Pharmacology of Reserpine and Its Implications for Anesthesia

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RAUWOLFIA preparations have been in medical use in India for many centuries.[158] Scientific investigation began with the isolation of several pure alkaloids by Siddiqui and Siddiqui in 1931.[162] Although chemical and pharmacological investigation continued from then on[36, 38] and therapeutic use became quite common,[37] it was not until 1949 that the first report on the therapeutic use of *Rauwolfia* appeared in the Western literature.[175] In 1953, the first confirmations of the therapeutic actions of *Rauwolfia* extracts were published in Europe and in the United States.[4, 182] However, the beginning of modern work on *Rauwolfia* dates from the isolation of reserpine from *Rauwolfia serpentina* Benth. in 1952.[128] Reserpine, the first pure alkaloid with the therapeutically useful actions of the extracts,[8] removed the uncertainty regarding the chemical composition of different extracts.[10] Clinical use began at once, and experimental as well as clinical information on reserpine has continued to accumulate.

In 1956,[39] attention was first drawn to the possibility of undesirable hypotension during anesthesia in patients under reserpine treatment. Since then, a number of authors have voiced the same concern.[41, 47, 120, 160, 165, 186] In this article we propose to examine the available evidence pertaining to reactions to general anesthesia of patients on reserpine therapy and to discuss the question of anesthetic morbidity and mortality in such patients.

The most recent comprehensive review of the pharmacology of reserpine appeared in 1956.[10] Hence, before the influence of reserpine medication upon anesthesia is discussed, pertinent aspects of the pharmacology of reserpine will be reviewed.

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Pharmacology of Reserpine

The two major pharmacological actions of reserpine are: (1) a behavioral effect, generally described as sedation, and (2) a slowly developing decline of arterial blood pressure of moderate degree. The following description of these actions of reserpine is based upon experimental work in dogs and cats, unless otherwise indicated.

ACTIONS ON THE CENTRAL NERVOUS SYSTEM

The sedative effect of reserpine has been demonstrated in many species.[8, 11, 42, 138, 156] In the dog and cat, after parenteral administration of an effective dose, there is a characteristic latency period of 20 to 30 minutes followed by a decline in motor activity and eventually sleep.[138, 156] However, even the largest doses of reserpine do not depress central nervous system activity to the level of general anesthesia.[8] Reserpine-induced sleep can always be interrupted by external stimuli. Before sleep ensues, changes in behavior, a calming effect, and a marked decline in aggressiveness can be noted.[138, 156] The term "tranquillization" has been introduced[80] to distinguish this type of sedation from that caused by barbiturates.

The sedative action of reserpine has been linked to depletion of 5-hydroxytryptamine (serotonin)[136, 137] and of norepinephrine[85] from sites in the central nervous system. There is no doubt that reserpine, as well as related alkaloids,[19, 161] does have this effect, but the relation this bears to changes in behavior is far from clear. Much more detailed study is needed before specific conclusions can be drawn.

There is no indication that reserpine has an analgesic action of its own,[8, 154] nor does it potentiate the effect of analgesic drugs. Indeed, in mice, rabbits, and rats, reserpine has been found to antagonize the action of nar-

cotic analgesics as tested by tooth pulp, hot plate, and tail flick methods.[144, 153, 154, 184] In this regard, reserpine is quite different from most sedatives, a difference which may be useful in elucidating the mode of action of analgesics.[153]

Cardiovascular Actions

The cardiovascular actions of reserpine have been studied largely in anesthetized dogs and cats, with occasional observations in trained unanesthetized animals.[8, 11, 45, 126, 127, 138, 156, 169] Following a single intravenous injection of from 0.1 to 1.0 mg./kg., there is at first either no change or a slight rise in blood pressure.[45, 113, 115] After 10 to 30 minutes (the latency is somewhat shorter with the larger doses), the blood pressure gradually declines, reaching its lowest level in 3 to 4 hours, and remaining there for about 24 hours. This effect occurs in both anesthetized and unanesthetized animals; the higher the initial level of blood pressure, the greater is the fall after reserpine.[10] The important hemodynamic mechanism is a decrease in peripheral resistance,[11, 126, 127, 169] most pronounced in the vascular bed of the skin. Cardiac output is either slightly increased or unchanged. Accompanying the hypotension there is a moderate fall in heart rate.[8, 138]

