THE PHARMACOLOGY OF RAUWOLFIA

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I. INTRODUCTION, CHEMISTRY, AND OCCURRENCE OF RAUWOLFIA ALKALOIDS

Since very ancient times, extracts from Rauwolfia (genus of the family Apocynaceae), which grows in the subtropical and tropical parts of India, the East Indies, Africa, and Central and South America, have been recommended by native doctors and employed in popular medicine for the treatment of a great variety of diseases throughout the regions in which it is found (253). Although Rauwolfia had, during the course of the centuries, repeatedly been described in works by herbalists, it was not until about 1930 that Indian workers carried out studies on the plant which were to arouse the interest of scientists and clinicians first in India and later throughout the entire world. The earliest reference in Western literature to Rauwolfia and to the curative properties attributed to it in India ("primum et laudatissimum remedium" (114)) is contained in a Portuguese work published in Goa as far back as 1563 (261). Whether Leonhard Rauwolf (1540?–1596), a physician of Augsburg who travelled through the middle East on behalf of a dealer in drugs to whom he was related, was in fact acquainted with Rauwolfia—as the French botanist Plumier called the plant in his honour a century later—is not certain. Readers interested in the history of Rauwolfia will find an excellent and scholarly account written by Rieppel (261).

Reports on the number of Rauwolfia species at present known vary greatly, from a figure of 50 (86) to 110 (227) and 125 (48). The task of botanical classification and of assigning permanent names to the various individual species is still far from completed. It is therefore hardly surprising that the pharmacognostical characteristics of the individual species have only in part been established with any degree of certainty (for pharmacognosy, see 76, 86, 227, 270, 343). Those species of Rauwolfia on which chemical and pharmacological reports exist represent only a comparatively small portion of the total.

In the 19th century, Greshoff (114) had already noted the presence of alkaloids in several species of Rauwolfia, *e.g.*, in *Rauwolfia serpentina*, *R. canescens*, and *R. trifoliata*. Chemical research in the full sense of the term did not begin until

[1] For his valuable help in preparing the English version of this paper, the author wishes to express his sincerest thanks to Mr. H. D. Philps (M. A. Cantab.).

1931, when the Indian chemists Siddiqui and Siddiqui isolated and characterized a number of alkaloids from *R. serpentina* (311, 312, 313). In recent years, further alkaloids of varying chemical structure and pharmacological importance have been isolated from *R. serpentina* and other species. As the chemistry of the Rauwolfia alkaloids has already been described on repeated occasions (48, 225, 273, 275), the isolated alkaloids are presented here in tabular form only (Tables I and II). These tables may also serve a purpose as regards nomenclature, since several alkaloids were isolated almost simultaneously by chemists working independently of one another and were in some cases not identified until later—a fact which has often led to confusion of names (225, 226). Moreover, some of the alkaloids described in the literature may be identical with compounds already known, but it is not always possible to decide whether this is so, since the chemical characteristics given are often too scanty. The alkaloids that have been described to date are listed according to chemical category. This type of classification, based on the broad outlines of their chemical structure, makes it easier to present an overall picture, even though there are only some alkaloids whose chemical configuration has been fully elucidated. Except for thebaine and papaverine, all the Rauwolfia alkaloids so far identified are indole bases.

From Table I it will be seen that, whereas in many Rauwolfia species various alkaloids are present, some alkaloids are typical of certain species only; in others they are either absent altogether or found only in very small quantities. Hence, the proportions of the alkaloids present in the various types of Rauwolfia investigated vary greatly from one species to another; in Table I an attempt has been made to draw up proportional figures for the alkaloids contained in certain species of Rauwolfia, these percentages being based either on those already quoted or calculated from data given by the respective authors. The figures listed can only serve as a rough guide, firstly, because quantitative specifications are not available for all the alkaloids that have been isolated, and secondly, because the amount of active substances present, even in one and the same species, may vary depending upon the region from which the plant originated, *i.e.*, upon factors such as the nature of the soil, climatic conditions, and the season of year.

Thus, for example, *Rauwolfia serpentina* roots collected in the Dunn Valley (India) are alleged to contain no ajmaline and only traces of ajmalinine and serpentinine, while on the other hand they contain two isomers (310), neoajmaline—the existence of which, however, is now in some doubt (275)—and isoajmaline. Similarly, the "Bengal variety" (India) of *R. canescens* is said to contain only rauwolscine, whereas other alkaloids listed in Table I are alleged to be found in a *R. canescens* species indigenous to the Indian province of Madras (53); finally, serpine has been traced in a variety of *R. serpentina* Bentham (the "Cochin variety") which contains no ajmaline (50). It is also stated that rauwolfinine occurs chiefly in *R. serpentina* plants growing in "northwestern India" and that it is sometimes found instead of ajmaline (48).

Using rauwolscine as an example, Chatterjee (48) has demonstrated that the alkaloid content of the leaves, branches, and roots is about three times greater in the period from October to January than in February and March.

The quantitative and qualitative distribution of the alkaloids in the roots, stem, and leaves may vary depending on the species employed and on the alkaloid under investigation. As a rule, the highest reserpine content is found in the bark of the roots, whereas rauwolscine is more abundant in the *R. canescens* leaves (203). According to Hochstein

TABLE I

Alkaloids of various Rauwolfia species

Name	Approximate yield %	Source	Reference	First identified, year and reference
A. *Rauwolfia Serpentina* Benth.				
Serpentine	0.08	root	311	1931 (311)
Serpentinine[1]	0.13	root	272	1931 (311)
Ajmalicine	0.02	root	311	1931 (311)
(δ-yohimbine,				1954 (138)
Substanz II, raubasin,				1953 (239)
py-tetrahydroserpentine)[2]				1954 (166)
Reserpinine	0.015	root	84	1954 (274)
(raubasinine, Substanz I,				1953 (122, 239)
alkaloid C of Hofmann,				1954 (138)
new a'kaloid)				1954 (345)
Reserpiline				1954 (165)
Sarpagine	0.02	root	321	1953 (321)
(raupine)				1953 (32)
Yohimbine				1954 (10, 138)
Corynanthine (rauhimbine)	0.03	root	137	1954 (137)
Isorauhimbine	0.08	root	137	1954 (137)
Serpine	0.02	root	50	1954 (50)
3-epi-α-Yohimbine (alkaloid 3078, ? = ajmalinine)				1954 (9)
Ajmalinine	0.05	root	311	1931 (311)
(? = alkaloid C of van Italie and Steenhauer)	0.08	root	137	1932 (342)
Methylreserpate				1954 (138)
Reserpine	0.14	root	137	1952 (214)
Rescinnamine				1954 (164)
(reserpinine)				1954 (122, 124)
Ajmaline	0.1	root	311	1931 (311)
(? = rauwolfine)	0.17	root	137	1932 (342)
Isoajmaline				1939 (310)
Serpinine	0.00026	root	36	1955 (36)
Neoajmaline				1939 (310)
Rauwolfinine	0.02	root	35	1951 (49)
Thebaine[3]				1954 (138)
Papaverine[3]				1954 (138)

TABLE I—*Continued*

Name	Approximate yield %	Source	Reference	First identified, year and reference
B. *Rauwolfia Canescens* Linn.				
Serpentine				1954 (125)
Ajmalicine				1955 (155)
Aricine	0.2	leaves	323	1955 (323)
Reserpinine				1955 (155)
Isoreserpinine	0.1	leaves	323	1955 (323)
Reserpiline	0.6	leaves	323	1955 (323)
Isoreserpiline	0.3	leaves	323	1955 (323)
Sarpagine (raupine)				1955 (155)
Yohimbine				1954 (125)
Pseudoyohimbine				1955 (322)
Rauwolscine	0.1	root-bark	203	1941 (203)
(α-yohimbine)	0.2	stem-bark	203	
	0.3–0.5	leaves	323	
	0.5	leaves	203	
β-Yohimbine	0.025	root	139	1955 (139)
Raunescine				1955 (141a)
Isoraunescine				1955 (141a)
Deserpidine				1955 (277)
(canescine,				1955 (168, 322)
recanescine)				1955 (215)
Reserpine[4]				1954 (167)
Ajmaline				1955 (155)
C. *Rauwolfia Vomitoria* Afz.				
Alstonine	0.018	root	276	1952 (276)
? Serpentinine				1943 (221)
? Ajmalicine				1943 (221)
Raumitorine				1954 (238)
Ajmalinine				1943 (221)
Seredine				1954 (238)
Reserpine				1954 (237)
Rescinnamine	0.015	root	159	1955 (122, 159)
Ajmaline	0.165	root	276	1943 (221)
	0.037		221	
Isoajmaline				1943 (221)
Rauvomitine				1955 (123)
(? = alkaloid of Poisson *et al.*)				1955 (236)

TABLE I—*Continued*

Name	Approximate yield %	Source	Reference	First identified, year and reference
D. *Rauwolfia Heterophylla* Roem. et Schult. (=*R. hirsuta*; Piñique-Piñique (Columbia), and Chalchupa (Guatemala)				
Serpentine	0.15	root	136	1954 (147, 81, 136)
	0.05	root	81	
Alstonine	0.05	root	339b	1954 (199, 200, 339b)
Ajmalicine	0.005	root	136	1955 (136)
Aricine	0.0042	root	136	1955 (136)
Sarpagine[5]				1955 (146, 339b)
Yohimbine	0.01	root	136	1955 (136)
Rauwolscine	0.015	root	136	1954 (199, 200, 339b)
	?0.5	root	339b	
Reserpine	0.047	root	81	1953 (80)
	0.05	root	339b	
	0.03	root	136	
Ajmaline	0.02	root	81	1954 (81)
Chalchupin A				1937 (78)
Chalchupin B				1937 (78)
E. *Rauwolfia Tetraphylla* L. (West Indies)				
Serpentinine				1955 (79)
Reserpine	0.03	root	79	1955 (79)
Tetraphyllicine				1955 (79)
Tetraphylline				1955 (79)
F. *Rauwolfia Sellowii* Muell. (Brazil)				
Serpentine				1954 (298)
?Alstonine				1955 (135)
Ajmalicine	0.001	root-bark	135	1955 (135)
	0.0009	root-bark	220a	
Tetrahydroalstonine	0.002	root-bark	135	1955 (135)
	0.0056	root-bark	220a	
Aricine	1	root-bark	135	1955 (135)
	1.5	root-bark	220a	
Ajmalinine				1954 (298)
Reserpine	0.002	root-bark	135	1955 (135)
	0.0015	root-bark	220a	
Tetraphyllicine	0.016	root-bark	220a	1955 (220a)
Ajmaline	1.35	root-bark	135	1955 (135, 298)
	1.2	root-bark	220a	
Ajmalidine	0.002	root-bark	220a	1955 (220a)
Alkaloid A of Hochstein				1955 (135)
Alkaloid B of Hochstein				1955 (135)

TABLE I—*Continued*

Name	Approximate yield %	Source	Reference	First identified, year and reference
G. *Rauwolfia Micrantha* Hook (India)				
Serpentine				1955 (302)
Serpentidine				1955 (302)
Ajmalicine				1955 (302)
Micranthine				1955 (302)
Sarpagine				1955 (302)
Reserpine	0.02–0.04		302	1955 (302)
H. *Rauwolfia Perakensis* King et Gamble (Malaya)				
Reserpine	0.05	root	53	1955 (53)
Perakenine	0.005	root	53	1955 (53)
J. *Rauwolfia Densiflora* Benth. et Hook				
Reserpine	0.02	root	53	1955 (53)
Ajmaline	0.25	root	53	1955 (53)
K. *Rauwolfia Indecora* R. E. Woodson				
Sarpagine				1955 (146)
Reserpine				1955 (146)
Ajmaline				1955 (146)
L. *Rauwolfia Cuminsii* Staph. (Africa)				
Reserpine	0.16	root-bark	291	1955 (291)
M. *Rauwolfia Obscura* (Africa)				
Alstonine	0.039	root	276	1952 (276)
N. *Rauwolfia Caffra* (*Natalensis*) (Africa)				
Rauwolfine	0.1	stem-bark	169	1932 (169)
O. *Rauwolfia Semperflorens* Schlechter				
Semperflorine				1953 (271)
P. *Alstonia Constrica* F. Muell. (Australia)				
Reserpine	0.05	root-bark	70	1955 (70)

TABLE I—*Concluded*

Name	Approximate yield %	Source	Reference	First identified, year and reference
		Q. *Tondusia Longifolia*		
Ajmaline				1956 (317)
Deserpidine				1956 (317)
Rescinnamine				1956 (317)
Reserpine	0.007	root	317	1956 (317)

[1] According to van Itallie & Steenhauer (342), alkaloid B is analogous to serpentinine (See in addition 312, 313), but in 1954 it was claimed by Steenhauer (318) to be identical with reserpine.

[2] Names in parentheses are synonyms.

[3] Chatterjee & Talapatra (53), who were unable to isolate thebaine and papaverine from samples collected in various parts of India, think that the occurrence of these two alkaloids could possibly be attributed to the presence of opium, which is said to be frequently mixed with samples of *R. serpentina* root in Bihar.

[4] Chatterjee & Talapatra (53) found no reserpine in *R. canescens*. They suggest that, where it has been found in this species, this may have been due to the addition of *R. serpentina*, as both species are botanically closely related and are also said to be often hybridized.

[5] Hochstein et al. (136) found no sarpagine, rescinnamine, narcotine, thebaine, or papaverine in their samples of *R. heterophylla*. They state that, if these do occur, the concentrations would be less than 0.001%.

et al. (136), in the case of *R. heterophylla* the qualitative distribution of the alkaloids in the branches and leaves is substantially the same as in the roots. They found that the reserpine content of the branches was lower than that of the roots; paper chromatograms of the leaf extracts showed little or no reserpine, but several spots not observed in root extracts.

