointed out, however, that these peculiar configuraaions of the quinine-type may also derive from tryptamine. (The splitting of the heterocyclic five-membered ring, and subsequent re-arrangement into a heterocyslic six-membered ring, is established in animal metabolism, and has been suggested in the case of *Cinchona.* Possibly a similar process occurs in the fungi ; for the principal structure of the ergot-alkaloids, lysergic acid, is a condensation of a carboline with a quinoline). This divergent development of alkaloid types may perhaps by future research be traced to a common origin and enzyme-outfit of the species of this versatile family.

(*To be continued*)