Reserpine has no adrenergic blocking properties and does not inhibit ganglionic transmission.[8, 10, 11, 131, 138, 171] The hypotensive action, unlike that of the *Veratrum* alkaloids, is still present after elimination of baroreceptor mechanisms.[8] Electrical activity of the carotid sinus pressor receptors is not changed after reserpine.[8, 46] However, the pressor response to carotid artery occlusion is reduced or abolished by relatively small doses of reserpine.[8, 9, 138, 169] Similarly, hypertensive responses induced by stimulation of the central end of a cut peripheral nerve (vagus[91, 116, 138, 152] or sciatic[8]) are inhibited. On the other hand, pressor responses elicited by increasing intracranial pressure,[14, 145, 169] or by raising the pressure of the spinal fluid,[14] are not abolished. Hypertension following direct electrical stimulation of vasomotor structures in the central nervous system has been found unchanged by most[9, 14, 72, 155] but not by all[3, 77, 87] investigators.

Inhibition of circulatory reflexes in the presence of intact afferent and efferent pathways was interpreted as indicating a central origin of the reserpine-induced hypotension.[10] The concept of a generalized decrease of central sympathetic activity following reserpine was supported by the appearance of miosis and relaxation of the nictitating membrane[8, 11, 138, 155, 173] and seemed confirmed when direct observation of the electrical activity of sympathetic nerves showed that preganglionic spontaneous sympathetic nervous activity was reduced after injection of reserpine.[9, 46]

Further investigation of sympathetic nervous outflow in cats, by Iggo and Vogt,[89] did not confirm these earlier findings.[9] Efferent sympathetic nerve activity was, if anything, increased after doses of reserpine which effectively lowered the blood pressure. Heymans *et al.*[82] found no decrease in vasomotor tone after injection of reserpine (1 to 2 mg./kg.) into the isolated, perfused head of a dog connected to the body only by the spinal cord. The pressor responses to carotid occlusion, to hypoxia, and to electrical stimulation of the sinus nerve were exaggerated after injection of reserpine into the blood supply of the head or into the cerebral ventricle.[82]

At present, the evidence for a central site of the circulatory action of reserpine is at best inconclusive. In most experiments, no safeguards were taken which would permit separation of central and peripheral effects. Results of experiments in which the central mechanisms were shown directly to be depressed (decreased response to central stimulation, decreased magnitude of sympathetic outflow) have not been confirmed by other investigators. The most consistent finding, depression and finally blockade of the carotid occlusion reflex, could have resulted from a peripheral action of reserpine. More evidence is needed before the suggested site and mechanism of the impairment of this reflex by reserpine can be accepted.

In the meantime, the attention of investigators was directed to peripheral effects of reserpine. A direct vasodilator action was described by McQueen *et al.*[118, 119] When reserpine was injected directly into the perfused hindleg of a rabbit, it caused vasodilation;

when it was given intravenously vasoconstriction occurred in the leg.

In 1956 and 1957, Maxwell and co-workers[113, 115] reported that intravenous injection of 0.5 to 1.0 mg./kg. of reserpine in anesthetized dogs treated with ganglionic blocking agents caused an increase in blood pressure and contraction of the denervated nictitating membrane. These effects were abolished by phentolamine but not by lysergic acid diethylamide. The results were interpreted as evidence for a peripheral effect of reserpine involving the sympathetic humoral mechanism.

Krayer and Fuentes, in 1956,[97] demonstrated in the heart-lung preparation of the dog, that injection of reserpine produced effects similar to that of a prolonged continuous infusion of epinephrine or norepinephrine. Within a minute after injection of 3 mg. of reserpine into the circulation of the isolated heart, the heart rate began to increase, reached a maximum after 10 to 20 minutes and a plateau for 10 to 30 minutes, then declined but remained above control levels for 2 to 3 hours.[98, 135] Myocardial contractility increased, as evidenced by a fall in right or left atrial pressure despite constant venous supply. If, however, the animal from which the heart was subsequently isolated, had been pretreated with an adequate dose of reserpine for at least 24 hours, injection of a "challenging dose" of reserpine produced only a negative chronotropic effect.[99, 135]

These experiments suggested that injection of reserpine led not only to a slow liberation of catecholamines from the tissues but also to a depletion of the tissue content of these amines.[99, 134, 135] An increased concentration of epinephrine in the plasma after acute intravenous injection of reserpine in rabbits (1 to 2.3 mg./kg.) was shown by Muscholl and Vogt.[130]