Apart from thebaine, papaverine, alstonine, and more especially the alkaloids of the yohimbine group, few typical Rauwolfia alkaloids have so far been found in plants other than those of the Rauwolfia genus itself (see P and Q of Table I and reserpinine, which was recently isolated from *Vinca minor*—a plant also belonging to the family Apocynaceae (269)). In the present pharmacological review, it is proposed to deal only with those alkaloids common to the Rauwolfia plant; not every alkaloid isolated, however, has been sufficiently characterized pharmacologically. Their clinical uses will not be discussed, although clinical observations will be mentioned if considered important in connection with experimental findings. Comprehensive and critical papers on clinical experiences with Rauwolfia, as well as further data on relevant literature, may be found, for example, in the Ann. N. Y. Acad. Sci. **59**: Art. 1, 1954 and **61**: Art. 1, 1955, and in references 29, 201, and 324.

Unfortunately, no studies have been published on the biogenesis of the Rauwolfia alkaloids, despite the fact that this genus of Apocynaceae is probably one of the most abundant single sources of alkaloids in the entire vegetable realm.

From Table I it will be seen that certain individual alkaloids are predominantly characteristic of each species. The decisive factor, so far as biological effects are

TABLE II

Chemistry of Rauwolfia alkaloids[1]

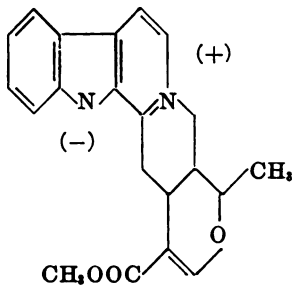
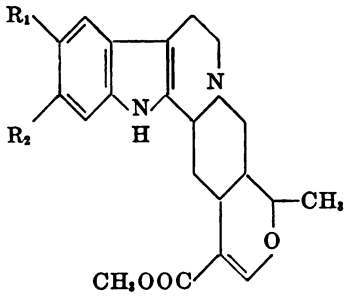
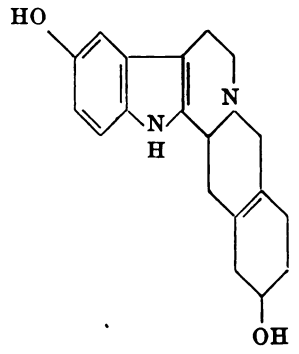
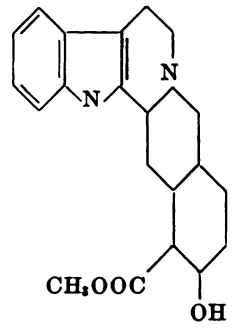
Compound	Molecular formula		References
A. Quaternary anhydronium bases (strong bases, yellow)			
Serpentine-type 			
Serpentine[2]	$C_{21}H_{20}N_2O_3$		11, 166, 311, 345
Alstonine			276
Serpentinine			272, 311
B. Tertiary indole bases (weak bases, colourless)			
Tetrahydroserpentine-type 			
Ajmalicine (tetrahydroserpentine, δ-yohimbine, raubasine)[4]	$C_{21}H_{24}N_2O_3$	$R_1 = R_2 = H$	125 138, 239, 311, 345 166
Tetrahydroalstonine (mayumbine, normelinonine-A)			135, 220a, 323
Aricine (heterophylline)	$C_{22}H_{26}N_2O_4$	$R_1 = OCH_3$ $R_2 = H$	136, 323
Raumitorine			112
Reserpinine (raubasinine)	$C_{22}H_{26}N_2O_4$	$R_1 = H$ $R_2 = OCH_3$	122, 155, 274
Isoreserpinine			323
Tetraphylline			79
Reserpiline	$C_{23}H_{28}N_2O_5$	$R_1 = R_2 = OCH_3$	165, 323
Isoreserpiline[5]			323

TABLE II—*Continued*

Compound	Molecular formula		References
Sarpagine-type 			
Sarpagine[6] (raupine)	$C_{19}H_{22}N_2O_2$		32, 321, 328
Yohimbine-type 			
Yohimbine	$C_{21}H_{26}N_2O_3$		9a, 10, 138
Rauhimbine (corynanthine)			137
Isorauhimbine			137, 177
ψ-Yohimbine[7]			322
Rauwolscine (α-yohimbine)			47, 203, 204, 205, 206
3-epi-α-Yohimbine (alkaloid 3078, ? = ajmalinine)			9, 9a
β-Yohimbine			139

[1] For the chemical classification of the alkaloids as presented in Table II the author is greatly indebted to Dr. Johannes M. Müller.

[2] Compounds listed within the same sub-segment are steroisomeric.

[3] Serpentidine (302) may eventually prove to be identical with serpentinine.

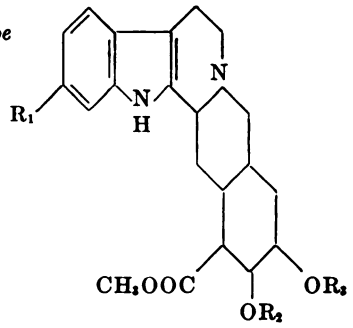
[4] Names in parentheses are synonyms.

[5] Micranthine (302) may belong to this group.

[6] Rauwolfine (Koepfli) may belong to this type (169).

[7] Serpine (50) is said to possess the ψ-yohimbane structure.

TABLE II—*Continued*

Compound	Molecular formula		References
Reserpine-type 			
Raunescine Isoraunescine	$C_{21}H_{26}N_2O_3$	$R_1 = R_2 = H$ R_3 = TMB[8]	141a 141a
Deserpidine (canescine, recanescine)	$C_{22}H_{28}N_2O_3$	R_1 = H, $R_2 = CH_3$ R_3 = TMB	143, 168, 215, 277, 322
Methylreserpate Seredine	$C_{23}H_{30}N_2O_5$	$R_1 = OCH_3$, $R_2 = CH_3$ R_3 = H	138 112
Reserpine[9]	$C_{33}H_{40}N_2O_9$	$R_1 = OCH_3$, $R_2 = CH_3$ R_3 = TMB	83, 84, 143, 144, 214
Rescinnamine	$C_{35}H_{42}N_2O_9$	$R_1 = OCH_3$, $R_2 = CH_3$ R_3 = TMC[10]	122, 124, 164

C. Tertiary indoline bases (bases of medium strength, colourless)[11]

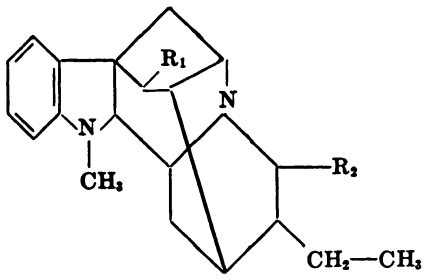
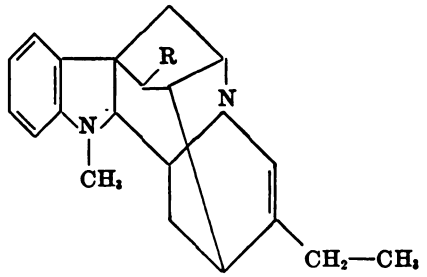
Ajmaline-type 			
Tetraphyllicine	$C_{20}H_{26}N_2$	$R_1 = R_2 = H$	79, 220a
Ajmaline Isoajmaline	$C_{20}H_{26}N_2O_2$	$R_1 = R_2 = OH$	275, 311, 351 310
Ajmalidine	$C_{20}H_{24}N_2O_2$	R = O R = OH (R = R_1 or R_2)	220a

TABLE II—*Concluded*

Compound	Molecular formula		References
Anhydrojmaline-type 			
Serpinine (anhydrojmaline)	$C_{20}H_{24}N_2O$	R = OH	36, 236
Rauvomitine	$C_{30}H_{34}N_2O_5$	R = O—TMB[8]	123, 236

[8] TMB = 3,4,5,-Trimethoxybenzoyl

[9] While this paper was in press, the isolation of a new alkaloid, raujemidine, claimed to be a stereoisomer of reserpine, was reported (339a).

[10] TMC = 3,4,5,-Trimethoxycinnamoyl

[11] The alkaloids rauwolfinine (35, 49), perakenine (53), and semperflorine (271) are shown by colour reaction to belong to this class, but their structure has not yet been elucidated. The existence of neoajmaline (310) is questionable (275).

concerned, is the pharmacological potency of the various single alkaloids. Moreover, in any given Rauwolfia species, this potency depends on the concentration of the alkaloid, *i.e.*, on both its absolute concentration and on its concentration relative to other active alkaloids. It is therefore first necessary to ascertain what experimental data are available on each of the various active substances, so that this information can then be used in assessing its importance as a pure substance (see II) and in estimating the extent to which it is responsible for any particular effect of an extract containing a variety of active substances (see III); secondly, the question must be discussed whether there exist extracts displaying effects that cannot be ascribed to any hitherto known substance. Such effects might either be due to the interaction of alkaloids already known or, alternatively, they might indicate the presence of active substances as yet unidentified.

It must be pointed out, however, that, as a rule, where so-called "total" or "partial" extracts are employed, it is extremely difficult to trace back every given effect to a particular known active substance, since—judged by modern standards—the preparations used for the experiments in question are, generally speaking, not sufficiently well characterized chemically. Bearing in mind several studies, including some only recently published (27), there appears to be reason for stressing the importance—obvious though it may seem—of differentiating between the pharmacological action of certain extracts and that of individual alkaloids.

In view of the fact that many Rauwolfia alkaloids have no specific action, it is clear that the total alkaloidal content is no indication of the hypotensive or other

action of a drug, as Holt and Costello (141) have pointed out, and that it is an unreliable criterion except where the proportion of each of the individual alkaloids is known. It is therefore quite understandable that preparations of extracts have often yielded contradictory findings, and that ratios quoted from clinical experience for the potency of isolated active alkaloids, *e.g.*, reserpine, vary considerably as compared with total extracts, from 1:250 (208) and 1:500–750 (337) to 1:1000 (348).

II. PHARMACOLOGICAL PROPERTIES OF RAUWOLFIA ALKALOIDS

A. Alkaloids with unspecified sites of action

Ajmaline. The first experiments carried out with alkaloids of the ajmaline and serpentine groups yielded results that were to some extent inconsistent, probably because the alkaloids were not available in sufficiently pure form. Thus, for example, the ajmaline whose pharmacological properties were first described in detail in 1933 (61) later proved to be different from pure ajmaline (59, 75, 92, 253). In contrast to the earlier findings, it was observed that ajmaline has no sedative and hypnotic effect, *i.e.*, unlike the Rauwolfia drugs, it does not produce sedation in non-anaesthetized animals (21, 57, 58, 60, 229). On the contrary, in the rabbit (19) and mouse (58, 60) it provokes nonspecific excitation with convulsions, while, in contradiction to earlier reports (61), in the mouse it does not cause a drop in body temperature but a slight rise (60). The prolonged miosis characteristic of reserpine is absent after ajmaline (21). In mice treated with picrotoxin, ajmaline has a synergistic effect (60). It does not counteract the emotional over-activity ("sham rage") of diencephalic cats (73).

Toxicity. Mice: LD_{50} i.p. 130 mg/kg (58); rabbits: LD_{50} i.v. 7 mg/kg (19).

Subsequent studies also failed to confirm the original claim (61) that ajmaline exerts a prolonged anti-hypertensive effect; on the contrary, it is reported that in the anaesthetized (57) and decerebrate cat (58) it raises the blood pressure—an effect which ergotoxine antagonizes (57)—and that in the spinal cat (58) it lowers the pressure. More recent findings on anaesthetized dogs (19, 153), cats (21), and rabbits (19) showed a sharp but rather brief fall in pressure after relatively large doses. The fall in pressure in the cat is not a reflex mediated via the vagus and cannot be inhibited with atropine (19).

It has been explained as the result of a depressant action on the heart (57). Hartog (132) and van Dongen (341), who experimented on frogs, rabbits, and cats using rauwolfine (which is said to be identical with ajmaline) reported a slight rise in the fibrillation threshold but no prolongation of the refractory period or of the conduction time—findings which have, however, not been confirmed by de Boer (33).

In contrast to the comparatively small drop in blood pressure recorded after intravenous injection, it is reported that monkeys respond with a marked fall in pressure when ajmaline is administered intracisternally (73). Cronheim, *et al.* (67) observed no hypotensive effect in dogs in response to repeated daily doses.

Typical of reserpine, alkaloids with an action resembling that of reserpine (see below), and extracts of *Rauwolfia serpentina* (243) is the inhibition of certain reflex blood pressure rises. Ajmaline, on the other hand, does not specifically inhibit the carotid sinus reflex in the cat (21), nor does it inhibit increases in blood pressure following electrical stimulation of the vagus and afferent sciatic nerve (21) unless given in extremely large doses (73). Curiously enough, in decorticated cats ajmaline was found to suppress such pressor re-

flexes in much smaller doses, but only provided certain rhinencephalic structures were left intact (73).

Rises in blood pressure elicited by electrical stimulation of hypothalamic (73) or medullary (92) pressor areas in the cat are not suppressed by ajmaline. This also shows that ajmaline has little blocking effect on the peripheral sections of the sympathetic nervous system. It does not inhibit the hypertensive action of adrenaline and noradrenaline in the anaesthetized cat (21), nor does it exhibit the typical properties of a ganglion-blocking agent (21). Accordingly, it does not influence the output of pressor substances from the adrenals following stimulation of the splanchnic nerve (19, 21).

Ajmaline has little effect on peripheral nervous structures, and does not produce surface or conduction anaesthesia (61). The activity of muscle and tendon stretch receptors in the frog is inhibited by high local concentrations (59).

In the isolated intestine of the guinea-pig and kitten it causes stimulation which cannot be counteracted with atropine (57), whereas it relaxes the small intestine of the dog *in situ* (253). Ajmaline does not protect guinea-pigs against lethal doses of histamine (19).

The adrenal ascorbic acid content in mice diminishes after 4 mg/kg ajmaline has been administered by the intraperitoneal route (65). It does not reduce the content of 5-hydroxytryptamine in the brain of the rabbit (229).

Ajmalinine. Only one short pharmacological report on ajmalinine is available. Raymond-Hamet (245), studying its effect on the circulation of bilaterally vagotomized dogs under artificial respiration, found that the carotid artery pressure, after a slight initial rise, underwent a brief fall, accompanied by an increase in renal volume; he also found that ajmalinine reversed the action of adrenaline on the blood pressure. It is doubtful whether, under normal experimental conditions, ajmalinine can have an adrenolytic action, since the quantity of ajmalinine required to produce adrenaline reversal totals 28 mg/kg, an amount which could hardly be tolerated without artificial respiration. Further evidence that special circumstances apply to the experiments in question is provided by the fact that—in contrast to the response to typical sympatholytics—the carotid sinus reflexes were not suppressed.

Neoajmaline and isoajmaline. The one pharmacological report known (28) gives ample evidence to show that neither of these alkaloids shares the peculiar sedative and vasodepressor properties of *Rauwolfia serpentina.*

In the frog, guinea-pig, and cat, they caused primarily excitation and tremors, followed by paralysis of the limbs and respiratory failure; in the frog, including the decerebrate preparation, the reflex time was increased.

The toxicity is rather high. Average LD: frog (lymph sac) neoajmaline 100 mg/kg, isoajmaline 70 mg/kg; guinea-pig (s.c.) neoajmaline 65 mg/kg., isoajmaline 60 mg/kg.

Both alkaloids, in doses of 1–4 mg/kg, bring about a temporary fall in carotid artery pressure in the anaesthetized cat, and in the spinal and decerebrate cat. They depress the action of the isolated heart of the frog, rabbit and guinea-pig and produce peripheral vasodilatation in isolated perfused preparations of the frog and cat. Whereas both alkaloids inhibit the activity of isolated strips of rabbit and guinea-pig intestine, they differ in their effect on the isolated uterus of the rabbit and guinea-pig, neoajmaline having a stimulant and isoajmaline a depressant action. No local anaesthetic action or influence on the pupil was observed in the rabbit, guinea-pig, or frog.

Rauvomitine. Rauvomitine, like reserpine and deserpidine, is also an ester of 3,4,5-trimethoxybenzoic acid, but its constitution probably puts it in the ajmaline group (123). It is therefore interesting that, unlike the other two alkaloids mentioned above, it produces central excitation and tonic-clonic spasms when injected intravenously into mice. It is very toxic (LD_{50} i.v. in the mouse: 8.8 mg/kg). In the cat, it elicits slight, very brief reductions in blood pressure; these are unaffected by atropine and are not mediated by reflex action via the vagus.

In the isolated ileum of the rabbit, relatively high concentrations result in an increase in tone which is not counteracted by atropine.

Rauvomitine has no adrenolytic or analgesic effect. It does produce mild surface anaesthesia (172).

Rauwolfinine. The pharmacological properties of rauwolfinine have rarely been mentioned in the literature. It is said to possess "antihypertensive properties" (49) and to block vasomotor reflexes when injected intracisternally. It has no sedative action, neither does it counteract "sham rage" in cats or specifically suppress rises in blood pressure elicited by electrical stimulation of medullary or hypothalamic pressor areas (92).

Reserpinine. Reserpinine appears to produce no particular central nervous effects in non-anaesthetized animals; in the rabbit it provokes spastic paralysis and dyspnoea (190); in the same species the content of 5-hydroxytryptamine in the brain was not diminished after reserpinine (229). In the anaesthetized cat it elicits only a brief fall in carotid artery pressure.

It has no typical blocking effect on reflex blood pressure rises provoked by electrical stimulation of afferent nerves, and no ganglion-blocking or adrenolytic action on blood pressure in the cat (190) or on the isolated uterus of the rabbit (1). It also has no specific influence on the carotid sinus reflex (190).

Reserpinine does not suppress local inflammation, such as the Arthus phenomenon in rabbits (190).

Serpentine. Serpentine, like ajmaline, is not characterized by any specific, sedative action on the central nervous system; instead, it produces spastic paralysis and dyspnoea in the rabbit (19, 21), and convulsions in the mouse (58, 60). It acts synergistically with picrotoxin (60). It is reported to have an anticonvulsive action in mice, but only if at least half the lethal dose is given (152); this action, however, does not seem sufficiently clear-cut to be taken as evidence of a specific central site of action.

In contrast to reserpine and total extracts of *Rauwolfia serpentina*, it causes a rise in rectal temperature (60), although no such rise was observed in the rat (152). It does not produce miosis (21). Its toxicity is similar to that of ajmaline. Mice, LD_{50}: i.v. 20 mg/kg (152), i.p. < 100 mg/kg (58), s.c. 164 mg/kg (152). Orally 2 g/kg is tolerated (152). Rabbits, LD_{50} i.v. 10 mg/kg (19).

Following intravenous injection in the anaesthetized (21, 57, 152), decerebrate, and spinal cat (58, 152) and in the anaesthetized dog (19, 152, 251), serpentine elicits an immediate, though brief, fall in arterial pressure, which is inhibited neither by atropine nor by vagotomy (152). Serpentine has no effect, however, when given orally to dogs in daily doses of 3 mg/kg (67).

Little is known about its site of action on the circulation: it is reported to stimulate the heart of the cat (57) and the frog (152) both *in situ* and isolated. In comparatively large doses of 5 mg/kg i.v. it proves toxic to the rat heart (152). According to Kadatz (152), serpentine has a vasodilator effect similar to that of papaverine. In doses exceeding 3 mg/kg i.v. it displays very slight ganglion-blocking activity (19). No such activity was observed by Kadatz (152). This finding may be related to the fact that serpentine is a quaternary anhydronium base, but this is not sufficient to explain its effect on the blood pressure.

Serpentine displays no sympatholytic activity as measured by the reaction of the blood pressure to adrenaline and noradrenaline in the cat; instead, a slight enhancement of the pressor response occurs (21, 152). It also has no significant adrenolytic effect on the isolated seminal vesicle of the guinea-pig (1, 152). The

fact that ergotoxine reverses its action from a hypotensive to a hypertensive one (57) can hardly be regarded as evidence of a specific point of action.

Rises in blood pressure in the cat, following electrical stimulation of the centripetal sciatic or vagus nerve or following occlusion of the carotid sinus, are not inhibited by serpentine (21)—or, at least, only to a minor degree and for a short period in response to very large doses (19, 152). Serpentine does not inhibit rises in blood pressure caused by electrical stimulation of the splanchnic nerve (21).

The isolated intestine of the guinea-pig, rabbit, and kitten and the small intestine of the cat *in situ* were observed to relax after serpentine (57, 152), whereas in the dog stimulation of the small intestine *in situ* occurred, together with secondary inhibition of peristalsis (251). In contrast to the action of reserpine (see below), there is little or no antagonism to barium chloride in the isolated intestine; in addition, no marked antagonism to acetylcholine (152) or to histamine (152) is apparent. Serpentine does not protect guinea-pigs against lethal doses of histamine (19). In sublethal doses, it does not impair neuromuscular transmission in the cat (19).

In doses of 4 mg/kg i.p. it diminishes the adrenal ascorbic acid content in mice (65). The active Arthus phenomenon in the rabbit (egg albumen) is not inhibited (19). Unlike reserpine, it does not release 5-hydroxytryptamine (229).

Serpentinine. Serpentinine acts on mice like convulsant poisons (60). A claim by Chopra and Chakravarti (58) that serpentinine has a certain general anaesthetic effect in mice was later disproved by Chopra *et al.* (60). It acts synergistically with picrotoxin (60). It produces neither sedation nor miosis in the rabbit (21).

Toxicity. Mice: LD_{50} i.p. between 100–125 mg/kg (58); rabbits: LD_{50} i.v. 10 mg/kg (19).

Whereas earlier findings point to a hypertensive action on carotid artery pressure in the anaesthetized cat which is unaffected by ergotoxine (57), in the decerebrate and in the spinal cat (58), recent investigations have shown a hypotensive effect similar to that of serpentine and ajmaline in the anaesthetized cat (21) and in the dog (19, 256). They also showed that the fall in blood pressure is followed by vasodilatation of the femoral bed (256) and some secondary vasodilatation in the kidney (256). No hypotensive action was observed in the dog following oral doses of 3 mg/kg daily (67).

A slight adrenolytic effect, with some inhibition of the carotid sinus pressor reflex and of the bradycardia due to vagal stimulation, is apparent in bivagotomized dogs under artificial respiration (252), but only in response to dosages which would otherwise prove toxic. Serpentinine does not inhibit, but slightly enhances the pressor action of adrenaline and noradrenaline on carotid artery pressure in the cat (21); it has no specific effect on the pressor part of the carotid sinus reflex (21) and causes only mild, transient inhibition of the rise in blood pressure provoked by stimulation of the centripetal sciatic nerve in the cat (21). It causes no inhibition of the rise in blood pressure following electrical stimulation of the splanchic nerve (21). It can therefore be assumed that it possesses no sympatholytic or adrenolytic potency of any significance.

Serpentinine is said to produce tonic contractions in the isolated intestine of the guinea-pig and kitten, which are not counteracted by atropine (57).

The experiments briefly summarized in this section indicate that ajmaline, ajmalinine, neoajmaline, isoajmaline, rauvomitine, rauwolfinine, reserpinine, serpentine, and serpentinine exert their effects only when given in large, sublethal doses (except where, as in the case of ajmaline, they are administered intracisternally), and that they apparently have no well-characterized site of action. This does not apply to the substances now to be discussed. They have either an adrenolytic action or an influence on central regulatory mechanisms. The latter has not so far been observed with other substances.

B. Alkaloids with a predominantly peripheral adrenolytic action

Sarpagine. In the mouse, which is able to tolerate intravenous doses as large as 60 mg/kg, sarpagine has no sedative effect (2). An adrenolytic action upon both the stimulatory and the inhibitory effects of adrenaline has been observed in various isolated test organs, *e.g.*, the uterus and perfused ear of the rabbit, and the seminal vesicle and rectum of the guinea-pig (2). Sarpagine has no parasympatholytic or histaminolytic effects, but, like ajmalicine, it exhibits some antagonism to nicotine in isolated preparations (2).

The action of sarpagine *in situ* (blood pressure and nictitating membrane of the anaesthetized cat), however, can hardly be described as genuinely sympatholytic (173). It does bring about adrenaline reversal, but in doses of not less than 2 mg/kg intravenously (173), which the cat is just able to tolerate (19); moreover, its adrenolytic action is of extremely short duration (173).

It reduces carotid pressure in the anaesthetized cat only for a very brief period (173).

Ajmalicine. The adrenolytic action of ajmalicine which, again, has no sedative effect in mice (173) or rabbits (229) is much more pronounced and prolonged than that of sarpagine; in addition it antagonizes noradrenaline (173). Its adrenolytic effect, as in the case of other well-known sympatholytics, varies in intensity depending on the test organ employed. On the isolated uterus of the rabbit, for example, it is 10–15 times greater than that of sarpagine and 3–4 times greater than that of yohimbine, its intensity being allegedly equal to that of dihydrogenated ergot alkaloids (1). On the other hand, on the isolated seminal vesicle of the guinea-pig it has less effect than yohimbine or ergotamine; similarly, in the guinea-pig colon, its antagonism towards the inhibitory effect of adrenaline is less than that of yohimbine. Ajmalicine is reported to exert a marked papaverine-like action on the perfused rabbit ear (3).

It is reported that in anaesthetized dog and cat it has only an inconsistent depressor effect on arterial pressure (3). Like other compounds with a peripheral adrenolytic action, it can exert its adrenolytic effect without significantly altering the arterial blood pressure (173). It had no hypotensive action in dogs when given in daily oral doses of 3 mg/kg (67).

There was no release of 5-hydroxytryptamine from the brain after treating rabbits with ajmalicine (229).

Rauwolfine. Rauwolfine, which is isolated from a different Rauwolfia species than that from which sarpagine and ajmalicine are obtained, causes convulsions

and respiratory failure in the rat, cat, and rabbit, and has no sedative action (169).

In the anaesthetized cat, dog, and rabbit, it evokes a fall in blood pressure—probably of short duration—as well as respiratory stimulation (169). According to Raymond-Hamet (244), rauwolfine exerts a prolonged adrenolytic action on the blood pressure of the dog.

As mentioned by Koepfli (169), it has little effect on isolated smooth muscle. It is said to have a curare-like action in frogs (169). Rauwolfine displayed no antimalarial activity against avian malaria (169).

Rauwolscine. This alkaloid of *Rauwolfia canescens* is reported to have a hypotensive (211) and adrenolytic action on blood pressure in the cat (45, 211, 303). Rauwolscine does not antagonize the glycogenolytic action of adrenaline (211). In doses of 5–7.5 mg/kg, it causes ascorbic acid depletion in the rat (212).

Serpine. Serpine, which is only obtained in limited yields from one variety of *Rauwolfia serpentina*, is described as having a sympatholytic action comparable to that of yohimbine (50). Precise details are lacking, so that it is not yet possible to assess and classify this obviously minor alkaloid.