The depletion of catecholamines was first directly measured by Carlsson and co-workers in 1956[13, 29] in the adrenal glands and in the hearts of intact rabbits. It has since been reported for many tissues and for many species.[24, 74, 101, 161] It appears that all catecholamines, both epinephrine and norepinephrine, are released, although considerable quantitative differences exist between different species, between animals of the same species, and between various tissues of the same animal. A part of these differences may be accounted for by the influence of efferent nerve activity on the rate of depletion. It has been shown in some species and some tissues that depletion occurs more slowly if the effector organ has been denervated[101, 131, 146] and after ganglionic blockade.[121] Thus, differences in the degree of efferent nerve activity may influence the time course of depletion after reserpine administration. Concomitant with the release of catecholamines, 5-hydroxytryptamine stores in blood platelets, in the gastrointestinal tract, and in the central nervous system are depleted.[161]

Pertinent information concerning the time course of catecholamine depletion is derived from studies on the canine heart.[134, 135, 178] The maximal norepinephrine-depleting effect of a single dose of 0.1 mg./kg. of reserpine was reached after 12 to 24 hours. The norepinephrine content remained very low for about 72 hours. Partial recovery was apparent in 6 to 8 days and complete restoration required 10 to 20 days. Because of the prolonged effect of a single dose, repeated doses are strongly cumulative. In the dog, the same degree of depletion of the cardiac norepinephrine stores (evidenced by lack of heart rate increase in the heart-lung preparation in response to a challenging dose of 3 mg. reserpine) was observed 24 hours after a single parenteral dose of 0.1 mg./kg. and after 10 daily injections of 0.003 mg./kg. Thus, very small doses of reserpine given for a prolonged period will result in considerable catecholamine depletion.

Release of the transmitter substance is the normal result of nerve activation and does not usually lead to depletion of transmitter stores even after prolonged stimulation.[48, 74, 163] The fact that the release after reserpine results in depletion indicates interference by reserpine with the normal process of replenishment. Reserpine does not inhibit synthesis of catecholamines,[92a] but evidence has been presented that reserpine interferes with active uptake of catecholamines, *in vitro*.[81] This defect prevents replenishment of the stores and eventually leads to depletion. It appears, however, that reserpine has additional biochemical effects which may contribute to its action.[161]

Depletion of the sympathetic transmitter substance leads to impairment and even blockade of impulse transmission in the sympathetic nervous system between postganglionic nerve and effector organ. Such a blockade has been demonstrated, in the dog and rabbit, for the positive chronotropic [76a, 88, 171] and for the positive inotropic effect [15, 124] of electrical stimulation of the cardio-accelerator nerve, for the vasoconstrictor effect of stimulation of the lumbar sympathetic chain [177] and for reflex venoconstriction.[66] Complete blockade occurred after doses of reserpine of 0.1 to 0.5 mg./kg. for 2 days or 0.01 mg./kg. for 10 days. In the cat, blockade of the response to nerve stimulation after reserpine was demonstrated for vasoconstriction [146] and for contraction of the nictitating membrane following stimulation of the cervical sympathetic trunk.[57, 170] In both species, tissue stores of norepinephrine, at the time of complete blockade of impulse transmission, are reduced to chemically undetectable levels.[67, 76a, 172a] The whole dose-response relationship between dose and duration of reserpine administration and decrease of the response to nerve stimulation has been thoroughly investigated in the nictitating membrane of the cat.[57]

Recently, Burnstock and Holman,[27] recording electrical potentials from single smooth muscle cells of the vas deferens of the guinea pig, have provided insight into the details of the impairment of transmission. After treatment with reserpine (5 to 10 mg./kg. for three days) the frequency and amplitude of spontaneous potentials were reduced, and many more stimulating shocks to the hypogastric nerve were required before a spike was provoked and a contraction occurred. This result is of particular interest since it has been shown [164] that the norepinephrine content of the vas deferens is reduced to undetectable levels by doses of reserpine considerably smaller than those used by Burnstock and Holman.

On the basis of the evidence presented, the following picture of the action of reserpine on the cardiovascular system emerges. The primary effect of reserpine is a slow, but prolonged release of biogenic amines, specifically 5-hydroxytryptamine and catecholamines. This release leads eventually to depletion of transmitter stores at the postganglionic nerve endings of the sympathetic nervous system. The lack of transmitter results in a generalized, graded, dose-dependent impairment of sympathetic impulse transmission. The degree of depletion and of transmission failure differs from tissue to tissue. Since the sympathetic nervous system is the efferent pathway for vasoconstrictor impulses, vasomotor tone (both arteriolar and venous) declines. The decline is most noticeable in vascular areas with normally high vasomotor tone, especially the skin.