C. Alkaloids with a predominantly central site of action

Reserpine. Of all the Rauwolfia alkaloids so far isolated, the one which has been most extensively studied both in the laboratory and in clinical use is reserpine, the first alkaloid to display the peculiar central and hypotensive effects associated with Rauwolfia preparations and later found to be properties of deserpidine and rescinnamine as well. It remains to be established, however, whether the latter are in every respect identical with reserpine in their actions.

Reserpine exhibits a complex pattern of activity. Its various effects constitute a syndrome, most elements of which may be due to a central action. These individual elements themselves are also of a complex nature. Characteristic features of reserpine are a peculiar sedative and hypnotic effect, which differs from that of other known substances having a CNS depressant activity, a lowering of arterial blood pressure accompanied by bradycardia, some respiratory inhibition, stimulation of peristalsis, miosis, relaxation of the nictitating membrane, and an effect on the temperature-regulating centre (16). This pattern of signs and symptoms corresponds to a syndrome obtained by Hess (134) upon electrical stimulation of certain diencephalic structures in the cat, and to a syndrome observed by Weiskrantz and Wilson (346) in monkeys in which lesions had been produced either in the anterior medial portion of the temporal lobes (including the amygdaloid complex and prepyriform cortex) or in the prepyriform cortex and anterior insula (but excluding the amygdala). An analogous clinical pattern, combining individual components in a uniform picture, is found in patients with tumours of the posterior hypothalamus (100). The fact that reserpine provokes such a well defined complex of signs and symptoms indicates that it influences what appear to be coordinatively linked and integrating central mechanisms; at the same time, however, such considerations do not necessarily throw light on the location of its sites of action (18, 22).

Nevertheless, it is typical of reserpine that only certain selected and specific functional systems within both the autonomic and somatic systems are suscep-

tible to its action (18, 22). The location of its central site of action depends, on the one hand, on the function under study, *i.e.*, small doses may exert their effect rostrally or caudally according to the system involved, and, on the other hand, on the size of the dose administered, *i.e.*, when tests are made on the same functional system, the tendency is, perhaps, for small doses of reserpine to act on rostral sites and for larger doses to affect other, probably caudal, sites (18). Some reports suggest that the mechanism of action of reserpine may depend, either wholly or in part, on an activation of inhibitory mechanisms (18, 284).

Studies on metabolism of nervous substrates, which might shed light on the peculiar mode of action of reserpine, have yet to be undertaken. It is reported that, in rats, S^{35}-labelled methionine is concentrated in the region of the hippocampus under the influence of reserpine (182). *In vitro*, reserpine depresses the oxygen consumption of slices of cerebral cortex taken from the rat, but only when present in very high concentrations (240). In hypertensive patients, it has no significant influence on the glucose and oxygen uptake of the brain (127, 128).

Nor are there any records of any behavioural studies (particularly those involving elimination of certain parts of the brain) which might afford positive clues concerning its site of action.

The different effects produced by the action of reserpine may vary in intensity from one species of animal to another (see below and 283). There are, however, two characteristics common to all its effects: firstly, the fact that its onset of action only occurs after a certain latency period, which can be somewhat shortened by increasing the dose (16, 284) but cannot be eliminated altogether, and which is also evident when reserpine is given by direct intra-arterial injection (336); and secondly, that single doses have an exceptionally long duration of effect. This may be connected with the physical and chemical properties of this alkaloid, which, as a rule, is only very sparingly soluble, or it might also indicate—as has been suggested in the first pharmacological studies—that it does not act *per se* (16, 22). It may be that it releases active substances, 5-hydroxytryptamine being possibly one of them, or that it is itself broken down into an active substance. Finally, it is also possible that reserpine itself, or a metabolite of reserpine, does not exert its characteristic pharmacological effects except in the presence of a liberated endogenous substance. On the basis of findings to date, no definite conclusions can be reached regarding these possible interpretations.

Reserpine *in situ* has no peripheral ganglion-blocking action, and no sympatholytic, parasympatholytic, or histaminolytic effects (16, 17). On the other hand, it strongly antagonizes barium chloride and pitressin in isolated smooth muscle organs, so that certain effects of peripheral origin may also play a part *in vivo* (334, 335). Assuming that an active metabolite is required to produce the pharmacological effects associated with reserpine *in vivo*, it would be necessary to investigate whether such a metabolite behaves differently from reserpine in isolated organs.

Sedative and hypnotic action. The sedative and hypnotic effect provoked by reserpine in various animal species (mouse: 16, 22, 69, 235; rat: 22, 234, 235; guinea-pig: 22, 235; rabbit: 16, 22, 234, 235; cat: 16, 22, 235; dog: 16, 22, 69,

234, 235; monkey: 62, 235, 280, 281, 314) is unique in character and different in many respects from that of other well-known drugs with a central depressant action. No analgesic action has been detected in various species of animals (16, 22, 278); not even very large doses of reserpine produce genuine anaesthesia in experimental animals. They can still be roused by external stimuli, but gradually lapse into sleep again afterwards; the waking period may even be comparatively long, depending on the size of the dose of reserpine given and the strength of the stimulus. In the case of cats and dogs, the animals are often observed to take up a natural sleeping posture after first going through the stereotype motions normally performed by their species prior to assuming a position of sleep. Frequently, especially when they are under the influence of relatively large doses of reserpine, it it also possible to place and keep them in certain positions (22). Given to rats in doses which have a marked sedative action, it depressed nest-building activity but stimulated the search for a warm environment (296). It often seems that the animals become readily susceptible to calming influences. A change in behaviour is thus apparent, this being particularly true of monkeys, which lose their normal aggressiveness under the influence of reserpine (62, 89, 235, 280, 281, 314, 346). Reserpine also inhibits induced aggressiveness in cats showing "sham rage" (279). In connection with its effects on animals that have been subjected to surgical operations, it should perhaps be mentioned here that reserpine also has a sedative influence on leucotomized patients (201).

Behavioural studies on animals with experimental brain lesions would appear to be particularly suitable as a means of determining the location of this central action. Weiskrantz and Wilson (346), experimenting on monkeys which had learned to avoid an electric shock, eliminated various portions of the brain by operation and concluded from their observations that reserpine protects the hypothalamus from modulating or activating impulses, its point of attack being probably situated somewhere in the region of the orbito-insula-temporal areas. In this connection, it is interesting to note that electroencephalographic studies on rabbits or cats reveal alterations in the rhinencephalon (102, 182).

The difference between the action of reserpine and that of the barbiturates or other general anaesthetics—a difference which may also be demonstrated in other organ systems (see below)—is likewise evident in the EEG pattern. Unlike the barbiturates, reserpine does not produce any distinctive electroencephalographic changes either in normal monkeys (280, 281) or in epileptic monkeys (62). Similar findings have emerged from studies on human beings (25, 63, 127, 202), although clear-cut alterations in the EEG pattern have been observed after prolonged treatment with large doses of reserpine (25). Arousal phenomena in curarized rabbits have been recorded after large doses of reserpine—which, once again, is in contrast to the findings with barbiturates (262).

According to Gangloff and Monnier (102), reserpine in rather high doses has a depressant influence on the diencephalocortical system of rabbits. In the cat, however, small doses do not alter the EEG arousal response to stimulation of the thalamus or reticular formation—again, in marked contrast to the action of barbiturates (160).

Another method of analyzing the central action of reserpine and differentiating it from that of other substances with a central site of action is to study the be-

haviour of animals in response to various pharmacologically dissimilar drugs having a central action (333). In the mouse, increases in activity caused by caffeine, cocaine, scopolamine, and morphine are effectively inhibited by small dosages of reserpine (333). Although reserpine does not markedly inhibit increased motor activity due to amphetamine (333), it does afford protection against lethal doses of this drug (69). Reserpine thus varies in its action when tested against different so-called psychomotor stimulants. Furthermore, it does not antagonize all their central effects; for example, in the mouse, it actually intensifies the convulsive action of caffeine (55). It is reported to have some inhibitory action on the analgesic effect of morphine (278); but, in the mouse, small doses of reserpine enhance the mydriatic effect of morphine (and of scopolamine), whereas large doses, which in themselves have a pronounced miotic effect, antagonize the action of parenterally injected morphine on the pupil (333). It also inhibits the tail reaction produced by morphine in mice, although it may itself elicit a slight tail reaction (333). A differentiated antagonism can also be seen in other animal species and in other effectors, *e.g.*, when morphine is injected into the cat by the intraventricular route or when methadone is injected subcutaneously, the sedation and miosis caused by reserpine are effectively counteracted, but the relaxation of the nictitating membrane in response to reserpine persists (101). Subcutaneous lysergic acid diethylamide (LSD), on the other hand, has an antagonistic action on the nictitating membrane as well (101).

In pronounced contrast to the action of phenobarbitone (Phenobarbital Sodium U.S.P.), not only is reserpine unable to suppress convulsions elicited in the mouse by strychnine, picrotoxin, nicotine, Pentylenetetrazol U.S.P. (Leptazol B.P., Metrazol®), or electroshock (333)—it is only slightly effective against audiogenic seizures (333)—but, on the contrary, it exacerbates tonic seizures provoked by convulsive doses of Metrazol or caffeine (but not strychnine) in mice (55) and lowers the electroshock threshold in mice (54, 55, 94, 151) and rats (314). This action of reserpine is not affected by cortisone or chlorpromazine (94).

As with the central stimulants, so also in the case of central depressant agents, the influence of reserpine on their individual effects was found to vary. Whereas it prolongs the sleeping time in animals treated with hexabarbitone (39, 314), ethanol (39), and pentobarbitone (69), in the same animal species it reduces the anticonvulsive activity of, for example, phenobarbitone, pentobarbitone, barbitone, diphenylhydantoin (Dilantin®), and mephenesin (3-*o*-toloxy-1,2-propanediol) (54). Its effect on these anticonvulsive agents varies in potency from one agent to another: its inhibitory action is strongest, and probably competitive, against diphenylhydantoin and weakest against mephenesin (54).

The ineffectiveness of reserpine against Metrazol-induced convulsions has also been demonstrated on monkeys rendered epileptic by applying alumina cream to a cerebral hemisphere (62). It is reported, however, that during the time in which the effect of reserpine was at its height, these same animals were less susceptible to clinical seizures provoked by the stick prodding technique (62).

In man, the results obtained are not consistent: it is not yet known whether seizures differ in their response to reserpine depending on their origin. It has been found that reserpine lowers the threshold when electroconvulsive treatment is applied (327) and that on

rare occasions it gives rise to grand mal seizures (161). It has no antagonistic effect against anticonvulsives; rather, it is claimed that in patients suffering from attacks of petit mal or grand mal it increases their potency (162, 354). It is also said to have some beneficial effect in status epilepticus (162), but no such effect was observed in psychomotor attacks (354).

Given in very large doses, reserpine enhances the patellar tendon reflex in the cat (284), an effect which is evidently species-dependent, since it is not seen in the rabbit (19).

The appearance of reversible extrapyramidal symptoms had already been noted by the first Indian research workers to study Rauwolfia (77, 241, 301); it was later observed in epileptic monkeys receiving reserpine (62), as well as on frequent occasions in the clinic after large doses had been given (25, 30, 85, 97, 142, 145, 161, 163, 201, 268, 344). These symptoms, which are probably evidence of a peculiar mechanism of action, are deserving of particular interest from the neurological aspect: firstly, because they are reversible and can be controlled with atropine; secondly, because reserpine may exert a beneficial influence on other hyperkinetic syndromes such as Huntington's chorea, athetosis, and congenital spastic paralysis (30, 162, 163, 332); and thirdly, because chlorpromazine, another drug whose action resembles that of reserpine in psychiatric cases, produces a similar syndrome (30, 161), which can also be experimentally provoked in primates (161), despite the fact that chlorpromazine differs from reserpine as regards the pharmacology of its peripheral and central effects (17, 20, 278) and that this substance also causes no liberation of 5-hydroxytryptamine in the brain (229). The mechanism of action of both reserpine and chlorpromazine in this connection has yet to be satisfactorily explained.

One peculiar feature of reserpine that has been receiving attention lately is its ability to release 5-hydroxytryptamine (HT, serotonin) from various organs situated both centrally and peripherally (brain: 38, 219, 230; intestinal tract and platelets: 228, 230). In the rabbit, the HT content of the intestine and brain—there is no difference between the brain stem and the rest of the brain—gradually diminishes following intraperitoneal injection of 5 mg/kg reserpine; it reaches a minimum only after a considerable latency period, the rate at which the HT content diminishes being somewhat faster in the brain than in the intestine. Subsequently, the level slowly rises again, returning to normal after about seven days (38, 230). In view of the fact that, throughout the phase in which the serotonin content of the brain was reduced, a metabolite of HT was present in the urine (309), Brodie *et al.* (38) have suggested that during this period HT is still being formed in the body but is not accumulating in the brain tissue (or in the intestine).

Shore *et al.* (308, 309) observed that, if given in very large doses, HT, like reserpine, increases the action of anaesthetics in mice and also that this effect of both substances can be counteracted by LSD. They therefore assume that the action of reserpine is mediated by HT. This view is further substantiated by the fact that so far only Rauwolfia alkaloids with a sedative action have been found to liberate HT (229). In mice, however, LSD is a central stimulating drug *per se*, its effect being to step up motor activity (195); the depression induced by reserpine can be antagonized by other central stimulating drugs as well (333). Regitine®, which has a stronger antagonistic action on the sympathetic nervous sys-

tem than on 5-hydroxytryptamine (150), also diminishes the effect of reserpine in mice (333), whereas atropine, which is likewise able to exert an antagonistic influence on 5-hydroxytryptamine (150), enhances the effect of reserpine in mice (333). Thus from such types of experiment, it does not yet seem possible to deduce whether the antagonism of LSD towards reserpine is indeed the clue to the mechanism of action of reserpine, although an intermediary action by HT or an HT-like substance may account for some of the effects observed.

Many of the effects of reserpine cannot be duplicated by HT; in fact, only a few of them bear some formal resemblance to its action. It is tempting, for example, to interpret the effect of reserpine on the intestine (see below) in terms of a liberation of HT, or, since HT is known to produce contraction of the bronchial muscles (99, 133), to regard it as responsible for the dyspnoea which is occasionally observed in clinical practice (4, 126, 201, 265, 299, 344, 350) and which is aggravated by methacholine (Mecholyl®) (299). Moreover, it is possible that the liberation of HT or of HT-like substances is also the explanation for certain reactions occurring in the cutaneous and mucosal vessels in response to reserpine; such reactions, which had been observed earlier in man and ascribed to the liberation of some vaso-active substance (98), include congestion of the conjunctiva and nasal mucosa, and flushing followed by blanching of the skin (especially in the face); they cannot be inhibited by the use of antihistamines (98).

When injected parenterally, the effect produced by HT on, for example, the respiration, heart rate, and nictitating membrane (93, 220) is contrary to that of reserpine: on the arterial pressure HT has either a depressor, pressor, or dual phase action, depending on the species of animal under investigation (93, 220, 286). In connection with these experiments, however, it should be noted that substances injected parenterally may possibly not reach their target, at least not in sufficient concentrations to be effective. Even when HT is injected centrally by the direct (intraventricular) route, it does not produce the characteristic central effects of reserpine on the pupil and nictitating membrane of the cat; moreover, while HT, like reserpine, gives rise to inertia, the picture presented by such inertia is not completely identical for both substances (101). It remains to be seen whether the liberation of HT after reserpine is purely coincidental or whether it does in fact provide a clue to the central action of Rauwolfia. It would also be interesting to know whether serotonin-induced depression in mice influences other centrally acting drugs in the same manner as does reserpine.[2]

[2] Since this paper went to print, the results of experiments have been published showing that the depression induced by reserpine can be pharmacologically differentiated from that occurring after HT (Brown, B. B.: Effects of LSD on different aspects of drug-induced depression. Abstracts of communications XXth Int. physiol. Congr., pp. 133–134, Brussels 1956; Taeschler, M.: Serotonin-blocking effect and some central actions of lysergic acid derivatives. *ibid.*, pp. 873–874. For discussion, see Bein, H. J.: The action of Rauwolfia alkaloids on central mechanisms. *ibid.*, pp. 455–465). In addition, it has been shown that reserpine causes a decrease in brain sympathin as well (Holzbauer and Vogt, 1956, see Gaddum, J. H.: Recent work on 5-hydroxytryptamine and lysergic acid derivatives. *ibid.*, pp. 442–455), and that amphetamine also lowers the HT content in the brain of the dog (219). According to the same authors, the concentration of substance P was not affected.

Cardiovascular effects. Single doses of reserpine cause a slowly developing fall in arterial pressure in the monkey (280), dog (22, 207, 210, 235, 330, 331), cat (16, 18, 22, 130, 314), and rabbit (22, 192). As a rule, in man (265, 300, 319, 350) as well as in experimental animals, the higher the level prior to the administration or reserpine, the greater is the subsequent reduction in blood pressure. Where the blood pressure in the anaesthetized cat is less than 100–105 mm Hg, even comparatively large doses of reserpine have only a very erratic vasodepressor action (19). In the normotensive monkey (280) and in normotensive man (162, 300, 327) its hypotensive effect is generally only slight; in the normotensive dog, which, according to Moyer (207), shows no significant fall in blood pressure after reserpine in about 25 % of cases, its vasodepressor action is less pronounced than in the cat and rabbit (19). On the other hand, large and prolonged reductions in blood pressure have been observed in patients suffering from hypertension of varied origin (96, 98, 145, 176, 209). A similar reaction cannot be elicited with other centrally acting drugs, such as barbiturates (127, 348). Increasing the dose of reserpine tends to prolong rather than intensify its effect on the blood pressure (192, 196).

It has been observed in cats (22), dogs (207, 210), and man (198, 292) that, while the pressure is falling, the total peripheral resistance is reduced. In human beings, a reduction in resistance in both skin and muscle is apparent (31) as well as a reduction in high pulmonary resistance (82) and in high cerebral vascular resistance in hypertensives (127), while in dogs there is a lowering of renal vascular resistance (207, 210). There was no consistent effect on the renal plasma flow or glomerular filtration rate in dogs (207, 210) and human beings (5, 176, 207, 210, 259). The cerebral blood flow in man was found to be unchanged (127, 128).

In the cat, the cardiac stroke and minute volume increase, except where the stroke volume is already high at the outset (22). In the dog, no significant or consistent change in the stroke volume is apparent (207, 210, 235, 331). In man, acute tests cause no significant effect on the cardiac output (259), but prolonged treatment is reported to reduce it (292).

Reserpine has a slight inhibitory effect on the activity of the isolated heart of rabbits and cats, but only when given in comparatively high concentrations (334, 335). It has no direct action on isolated peripheral vascular preparations (334, 335); in innervated perfused vascular preparations, it has been shown to cause dilatation (189).

It may therefore be concluded that the fall in blood pressure produced by reserpine is due to vasodilatation unaccompanied by reduction in cardiac performance. Additional evidence of vascular relaxation is provided by the fact that an increase in the arteriovenous oxygen difference, which is not caused by a rise in the oxygen consumption (331), is observed in dogs.

It is unlikely that the fall in blood pressure is due to stimulation of the vagal system, since it is not diminished by atropine or by eliminating the vagus and depressor nerves (16), nor is the action of intravenously injected Veratrum enhanced by reserpine (16, 96). Faradization of the cardiac vagus in dogs resulted

in the usual hypotension and bradycardia (235). In the cat, no change in the histamine content of the plasma occurred during hypotension evoked by reserpine (149). In the mouse, no reduction in the histamine content of the small intestine was apparent after doses large enough to cause sedation and diarrhoea (149).

Reserpine has no sympatholytic or glanglion-blocking actions either *in situ* or in isolated organs (16, 17, 22, 207, 210, 234, 235, 330), nor are such actions evident in man (31, 319, 350). In contrast to the action of true sympatholytics, it does not prevent arrhythmias in the dog induced by chloroform-adrenaline or by trichloroethylene-adrenaline (319, 331). In the cat, it does not inhibit the output of pressor substances from the adrenals in response to stimulation of the splanchnic nerve (16, 18, 21). Nor has it any significant influence on the action of histamine and HT on isolated organs (334, 335). In spinal dogs subjected to bilateral vagotomy, however, it has a relatively slight inhibitory effect on rises in blood pressure caused by HT (285), whereas in the intact animal it enhances such rises (285)—probably in somewhat the same way as it enhances increases in pressure caused by adrenaline and noradrenaline (16, 22). It has also been found to intensify the action of adrenaline *in situ* on the nictitating membrane of the cat, but no such intensification could be discerned in various isolated organs (22). Since it also has no influence on adrenaline-oxydase *in vitro*, these findings are interpreted by Bein *et al.* (22) as evidence that reserpine exerts a direct action on central mechanisms regulating the circulation.

Although reserpine does not block the peripheral portion of the sympathetic nervous system, there are signs indicating that it depresses the sympathetic nervous system, *e.g.*, relaxation of the nictitating membrane in cats (16, 18, 22, 101) and dogs (16, 22, 69, 235). This relaxation of the nictitating membrane under the influence of reserpine may be regarded as evidence of a diminution in sympathetic tone, which is either of central origin or centrally transmitted (16, 18). The observation that reserpine produces vasodilatation only in the innervated, but not in the denervated, ear of the non-anaesthetized rabbit would also appear to support the hypothesis of a central site of attack (187).

That central sympathetic structures are influenced by the action of reserpine is also probable in view of the fact that relatively small doses suffice to inhibit pressor responses to (a) occlusion of the carotid sinus (dog: 235, 331; cat: 16, 18, 21, 22, 279, 314); in the cat, reserpine has no direct action on the stretch receptors and chemoreceptors of the carotid sinus (16, 18)) and (b) stimulation of afferent nerves, *e.g.*, the centripetal vagus nerve of the dog (235, 331) and cat (16, 21, 22) and the sciatic nerve (16, 21), and the tibial nerve (314) of the cat. In the dog, however, reserpine is unable to prevent pressor responses due to increased intracranial pressure (27, 331), whence Trapold *et al.* (331) suggest that reserpine affects centres higher than medullary structures, *e.g.*, the hypothalamus.

In man, too, reserpine—in contrast to phenobarbitone—is able to inhibit certain vasomotor reflexes such as the digital vasoconstriction produced by deep inspiration or pain (350). On the other hand, it has no effect on the cold pressor test (348, 349, 350) and it does not inhibit the Valsalva reflex (98, 348) or the psychogalvanic reflex after sharp inspiration (350). It is reported that, in the "Funkenstein" test, reserpine yields a different pattern from that of barbiturates (287).

On direct electrical stimulation of central sympathetic structures in the cortex (17, 18), hypothalamus (279), and spinal cord (27) reserpine produces no alteration in electrical excitability, although inhibition of such excitability has been reported in the hypothalamus (130) and to a very slight degree in the medulla after very high doses (27). Schneider (279) assumes that reserpine causes a central inhibition of those afferent impulses which normally stimulate sympathetic activity, rather than any direct depression of central sympathetic structures.

Section of the brain stem immediately caudal to the quadrigeminal bodies partly abolishes the action of reserpine on the carotid sinus reflexes in the cat. Once the brain stem is severed, much larger doses of reserpine are needed to inhibit the pressor reflex of the carotid sinus than when the brain stem is intact (18). Since a carotid sinus reflex blocked by reserpine is partly restored after severing the brain stem, Bein *et al.* (23) have assumed that the intact animal possesses one or several structures which inhibit the carotid sinus pressor reflex and which are activated by reserpine. Moreover, section of the brain stem behind the quadrigeminal bodies partly counteracts the drop in arterial pressure brought about by small doses of reserpine, whereas larger doses lower the pressure again—an indication that central structures located more caudally are also affected by the action of reserpine (18). In the spinal dog, reserpine provokes a pronounced and consistent rise in blood pressure (285); in the spinal cat it has no pressor or depressor action (16, 22, 44).

During the fall in pressure elicited by reserpine, the pulse rate is slowed down to a greater or lesser degree, depending on the species of animal involved. This effect is particularly evident in the dog (235, 331) and rabbit (283), whereas in the monkey (280) and cat (16, 18, 22) it is either less pronounced or less consistent. In isolated heart preparations it is either missing altogether or only faintly discernible (isolated rabbit Langendorff heart, see 334, 335). In the heart-lung preparation of the dog, tachycardia is observed instead (235). Where bradycardia occurs in the cat, a diminution of the sympathetic outflow in a sympathetic cardiac nerve takes place at the same time as the bradycardic action (18). Thus, this effect, too, may be regarded as being of central, or mainly central, origin.

Almost all authors who have carried out clinical trials with reserpine report a bradycardic effect in man as well. According to Schumann (294), the mechanism of action responsible for this effect bears no resemblance to that of digitalis; various reports have been published on this subject in connection with the treatment of certain cardiac disorders (103, 129, 293, 294, 353). Reserpine produces no marked change in either the ballistocardiogram (126, 293) or the cardiac volume (103, 293).

A prolonged antihypertensive action is also observed in animals in which hypertension has been induced by various methods. Although reserpine, like other vasodepressor agents at present known, may not basically influence the underlying pathogenic mechanisms responsible for the rise in blood pressure in experimental hypertension (116), it does, however, lower the systolic pressure, reduce the extent of the pathological vascular changes, and lengthen the survival time (104). Reserpine appears to be equally effective against various forms of hypertension, and there does not seem to be any significant difference in the potency of its vasodepressor action whether the experimental hypertension be of nervous, renal, or endocrine origin. This observation may well be in accordance

with the results of clinical studies indicating that there is no difference between its action in "essential" and "nephrogenic" hypertension. It has not yet been established, however, whether the intimate mechanism, or mechanisms, of its vasodepressor action are the same in hypertensive as in normotensive animals (192).

In rats rendered hypertensive with cortexone (desoxycorticosterone, DOC) the blood pressure is reduced by single subcutaneous injections of 2.5 mg/kg reserpine, the effect lasting about 72 hours (104). In dogs with neurogenic hypertension (carotid sinus denervation), it lowers the diastolic pressure and antagonizes pressor spikes provoked by irritant stimuli (183). In rats with hypertension caused either by operative procedures on the kidney, *e.g.*, encapsulation (116), by clamping the renal artery, with or without unilateral nephrectomy (193), or by an overdosage of steroids (DOC: 104, 116; cortisone: 104, 116; hydrocortisone: 116), 0.1 mg/kg and day injected subcutaneously or 0.5–1 mg/kg and day by the oral route is sufficient to prevent hypertension or to reduce the blood pressure. In DOC-induced hypertension in rats, 0.05 mg/kg and day s.c. was ineffective (104), and in the hypertensive dog (figure-of-eight ligature) a single dose of 0.1 mg/kg p.o. was also without effect; but in the same test object, 0.3 mg/kg p.o. had a prolonged antihypertensive effect (115)—said to be related, however, to a nonspecific loss of extracellular fluid (115).