The release of 5-hydroxytryptamine and of catecholamines after large intravenous doses of reserpine may be sufficient to produce additional circulatory as well as metabolic effects (see section—Other Actions of Reserpine). Under certain conditions, a temporary increase in blood pressure is seen [45, 115] and it is possible that other early effects (*e.g.*, the blockade of the carotid occlusion reflex) are explained by this "slow infusion" of biologically highly active agents. It is important to distinguish the cardiovascular effects of reserpine following soon after a single large parenteral injection from those observed after continual administration of small doses leading to a very gradual catecholamine depletion.

Influence of Reserpine on the Action of Sympathomimetic Amines

As a consequence of the depletion of tissue catecholamines by reserpine, the effect of exogenously administered sympathomimetic amines may be altered. Evidence has been reported from time to time, indicating that the group of sympathomimetic amines is not homogeneous and includes substances with different mechanisms of action. Pretreatment with cocaine increased the sensitivity to certain sympathomimetic amines,[26, 63] Similarly, denervation of the nictitating membrane resulted in increased potency of one group (norepinephrine, epinephrine), while the activity of another group (tyramine, phenylethylamines) was decreased or abolished.[54, 55] One explanation for these observations was based on the disappearance of norepinephrine from nerve endings after denervation.[50, 70] Sympathomimetic amines which lost activity after denervation were thought to lack a direct action on adrenergic receptors and to act

indirectly, by releasing the physiological transmitter. *Pari passu,* depletion of the transmitter after denervation was said to lead in some way to supersensitivity towards the directly acting amines. The discovery that reserpine, like denervation, causes a depletion of catecholamines provided a convenient means to test this hypothesis. In 1957, Carlsson *et al.*[31] reported that pretreatment with reserpine abolished the pressor response to tyramine. Since then, reserpine has been used by many investigators to study supersensitivity and subsensitivity and to establish the mode of action of the several sympathomimetic amines. It has been amply confirmed that diminution or loss of activity of some amines does indeed result from the disappearance of sympathetic transmitter substance from the adrenergic nerve endings.[68, 172a] Supersensitivity to the directly acting amines is not caused by depletion of transmitter *per se,* but results from inactivity of the effector organ,[57] irrespective of whether such inactivity is the consequence of denervation, of loss of transmitter caused by reserpine, or of the administration of cocaine.

TABLE 1. Mode of Action of Sympathomimetic Amines

Substance	Species of Animal	Organ or Function*	References
Group I—Direct			
Norepinephrine (Levophed)	Dog Cat	1, 2, 3 1, 2, 4, 7	2, 49, 114, 124 25, 57, 172
Epinephrine (Adrenalin)	Dog Cat Rabbit Guinea pig	1, 2 1, 2, 4 5 2	2, 49 172 56 43
Synephrine	Dog Cat	1, 2 1, 2, 4	2, 106, 114 172
Phenylephrine (Neo-Synephrine)	Dog Cat	1, 2 1, 2, 4	2, 49, 114 25, 172
Methoxamine (Vasoxyl)	Dog	1	49
Isoproterenol (Isuprel)	Rabbit	5	56
Cobefrine	Dog	1	114
Group II—Direct and Indirect Action			
Ephedrine	Dog Cat Rabbit	1, 2, 3 1, 2, 3, 4 5, 6	49, 90, 114, 124 25, 28, 172 25, 56
Phenylpropanolamine (Propadrine)	Dog Cat	1 1, 2, 4	114 172
Group III—Indirect Action			
Tyramine	Dog Cat Rabbit Guinea pig	1, 2, 3, 6 1, 2, 4, 7 5, 6 2	106, 114, 124 25, 170, 172 25, 31, 56 43
d-Amphetamine (Dexedrine)	Dog Cat Rabbit	1, 2, 3, 6 1, 2, 4 6	106, 114, 124 25, 172 25
Methamphetamine (Methedrine)	Dog	1, 2, 3	49, 114, 124
Mephentermine (Wyamine)	Dog Cat	1, 2, 3 1, 2, 4	49, 51 172
Phenylethylamine	Dog Cat	1, 2, 3, 6 1, 2, 4	114, 124 25
Hydroxyamphetamine (Paredrine)	Dog	1	114
Phenylpropylmethylamine (Vonedrine)	Dog	1	114

* (1) blood pressure; (2) heart rate; (3) myocardial contractility; (4) nictitating membrane; (5) intestine; (6) flow resistance; (7) spleen volume.