Action on respiration. Large doses of reserpine have a depressant effect on respiration in all species of animals studied, while acutely lethal doses produce a centrally conditioned cessation of breathing (22, 235, 280, 331). Anaesthesia usually renders the animal more sensitive to reserpine. According to Meier and Bein (191), only some of the respiratory reflexes are affected. Vagal respiratory reflexes, for example, and the sensitivity to electrical stimulation of the medullary structures associated with these reflexes are not influenced by reserpine. It is thus clearly evident that reserpine differs in its action from morphine, morphine-like central analgesics, and barbiturates (18). It does not depend on peripheral mechanisms for its effect, since it neither modifies the sensitivity of vagal pulmonary stretch receptors nor does it act on the motor pathway or on neuromuscular transmission (18).

On the other hand, reserpine has a marked influence on chemoreflex respiratory mechanisms: it inhibits the augmentation in respiration caused by carbon dioxide (22) and the concomitant rise in blood pressure. That peripheral inhibition by reserpine is unlikely can be shown by examining the activity of the chemoreceptors of the carotid sinus (18). Apnoea in rabbits, due to hyperventilation, is inhibited by small doses of reserpine—also when the animals have been subjected to vagotomy and decerebration (191). It can thus be demonstrated that reserpine, even in small doses, is also able to exert an influence on caudally situated centres. Another illustration of its ability to inhibit these chemoreflexes is provided by the fact that rate and volume of respiration slowly decline, even when the oxygen content in the periphery is slightly reduced (22, 331), resulting in stimulation of the chemoreceptors as reflected in an increase in their action potentials (19).

Miotic action. In mice, rabbits, cats, and dogs (16, 22, 235, 333), reserpine, while not suppressing the normal ocular reflexes to light, causes pronounced contraction of the pupil—usually the first and most prolonged sign of its action (16, 22, 235). In monkeys (280, 314) and in man (161, 201, 344, 348, 350), this effect, though rare, is nevertheless occasionally seen, especially when an exam-

ination is made in the dark (179). It is very probably of central origin, since parenteral injections of reserpine produce no miosis on the denervated side in cats following unilateral extirpation of the ciliary ganglion. Reserpine also fails to elicit miosis when instilled into the eye of the rabbit (22, 333). Further evidence for the absence of a peripheral action is afforded by the fact that little or no miotic action was found with reserpine in thalamic cats (279). (For antagonistic reactions, see p. 454.)

Influence on temperature regulation. In mice, rats, guinea-pigs, cats, dogs, and monkeys (16, 22, 24, 94, 235, 280, 326), reserpine lowers the body temperature. At a high environmental temperature, a slight increase in body temperature may occur, suggesting depression of the temperature-regulating mechanism (16, 22, 235, 280). In man, reserpine has an inconsistent effect on body temperature (201, 344). No real antipyretic action was apparent in the rabbit (16, 22), and hardly any in the rat (333).

Reference has already been made to the fact that reserpine inhibits the central stimulating effect of morphine in cats and mice, and that in these species morphine displays some antagonistic action. In the cat, morphine also provokes a sharp rise in temperature, provided certain central structures are intact (186).

Effects on the gastrointestinal tract. Given by the oral or parenteral route, reserpine stimulates intestinal activity in the mouse, rat, guinea-pig, rabbit, cat, and dog, and to a much lesser degree in the monkey (280). Fairly large doses may give rise to diarrhoea (16, 22, 235). In the anaesthetized dog, it increases the motor activity of the small intestine (232). In the anaesthetized rabbit, it stimulates intestinal motility, especially in the lower parts of the intestine (22).

In the dog, even when given in very small doses (0.015 mg/kg i.v.), it increases gastric secretion as regards both volume and hydrochloric acid content (14, 15, 235). Gastric secretion is also stimulated in the human being (8, 62a, 132a).

The mechanism of action of reserpine has only been partially elucidated. It exerts no parasympathomimetic action. It does not increase the activity of the isolated ileum of either guinea-pigs (22, 232), rabbits (22, 232, 235), cats (232), or dogs (232); on the contrary, it depresses such activity if given in concentrations exceeding 1 μg/ml—concentrations which also inhibit contractions produced by acetylcholine, barium chloride, and histamine (14, 15, 22, 232, 235). Similar responses are observed in the isolated colon of the rabbit, rat, cat, and dog, although in this organ reserpine is less antagonistic to acetylcholine (14, 15, 232).

The stimulation of colonic motility in the rabbit in response to reserpine is counteracted by papaverine, but not by parasympatholytic or ganglion-blocking agents or by tripelennamine (Pyribenzamine®) (22). The action of acetylcholine on the motility of the colon and small intestine in cats and rabbits *in situ* is not enhanced (16).

Intestinal stimulation is also observed in dogs subjected to transection of the spinal cord at C_6, as well as to cervical and transabdominal vagotomy (232). It is reported that the increased motor activity occurring in animals operated upon in this way is reduced by hexamethonium (232); on the other hand, the depressant action of ganglion-blocking agents on intestinal motility in patients can be

antagonized by reserpine (87, 207). Results obtained in clinical practice indicate that no increase in the activity of the stomach, duodenum, jejunum, and colon occurs in response to 1 mg reserpine given intravenously (8).

In dogs, an increase in gastric secretion takes place both in the vagally innervated gastric fistula pouch and in the vagally denervated Heidenhain pouch (14, 15). In a patient upon whom bilateral vagotomy had been performed, an increase in the volume and acidity of gastric secretion occurred after an intravenous injection of 1 mg reserpine (8). Assuming that influences emanating from the vagal system are completely eliminated (the difficulties met with in this field when working with Heidenhain pouches have recently been discussed by Burstall and Schofield (41)), it might be concluded that the vagi are apparently not concerned in the stimulating action of reserpine on gastric secretion. It has been suggested, however, that reserpine may act by stimulating the parasympathetic ganglia, since in the Heidenhain pouch hexamethonium, as well as a parasympatholytic agent, inhibited reserpine-induced stimulation (14, 15). On the other hand, it is also possible that reserpine exerts a direct effect on the peripheral motor and secretory cells, particularly because reserpine liberates 5-hydroxytryptamine from the gastrointestinal tract (228). Since HT is a potent stimulant of gastrointestinal motility in various species (93, 220), it might seem justifiable to assume that the action of reserpine on the gastrointestinal tract is due to the liberation of HT or to a depletion of HT in these organs—although, however, hexamethonium does not counteract the effect of serotonin on the smooth muscle cell in isolated organs (93, 220). It is not yet possible to reach any final conclusions on this question, since no suitable data are so far available concerning the interaction of HT and a ganglion-blocking agent *in situ* or, surprisingly enough, concerning the effects that HT may have on gastric and intestinal secretory cells. Moreover, it should be remembered in this connection that, in addition to HT, another smooth muscle stimulant, probably an indole derivative of related structure, is also present in the gastrointestinal tract (71).

Effects on the endocrine system. In clinical use, treatment with reserpine or Rauwolfia extracts is frequently reported to give rise to symptoms which suggest that the endocrine system is affected. Besides a general increase in appetite (30, 117, 161) amounting at times even to polyphagia (327), other effects are observed which point to a more specific site of action involving water and electrolyte metabolism, the thyroid gland, and the sexual functions.

A gain in weight, which is mentioned in almost all clinical reports (4, 30, 97, 107, 315, 327, 348) and is usually regarded as being related to the improvement in appetite, is sometimes also accompanied by fluid retention. The latter may in some cases be very circumscribed (*e.g.*, oedema of the eyelids), while in other cases, sometimes in the premenstrual period (113), it may be quite generalized and pronounced (97, 142, 163, 223).

In male patients, but not in women (348), there may be a decrease in libido, while in women an improvement in receptivity has been observed (113). Gynaecomastia has been reported in the male (348). Reserpine is said to have no definite influence on the menses (113, 348).

Its effect on body weight may perhaps be due to some influence on the thyroid gland. In patients suffering from Graves' disease, it is said to have a very pronounced effect on circulatory disorders and tachycardia (72, 218), but no consistent change in the basal metabolic rate is reported in patients (350) and there is no change in the radioiodine uptake (109).

While experimental findings indicate that reserpine may produce certain effects on the endocrine system, such findings are still inadequate for an analysis of all the relevant clinical observations.

Tests on the rat have shown that, unlike the increase in metabolism in response to 2,4-dinitrophenol, the increase in oxygen consumption caused by thyroxine is inhibited by reserpine (175). Other authors deny that reserpine has a direct action on the thyroid gland, since they were unable to discern any reduction in the radioiodine uptake (109, 154) or any alteration in the distribution of radioiodine in the thyroid (154). In rats, prolonged administration of reserpine causes slight enlargement of the thyroid, histological evidence indicating mild functional inhibition (290). In wild rabbits treated with reserpine, the usual "fright thyrosis" with exophthalmos, and the typical histological changes occurring in the thyroid gland are not encountered (320).

In rats, reserpine causes no alteration in the total voluntary food intake when given in doses of 50 μg/kg and day for 12 days (295). At this dosage, however, it causes a reduction in the voluntary salt intake of rats rendered hypertensive with DOC (104). As other vasodepressor drugs have no influence on the salt intake, this particular effect of reserpine may possibly be a typical feature. Doses of 0.1 mg/kg and day give rise to weight losses in rats (105).

Mild, probably nonspecific stimulation of the adrenal cortex is reported in rats (65, 105). In guinea-pigs, no significant change in the urinary excretion of 17-hydroxycorticoids and no alteration in the responsiveness to ACTH were observed (105). In human beings, reserpine does not prevent the decrease in the number of circulating eosinophils in response to ACTH (350), whereas it was found to inhibit the eosinopenic effect of adrenaline (109). It does not counteract the catabolic effect of cortisone and hydrocortisone (116). It remains to be seen whether the action of reserpine in inhibiting egg albumen-induced oedema in the paws of rats (260) is due to some interference with the adrenals.

The sodium ion and potassium ion concentration in the plasma, as well as the excretion rates for these electrolytes, showed no change in patients to whom reserpine was given over a long period (207, 210) or in dogs which received intravenous injections (207, 210). In rats, high doses delay the excretion of radioiodine (109). Water retention occurs in rats following water loads (105, 194) or sodium chloride loads (194). Meier *et al.* (194) assume that the mechanism of action of reserpine differs from that of pitressin.

While there is no clear evidence to show that reserpine has a specific action on the testes of rats (105), it does interfere with the oestrus cycle in rats (105). According to Mercier and Tuchman-Duplessis (197) this interference is not due to secondary effects on the body weight or other factors, but is a specific action of reserpine. It is claimed that reserpine lowers the conception rate in rats but

that it has no concomitant effect either on lactation or on the average weight of new-born rats at birth (105). The release of pituitary gonadotrophin is reported to be blocked by reserpine (13). In rats, following prolonged administration of reserpine, the basophil cells in the anterior pituitary and the basophil granula in the posterior pituitary may be increased, especially in size (181).

It has also been alleged that, in the rabbit and to a lesser degree in the dog, reserpine has a hyperglycaemic action (174), but Schuler was unable to confirm this (289).

Miscellaneous findings. Neuromuscular transmission in rabbits and cats is not impaired by reserpine (16). In the isolated rectus abdominis muscle of the frog, no direct effect is apparent, nor any antagonism to acetylcholine or potassium (178). In several species of fish, low concentrations of reserpine cause dilation of the melanophores and prevent colour reactions in response to excitation. It produces sedation in the Siamese fighting fish, while in the same species it does not inhibit the effect of LSD (339).

Metabolism and metabolites of reserpine. In rats, Sheppard *et al.* have extensively studied the fate of reserpine labelled with C^{14} either in the 4-methoxy group or in the carboxyl carbon of the 3,4,5-trimethoxybenzoic acid moiety (304, 305, 306). Calculations based on the C^{14} concentration show that, following intravenous injection, reserpine is very rapidly eliminated from the blood stream (2 minutes after injection, only 0.3% still remains) and is concentrated in the fatty tissue in the form of a reserpine-like substance, attaining a maximum concentration after 4–6 hours.

At this point, the concentration of C^{14} in the fat is several times greater than in any of the other tissues; in these latter it reached its peak of activity after 10–60 minutes. Fat and liver tissues are the only tissues still containing C^{14} after 24 hours. The concentration in the brain is so low (216a) that, in the first series of experiments conducted, no activity could be detected at all (305). The pattern of the activity-time curve for the brain resembles that for the other tissues studied, with the exception of fatty deposits (306). The onset of action of reserpine (sedation) does not coincide with the time at which the maximum concentration of C^{14} is reached in the brain as a whole (306) or in different parts of the brain (336), neither is there any parallel between the content of reserpine in the brain and its duration of action (38). This disparity suggests that the active substance is possibly not reserpine *per se*. In this connection, two further facts may be worthy of special attention: firstly, 10 μg reserpine—equivalent to about $\frac{1}{10}$ of an effective intravenous dose—is found to have no effect on cats when injected by the intraventricular route (101); secondly, the release of serotonin following the administration of reserpine proceeds rather slowly (38, 228, 230). It seems to be a common pharmacological finding that there is no parallelism between the site of concentration and a specific action; nevertheless, it should be borne in mind that, in the studies referred to, the authors used reserpine labelled in a group of the acid moiety and that this group may well be subject to hydrolysis, which, in fact, occurs on a large scale *in vivo*.

It has been suggested that de-esterification takes place *in vivo* in the liver; but

there are also other tissues that are capable of hydrolyzing reserpine, as tests on the isolated intestine have shown (108, 306). Quite apart from hydrolysis, there is evidence that the rat, though obviously not the mouse, readily oxidizes the 4-methoxy group, even before hydrolysis has occurred, and that it may oxidize other methoxy groups as well. Syringoylmethyl reserpate, which is the probable product of the demethylation occurring on a fairly large scale in rats, is thought to be hydrolized only to a very limited extent.