At present, the sympathomimetic amines may be separated into three classes according to their effects following catecholamine depletion by reserpine: (1) those which are as effective or more effective, and therefore act directly on the effector organ; (2) those which are inactive, depend upon norepinephrine stores, and act indirectly by releasing norepinephrine; (3) those which are less effective, acting in part directly and in part indirectly.

Because of its practical importance, this classification of sympathomimetic amines is presented in table 1. It has recently been pointed out that the separation of the amines into distinct groups does not reflect accurately all the available evidence.[56, 172] There is a gradual transition from those substances with entirely direct action to those whose action is wholly indirect. The extremes are exemplified by norepinephrine and epinephrine on the one hand (direct) and by tyramine on the other (indirect). Substances such as ephedrine, which occupy a position between the extremes, do not all possess the same proportion of direct and indirect activity. Moreover, with any one substance, the proportion of direct versus indirect activity varies from species to species, from tissue to tissue within the same species, and possibly even in tissues of the same animal from time to time.

OTHER ACTIONS OF RESERPINE

The pharmacological effect of reserpine in areas other than the nervous system and the

circulation is likewise related to its depleting action. Diarrhea, observed occasionally, [8, 138, 155, 156] is probably due to release of 5-hydroxytryptamine and to the preponderance of parasympathetic activity following depletion of sympathetic transmitter.[22]

Temperature regulation may be impaired after reserpine.[8, 83, 138] In a cold environment, fall of body temperature is observed, similar to that seen after ganglionic blockade.[71] The disturbance of temperature regulation has been ascribed to blockade of thermoregulatory mechanisms [174] or to uncontrolled heat loss secondary to compromised vasoconstrictor ability in the skin.[83] Also, there is evidence of decreased heat production due to diminished output of thyroid hormone after reserpine.[168] This has been demonstrated in rats after doses of reserpine of 0.05 to 0.5 mg./kg. per day.[123] Decreased response of the thyroid gland to thyroid-stimulating hormone has been suggested as the mechanism.[168]

Single injections of reserpine cause release of ACTH from the pituitary gland.[108, 150, 179] Prolonged administration results in hypersecretion of ACTH [122] and adrenal cortical hypertrophy.[69, 93] Because depletion of adrenal ascorbic acid in response to stress was prevented by reserpine pretreatment,[107, 179] it was concluded that reserpine blocked the response to stress of the pituitary-adrenal system. However, direct measurement of plasma corticosterone levels did not confirm blockade of the normal adrenocortical response after reserpine.[122]

Reserpine has little effect on respiration.[155] After intravenous administration of a single large dose, ventilation is slightly increased,[11,169] perhaps due to chemoreceptor stimulation.[46] This could also account for the reported shortening of the apneic pause following hyperventilation.[9]

There is no evidence for a specific effect of reserpine on renal function.[52, 102, 126, 127] A slight fall in urinary output and electrolyte excretion has been observed, but this is also seen with lowered blood pressure from other causes.[102]

Slowly developing and long-lasting hyperglycemia has been observed after single intravenous injections (0.1 to 1.0 mg./kg.) of reserpine in dogs and rabbits.[103] The increase in blood glucose was not diminished by cutting the splanchnic nerves and was blocked by dihydroergotamine. It seems likely that the release of catecholamines mediates this effect.

Actions of Reserpine in Man

The many clinical reports of the use of reserpine in man, in the therapy of mental illness and of hypertension, will not be reviewed. There is no doubt that reserpine produces sedation and lowers blood pressure in man as well as in animals. However, the number of careful quantitative studies of mechanism of action in man is small. Hypotension is associated with decrease in peripheral vascular resistance and little change in cardiac output.[33, 92,183] Bradycardia is commonly observed.[143, 183] Muscle blood flow and cerebral blood flow are unchanged [16, 73, 94] but a distinct increase in skin blood flow occurs.[16] There is evidence of direct action by reserpine on blood vessels in man. Infusion of reserpine into the brachial artery of normal subjects resulted in prolonged vasodilatation, largely confined to the vessels of the skin.[104]