Following parenteral administration, some of the reserpine is evidently excreted into the gastrointestinal tract, since in the rat 1–3 % of the injected dose is found in the faeces, 80–90 % consisting of reserpine. In the mouse, the percentage of intact reserpine present in the faeces is higher after intravenous (35 %) than after oral administration (8 %) (216a).

By using the fluorescent properties of reserpine (34, 307), it was shown that reserpine administered orally to rats is converted by enzymatic hydrolysis into methyl reserpate in the intestinal tract (108); the reserpine was rapidly absorbed by the intestine (108). The same technique also revealed a low concentration of reserpine in the brain (108). Interestingly enough, methyl reserpate was present in the urine in large quantities only when the reserpine was given by mouth (108). (A fluorescent method has also been applied to the detection of alkaloids in the urine of patients (121), but it is not clear from the report in question whether specific alkaloids or metabolites were determined.)

There is no doubt that esterification is necessary to produce the characteristic sedative and hypotensive effects associated with reserpine. Both of these latter effects are absent in reserpic and trimethoxybenzoic acid, although various organic esters can be substituted in the reserpine molecule in place of trimethoxybenzoic acid, giving rise, however, to marked variations in sedative and hypotensive potency (233). Reserpic acid was also found to be inactive when the ptotic response of albino mice was taken as a criterion of reserpine-like activity (266).

In the same test, methyl reserpate, which is alleged to occur in *Rauwolfia serpentina* as such (138), had about one-third the potency of reserpine (266), while in the dog it was inactive at a dosage ten times larger than the dose of reserpine sufficient to produce sedation, hypotension, and relaxation of the nictitating membrane (231). Like reserpic acid, it produced no sedation in rabbits (229), and it did not diminish the HT-content of the brain (229).

With the doses quoted in Table III, D, there is no change in the blood picture (235). In psychiatric patients receiving large doses of reserpine over a long period, it is reported that, despite uninterrupted treatment, a temporary drop in the eosinophil and monocyte count, and a rise in the number of polymorphonuclear leucocytes (40) occurs. Hollister *et al.* (140) do not confirm the suggestion that reserpine inhibits blood coagulation (158).

Reserpine has a gradual onset of effect and a very prolonged action, so that single oral or parenteral doses may remain effective for several days in both animals and human beings (7, 16, 22, 55, 127, 162, 235, 258, 348, 350); hence it is difficult as a rule to establish a dose-activity relationship.

TABLE III

Toxicity and bio-assays of reserpine

Species	Route of administration	Time of observation	Dose mg/kg	Reference
		A. Acute toxicity		
Mouse	p.o.	after 5 days	LD_{50} 500	333, 131
Mouse	i.p.	after 16 days	LD_{100} 16	258
Rat	i.v.		LD_{50} 15.75	283
Rabbit	i.v.	after 3 days	LD_{50} 15	19
		B. Chronic toxicity		
Rat	p.o. (diet)	30 days	approx. 1/ day	131
		C. Tolerated single doses		
Monkey	i.v.		4	235, 280
Monkey	p.o.		400	235, 280
		D. Tolerated doses administered chronically		
Rat	p.o.	6 months	4/day	235
Hypertensive rat	s.c.	several months	0.1/day	105, 193
Dog	p.o.	6 months	0.035/day	235
Monkey	p.o.	6 months	3/day	235

Rubin and Burke (266) have suggested the ptotic response of mice as a bio-assay; measured in this way, the potency ratio as between the intravenous and oral route is 1:16. According to Earl (90, 91, 284, see 46 for *Rauwolfia* extracts), its emetic action on pigeons is a useful guide to a quantitative evaluation; the ED_{50} is given as 0.085 mg/kg i.m. (91, 283).

For toxicity and bio-assays of reserpine, see Table III.

Deserpidine (*11-Desmethoxyreserpine*). Communications published so far point out that the methoxy group in ring A of reserpine is not essential for its pharmacological activity (44, 66, 283, 314). These authors conclude that there is no qualitative or quantitative difference in action between reserpine and deserpidine as investigated in various species of animals, whether anaesthetized or not. Deserpidine is also able to release 5-hydroxytryptamine from the rabbit brain (229).

In the monkey, dog, cat, rabbit, and mouse, the action of deserpidine has a characteristic latency. It produces sedation and miosis (44, 66, 131, 283, 314). In mice it prolongs the sleeping time in response to hexobarbitone (Evipal®) (314) and phenobarbitone (66). It lessens the amount of pentobarbitone sodium required to induce anaesthesia in dogs (66), raises the tolerance of mice to lethal doses of amphetamine, and suppresses the hypermotility caused by this latter drug (66). In mice, the qualitative and quantitative influence of deserpidine on various centrally acting drugs is identical with that of reserpine (see p. 454);

it markedly inhibits caffeine stimulation (195). It lowers the convulsion threshold in rats (electroshock seizures) (314). A polysynaptic spinal reflex in the anaesthetized cat was not decreased but intermittently increased (314). No change was observed in the arousal reaction of the cat during repetitive stimulation of the tibial nerve (314).

Following intravenous injection, a gradual and sustained fall in blood pressure occurs in both dogs (66, 283) and cats (44, 283, 314). This is accompanied by inhibition of pressor responses to stimulation of the central vagal (dogs: 66; cats: 314) and tibial nerves (cats: 314) and inhibition of the carotid sinus occlusion reflex in dogs (66, 283) and cats (283, 314). A fall in blood pressure also takes place after oral administration in the non-anaesthetized dog (66). The vasodepressor effect of deserpidine is said to be still apparent in the decerebrate cat, but absent in the spinal cat (44). The pressor effect of adrenaline is not blocked, but can actually be intensified in dogs (66, 283) and cats (44, 283, 314); the depressor effect of histamine and methacholine in cats is not affected (314). No ganglion-blocking activity is apparent in the cat (314). Bradycardia was noted in anaesthetized dogs (283) and cats (44, 283), as well as in non-anaesthetized dogs (66) and rabbits (283).

Deserpidine, like reserpine, has been observed to cause ptosis of the eyelid or relaxation of the nictitating membrane in various species, including monkeys (314), dogs (66, 131, 283), rabbits (314), and mice (131, 314). It depresses respiration in anaesthetized dogs (283) and cats (44) and lowers the body temperature in non-anaesthetized dogs and rabbits (283). In non-anaesthetized animals, it produces diarrhoea (dogs: 66, 131, 283; rabbits: 283; and mice: 131) and stimulates gastric secretion (dogs: 283). Its reserpine-like activity, as revealed in the pigeon emesis test, was found to be about the same as that of reserpine (283).

When given orally, deserpidine is well absorbed and exhibits its typical pharmacological features (66). The ratio between the acute intraperitoneal and the acute oral dose in mice is approximately 1:8 (131).

Toxicity of deserpidine. (a) Acute. Mice: LD_{50} i.p. (after 3-day observation) approx. 55 mg/kg (131), LD_{50} p.o. (after 3-day observation) approx. 320 mg/kg (131); rats: LD_{50} i.v. 15.7 mg/kg (283). (b) Chronic. Rats: LD_{50} p.o./30 days (diet) 1 mg/kg (131); dogs p.o.: 0.32 mg/kg and day may kill a dog after 3–4 days (66); other authors report that dogs survive on 10 mg/kg and day p.o. over a 5-day period (131).

Rescinnamine. Rescinnamine, differing from reserpine only in the acid moiety of its molecule, has sedative and hypotensive properties qualitatively similar to those of reserpine and deserpidine (64, 69, 171). This includes the capacity to release 5-hydroxytryptamine from the rabbit brain (229). There are, however, quantitative differences. According to Cronheim and Toekes (69), there exists a species-specific difference inasmuch as, in mice, rescinnamine is less active than reserpine, whereas in dogs it is slightly more active than reserpine, although other investigators also found it less active in dogs (171, 231). In the rabbit, its activity is about one-third that of reserpine (19). When, however, its different effects are tested in the dog, in which the actions are said to resemble more closely its therapeutic effects in patients (69), a direct parallelism between hypotension, bradycardia, and sedation is observed (217). On the other hand, it is not yet known whether rescinnamine or similar alkaloids differ as regards their duration of action in various animal species or whether there is any difference in their cumulative potency. In the rabbit, the duration of sedation, but—interestingly enough—not the latent period, is shorter than with reserpine (19). In experiments on isolated organs, the effect of rescinnamine was found to be less prolonged than that of reserpine (188).

In various species, rescinnamine evokes sedation (dogs: 64, 69, 171, 217; rabbits: 171; mice: 64, 69; rats: 64), hypotension (dogs: 64, 69, 217; cats: 171), and bradycardia (dogs: 64, 217), displaying in each instance a characteristic latency.

It prolongs the pentobarbitone-induced sleeping time in mice (64), has an additive effect with pentobarbitone in dogs (217), and affords protection against lethal doses of amphetamine in mice (69). Rescinnamine is about four times less active than reserpine in inhibiting central stimulation induced by caffeine in mice (195).

Besides causing an increase in pressor responses to adrenaline (64, 171) and noradrenaline (171), and reversal of the pressor response to hypoxia in dogs (64), it diminishes rises in blood pressure in dogs elicited by carotid sinus occlusion and electrical stimulation of the afferent vagus nerve (64). It may therefore be assumed that rescinnamine inhibits central portions of the sympathetic nervous system in a manner apparently analogous to reserpine.

In the perfused hind limbs of rabbits and rats, a direct peripheral vasodilator effect similar to that of reserpine and deserpidine has been noted (188). Rescinnamine produces relaxation of the nictitating membrane in dogs and ptosis of the eyelid in mice (64, 69). Diarrhoea is reported in dogs, and copious nasal discharge in rats (64). No adrenolytic or spasmolytic activity has been observed (171). Its antiacetylcholine effect on the isolated ileum is only very slight (19).

Its acute intravenous toxicity in rabbits (15 mg/kg (19)), is similar to that of reserpine. It is stated that the highest daily dose which dogs can tolerate for a period of five consecutive days is 0.032 mg/kg p.o. (217).

III. PHARMACOLOGY OF RAUWOLFIA EXTRACTS CONTAINING VARIOUS PRINCIPLES

Rauwolfia serpentina. Sen and Bose (301), who carried out the first clinical studies on *Rauwolfia serpentina* (1931), clearly perceived the various clinical effects, all of which are today of interest to the clinician, *i.e.*, its antihypertensive and bradycardic action and its effect in improving "certain types of insanity cases, especially those with violent maniacal symptoms". They also described a number of side effects which are today interesting from the theoretical aspect as well, *e.g.*, diarrhoea, reversible extrapyramidal symptoms following large doses, and a decrease in libido.

Thanks to the persistent efforts of Indian pharmacologists and clinicians, it was discovered that the alkaloids known at that time and belonging to the ajmaline and serpentine groups did not constitute the therapeutically active principle or principles (60, 88, 118, 120). In 1944, Gupta *et al.* (118, 120) prepared for the first time a concentrated extract containing none of the known alkaloids, a so-called resin fraction, with a pronounced hypnotic action.

On the basis of these findings, a new chemical fractionation of oleoresins, coupled with research to define the pharmacological characteristics of the individual fractions, led, in 1952, to the isolation of reserpine by Müller *et al.* (214). For the first time, the pharmacological properties sought for had been identified in a pure active principle of Rauwolfia.

The resin prepared by Gupta *et al.* (118) produced, after a certain latent period, prolonged sedation and hypnosis in cats, rabbits, guinea-pigs, rats, and frogs, but no general anaesthetic effects. This action is typical of Rauwolfia root extracts (68, 267) and of reserpine or Rauwolfia alkaloids with reserpine-like properties. (Throughout this chapter, the term "reserpine-like effect" is applied not only to the action of reserpine but also to other alkaloids with similar properties, *e.g.*, deserpidine and rescinnamine).

The resin prepared by Gupta *et al.*, and also other *Rauwolfia serpentina* extracts, act synergistically with typical anaesthetics, such as chloralose in the cat (118) and phenobarbitone in the mouse (68). They antagonize picrotoxin-induced convulsions in cats, guinea-

pigs, and especially rats (60, 120) as well as amphetamine-induced motor activity in mice (68). However, they have no antagonistic effect against strychnine, Metrazol, ammonium acetate, semicarbazide, and electroshock in mice, but actually lower the convulsion threshold (151).

In the decerebrate and spinal cat, these extracts diminish the knee jerk reflex (119). Reserpine, on the other hand, if given in very large doses, intensifies the patellar tendon reflex in the cat (284) and has no effect on picrotoxin-induced convulsions in the mouse (333). In mice, it inhibits amphetamine-induced excitation (69), although only to a slight degree (333).

The emetic response of dogs to Veratrum is prevented if sedation is first induced with Rauwolfia, whereas sedation with phenobarbitone has no such effect (110).

In dogs (3, 111, 170, 267), cats (74, 75, 153, 242, 243, 347), and rabbits (19), *Rauwolfia serpentina* extracts reduce the arterial blood pressure. In monkeys, intracisternal injections evoke a sharp fall in pressure, the intravenous dose required to produce the same hypotensive effect being about twenty times greater (75). The fall in pressure elicited in dogs is said to be due to a reduction in vascular resistance in the greater circulation coupled, however, with an increase in resistance in the pulmonary circulation (170). In the heart-lung preparation, no direct effects on the heart were discerned (170).

Ray *et al.* (242) assume that the extracts in question reduce arterial pressure in the cat by acting upon rostrally situated central structures, since these extracts—unlike ergotamine, for example—are no longer effective when injected intracranially following decerebration. In contrast to this view, Bhargava and Borison (26, 27) suggest that Rauwolfia extracts exert a marked effect on spinal vasomotor activity, although it should be noted that the preparations used by them were not derived from the same source as those of Ray *et al.* The findings of the two research teams differ concerning the effect of these extracts upon the rise in arterial pressure in the decerebrate cat in response to an increase in cerebrospinal fluid pressure. One team reported marked, though only transient, inhibition of the rise (27), while the other observed that, like reserpine, the extracts exerted no effect (242). In the experiments of the first team (27), however, the possibility of a peripheral adrenolytic action was not definitely excluded.

Vasomotor reflexes, such as the carotid sinus reflex, are inhibited in the cat in the same way as after reserpine, and also when the extracts are injected intracisternally in the monkey (75, 243). Respiratory and circulatory reflexes due to stimulation of the KCN-sensitive chemoreceptors are not, however, affected in any specific way (243).

According to Werner (347), the sympatholytic action appears to play no decisive role in bringing about the reduction in blood pressure. Preparations derived from total extracts always have a much less pronounced adrenolytic or sympatholytic effect than the adrenolytic Rauwolfia alkaloids. Although certain adrenaline-inhibiting effects of a competitive nature have been reported (74, 170, 347), no actual reversal of the action of adrenaline has been observed (347). The reason for this may possibly be an interference of the adrenaline-potentiating effect of reserpine, an interference which may arise from the competitive character of the adrenaline antagonism displayed by Rauwolfia alkaloids. The sympatholytic action of Rauwolfia alkaloids is of much shorter duration than the hypotensive effect of extracts.

It has been found that, when total extracts of Rauwolfia are fractionated by chromatography, there are fractions having almost no sympatholytic action but a clear-cut vasodepressor effect (347).

When administered *parenterally*, the various preparations made from extracts differ in their action on the blood pressure, depending on the quantity and quality of the individual active principles they contain.

Gupta *et al.* (88, 118) observed only sedative and hypnotic effects with their oleoresin fraction; it had no hypotensive action but, instead, a slight pressor effect. Our own experiments with a *Rauwolfia serpentina* preparation made by Dr. J. Müller according to the method of Gupta *et al.* showed that, despite a high concentration of about 2% reserpine, it failed to evoke any fall in blood pressure such as is typical of reserpine, and that in some experiments it even caused a slight rise in pressure (19). On the basis of these findings, it must be assumed that an extract prepared in this way contains not only reserpine but other substances which, when administered parenterally, either produce an increase in blood pressure or antagonize the action of reserpine. *Rauwolfia serpentina* does, in fact, contain substances, probably not identical with any of the alkaloids so far isolated, which, in the cat, provoke a sharp and pronounced rise in blood pressure (22) of sympathomimetic character (19) and which have no sedative and hypnotic action (19).

In the dog, a much prompter decline in blood pressure is elicited with total extracts than with corresponding doses of reserpine (3). This has been attributed to the action of a combination of reserpine and serpentine (152); but in this case serpentine can hardly be said to exert a specific effect, since tests on both cats and dogs reveal that the vasodepressor effect of reserpine is similarly intensified by other substances as well, *e.g.*, ganglion-blocking agents and hydrazinophthalazines (19).

The results are different with *oral administration*. Although no extensive comparative pharmacological studies have yet been undertaken to investigate whether total extracts given by the oral route have a different type of action from reserpine, findings to date indicate that this is hardly likely. In the dog, total extracts bring about a fall in blood pressure which sets in only gradually and is accompanied by bradycardia (111, 266, 267), like the response elicited by reserpine. Qualitatively, the effects observed on the circulation correspond to those associated with the action of reserpine, namely, enhancement of the effect of adrenaline, inhibition of reflex rises in blood pressure, and absence of any parasympatholytic, histaminolytic, or ganglion-blocking action (111). (Since the total extracts have no sympatholytic action when given by mouth, it must therefore be assumed that the adrenolytic alkaloids are either not present in sufficient quantity to be effective orally or cannot take effect orally.)

In the mouse, serpentine is over 100 times less toxic when given by mouth than when administered intravenously (152). Thus, like other quaternary ammonium bases, it is unable to exert anything more than a slight effect via the intestine, and when given by mouth in the form of the total extract it probably has hardly any effect. This also appears to agree with the findings of Cronheim *et al.* (67), who report that serpentine, serpentinine, ajmaline, and ajmalicine produced no hypotensive response in dogs in oral doses up to 3 mg/kg and day.

Furthermore, experiments on hypertensive rats showed that *Rauwolfia serpentina* root did not produce a significant fall in blood pressure until a dosage of about 4 g/kg and day p.o. was reached (325), whereas in the case of reserpine about 1–1.5 mg/kg only p.o. was sufficient (116). A large disparity in the oral potency of these two substances has also been reported in clinical practice.

Studies by Yonkman *et al.* are of interest in this connection (352). They found that certain extracts (containing neither reserpine nor serpentine) which cause a very marked fall in the blood pressure when administered parenterally to cats and dogs, have no effect when given orally to dogs and hypertensive rats.

None of the known alkaloids has yet been found to possess any clear-cut parasympatholytic or histaminolytic properties such as might account for the occasionally pronounced antiacetylcholine (12, 52, 329) and antihistaminic effects (52) of *Rauwolfia serpentina* extracts observed by various authors on isolated organs—effects which are absent in the "oleoresin fractions" (19).

Rauwolfia extracts cause depletion of adrenal ascorbic acid (65) and prevent both atrophy of the thymus and an increase in the weight of the adrenals following subcutaneous injections of formalin (263).

Pharmacological tests would thus appear to indicate that the action of preparations derived from extracts, when studied either on isolated organs or after parenteral administration, differs in various respects from that of reserpine alone. From the information at present available, it is extremely difficult to assess the precise significance of these often very slight differences in action, particularly to attempt to correlate them with specific therapeutic effects. When administered by the oral route, total extracts of *Rauwolfia serpentina* have so far been found to elicit the same qualitative effects as reserpine and reserpine-like alkaloids.

This has also been confirmed by clinical observations, comparative studies having shown that the total extracts and reserpine are virtually identical both as regards their effectiveness and as regards the type and frequency of the side effects they provoke—side effects which may either involve the somatic nervous system or affect the patient's psyche in such a way as to cause depression (4, 6, 95, 106, 107, 180, 184, 207, 213, 337, 340, 348). For obvious reasons, total extracts cannot be administered parenterally in the clinic. Under the circumstances, it is to be hoped that research will soon be undertaken on the oral action of the various known individual alkaloids, and with combinations of alkaloids.

Earlier studies on the pharmacological effects of extracts of *Rauwolfia caffra*, *R. vomitoria*, and *R. heterophylla* were generally confined to certain specific points and, unlike the Indian research on *R. serpentina*, they provided no decisive incentive to further study. The adrenolytic action of such extracts may perhaps be attributable to the adrenolytic alkaloids which have recently been isolated from *R. vomitoria* and *R. heterophylla* (see Table I). It remains to be seen whether the emetic effect (observed by the natives themselves, hence the designation "vomitoria") may be ascribed to a specific alkaloid.

More recent investigations with an extract of *Rauwolfia heterophylla* have shown that it presents a pharmacological picture somewhat similar to that of *R. serpentina* extracts (199, 200). This might be explained by the fact that many of the *R. serpentina* alkaloids, including reserpine, are also found in *R. heterophylla* (see Table I).

Rauwolfia caffra. According to Raymond-Hamet (257), aqueous extracts have a sedative and hypnotic action, though only of short duration, and they also prevent the excitation stage of chloralose anaesthesia. The same author states in addition that their adrenolytic effect on the blood pressure of the dog is more pronounced than that of aqueous extracts prepared from the bark of *R. serpentina* and *R. vomitoria*. It is not known whether this effect can be ascribed to rauwolfine.

Rauwolfia canescens. Chakravarti (45) states that extracts prepared from the leaves of *Rauwolfia canescens* are more adrenolytic than extracts from the root of *R. serpentina*. They are used for clinical purposes in India, have a marked sedative effect, and are employed to treat insomnia and some forms of insanity. According to the same author, *R. serpentina* appears to have a more pronounced hypnotic action than *R. canescens*.

Rauwolfia heterophylla. Tests with aqueous extracts of the bark of *Rauwolfia heterophylla* yielded responses in the dog resembling those obtained with similar extracts of *R. vomitoria*, *i.e.*, only diarrhoea and emesis were apparent (246, 247).

The adrenolytic effect observed in dogs (222, 246, 248) does not appear to constitute a genuine sympatholytic action, since at the same time the carotid sinus reflexes are not diminished but even slightly intensified (247). Using the cardiac vagus nerve as a test object, Raymond-Hamet (249) concluded that the extracts in question contained "nicotine-like" (ganglion-blocking?) substances. The small intestine in anaesthetized dogs is paralyzed by such extracts (248).

Mezey and Uribe (199, 200), however, who employed an extract of piñique-piñique (= *Rauwolfia hirsuta*, although these authors consider it identical with *R. canescens*. According to Hochstein *et al.* (136), *R. hirsuta* is the same as *R. heterophylla*), observed marked tranquillization, apathy, adynamia, and dyspnoea in mice and rabbits. In cats and dogs, it produces an immediate and prolonged drop in blood pressure, accompanied by bradycardia (followed sometimes by tachycardia), and respiratory depression. An adrenolytic effect on the blood pressure was evinced only after a considerable latent period, but no typical blocking effect on the sympathetic nervous system and no influence on glycaemia were apparent. A certain degree of antagonism to barium chloride was noted in the isolated intestine of the rabbit. No curare-like action was found.

Rauwolfia sellowii. According to Seba *et al.* (297, 298), root extracts (leaf extracts are said to be ineffective) of *Rauwolfia sellowii* which contain no ajmaline or serpentine provoke a sharp and prolonged fall in blood pressure in anaesthetized dogs. Clinical trials—admittedly, only of limited scope—are stated to have shown that this extract has a reserpine-like action in hypertensive (216) and psychiatric (43) patients. According to Pakrashi *et al.* (220a), the only fraction with a sedative action in rabbits was one containing reserpine. However, reserpine can only be isolated from *Rauwolfia sellowii* in a poor yield (135, 220a) (see Table I).

Aricine, of which a comparatively large yield was obtained, has no reserpine-like properties (135, 220a), nor do ajmalidine, tetraphyllicine, and py[3]-tetrahydroalstonine display any reserpine-like activity (220a).

Rauwolfia vomitoria. Raymond-Hamet observed no sedative effect with aqueous bark extracts; rather, in non-anaesthetized dogs, he reports vomiting, sanguineous diarrhoea, excessive salivation, and paralysis of the limbs (250). In the anaesthetized dog, a slight fall in blood pressure was noted (255), together with an inhibitory action on the effect of adrenaline on blood pressure and small intestine (250, 254, 255).

Throughout the regions in which it occurs, Rauwolfia has been used in popular medicine for every conceivable condition (56). In ancient Indian ajurvedic medicine, its use in the treatment of mental disorders appears to have been unknown (56), but the popular term for the plant, "insanity herb", would seem to indicate an awareness of its peculiar action in such conditions. Moreover, this knowledge was not confined to modern medicine in India. According to Smith (315), "snake-root" was mentioned in London in connection with "nervous disorders" as early as 1670, and Raymond-Hamet (250) states that *Rauwolfia*

[3] Pyridine ring saturated.

vomitoria was employed by Africans to treat agitation. One striking fact is that in all countries to which Rauwolfia is indigenous, in India (56), Africa (157), and South America (78, 148, 246), it is associated in various ways with the snake. In some regions it is renowned as a remedy against snake bites or against poisonous insect bites and stings. On and around the Gold Coast, members of the so-called "snake sect" revere it as a special fetish (157). In India, for example, it is claimed by some that snakes have a particular preference for *R. serpentina* when choosing a place to nest, whereas on the other hand it is said that snakes avoid Rauwolfia in a panic and can be frightened away by a piece of the root. Thus the relationship between the Rauwolfia root and the snake would appear to be ambivalent. Except for Deger (78), all authors have so far denied that it has any therapeutic value against snake bites. In our own experiments on mice (19), neither reserpine nor Rauwolfia extracts afforded any protection against lethal poisoning with cobra venom.

It is well known, of course, that the snake—a symbolic reptile of southern origin, shown entwined around the staff of Aesculapius—has been described not only as playing an awesome role associated with Hades but also as a harbinger of light and health. From Greek sources dating back to before the birth of Christ, it appears that the lick or bite of the snake was taken as a symbol of medical treatment (156). According to beliefs held in India and among many other peoples as well, the snake has a twofold significance: it is regarded both as a bringer of disease and as a bearer of healing powers. Thus, while the lick of one particular snake is supposed to cause leprosy, there are Indians who even today pray before snake symbols for the boon of children (42)—a fact which may remind us that in ancient Greece, too, the snake was considered a sign of fertility. In this connection, it is certainly not without interest that Rauwolfia is recommended as a remedy for leprous diseases (157), while in certain parts of Africa it is also related to the idea of fecundity. On the Gold Coast, Rauwolfia is said to be used as an aphrodisiac (157), and in one locality of the Belgian Congo[4] it is taken as an omen of fecundity if a young would-be mother plants a Rauwolfia cutting obtained from the witch doctor and the sprig takes root (316).

In view of all this, it seems not unlikely that the association of the snake with the Rauwolfia plant, of which the designations "serpentina" and "snake-root" may be expressions, is simply a reflection of the profound effects which Rauwolfia is capable of exerting upon the psyche. These effects were already recognised long ago, but it remains the task of future research to elucidate their actual causes and consequences.

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[4] The village of Kimpatikw, on the road from Kikwit to Port Francqui.

[5] Concluded December, 1955.

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