Often, part of the price paid for the control of hypertension with ganglionic or adrenergic blocking agents is a high incidence of postural hypotension.[86] The absence of significant postural hypotension is a striking feature in the clinical use of reserpine.[62, 149, 180, 183] That circulatory homeostatic reflexes function adequately is borne out by detailed experimental studies. The pressor response to immersion of an extremity in ice water (cold pressor test) was found not to be attenuated [180, 183] even after 13 weeks of therapy with an average daily dose of 0.45 mg. of reserpine.[159] The hemodynamic response to 60-degree head-up tilt was not altered 4 hours after a single intramuscular injection of 2.5 mg. of reserpine.[110] Administration of large doses (4.8 mg. per day for 7 days) of syrosingopine, a reserpine analogue which possesses only one tenth the sedative potency of reserpine in doses which produce equal degrees of peripheral catechloamine depletion,[20, 133] did not reduce the increase in cardiac output in response to hypoxia and exercise, although the response of the heart rate to these stimuli was decreased.[33] Digital vasoconstriction upon deep inspiration,

a test of sympathetic activity, was diminished after daily doses of reserpine of 0.25 mg. for 7 days [149] and abolished after three daily doses of 2.8 mg. each.[183]

Available evidence, although less detailed than in animals, indicates that reserpine does deplete norepinephrine tissue stores in man. The only direct tissue analyses have been reported for the atrial appendages of the hearts of 3 patients who had each received 0.25 to 0.50 mg. of reserpine daily for six to seven weeks. The norepinephrine content after reserpine was 0.04, 0.10, and 0.30 μg./g. respectively, while the mean content for 22 controls was 1.87 μg./g. (range: 0.54 to 5.04 μg./g.).[32] These limited data demonstrate the occurrence of depletion in man as in animals, with very small repeated doses of reserpine.

Indirect evidence for norepinephrine depletion in man derives mainly from the work of Mashford and Mahon [111, 111a] who used the pressor response to tyramine infusion as a measure of norepinephrine stores. The response to infusion of tryamine (0.2 mg./kg.) was markedly reduced 24 hours after administration of 0.06 mg./kg. of reserpine (total of 4.2 mg. in a man of 70 kg.) The authors stress the variability of the response to tyramine in their control observations [112] and the importance of testing with more than one dose, a well-recognized pharmacological principle.

In studies of the influence of reserpine on blood levels of catecholamines, a reduction of the plasma content of norepinephrine was reported [23] but was not confirmed.[110] Urinary excretion of catecholamines was reduced after long-term reserpine therapy [30] but not after the first 24 hours.[65] Excretion of 3-methoxy-4-hydroxymandelic acid (VMA), the major metabolite of the catecholamines, was markedly increased in the first 8 hours following the injection of 2.5 mg. of reserpine.[117] All these observations are consistent with a norepinephrine-releasing action in man.

Another well-documented effect of reserpine in man is reduction of the concentration of 5-hydroxytryptamine in blood platelets.[61, 76, 78] The long duration of drug effect in man is inferred from the observation that three to five weeks were required for restoration to normal of blood serotonin after a single injection of reserpine.[61] In the same study, pupillary size returned to normal within seven days. After doses of reserpine of 5 to 10 mg. daily, no change was observed in blood hydrocortisone levels and in urinary 17-hydroxycorticosteroid excretion.[40]

The available evidence indicates that the mechanism of action of reserpine in man is identical with that in animals. Depletion of tissue catecholamines occurs and, according to the limited data available, the sensitivity of man is not markedly different from that of the dog and cat, where our information is most extensive. Reserpine in clinically used doses does not lead to postural hypotension, does not block vasoconstrictor responses to a variety of stimuli, nor does it interfere with the ability of the heart to increase its output. The only reflex known to be blocked in man is digital vasoconstriction in response to a single deep breath. While, as noted above, the circulatory response to a variety of stimuli is well preserved, it is not known whether the capacity of the circulation to respond to maximal stress is compromised by clinically used doses of reserpine (0.001 to 0.01 mg./kg. daily).[181]

Reserpine Treatment and General Anesthesia

Two questions concerning the influence of reserpine pretreatment upon the action of general anesthetics are of major importance.

(1) Does reserpine pretreatment have an effect upon the concentrations of general anesthetics needed to produce a given depth of anesthesia? In other words, does reserpine affect the potency of anesthetics?

(2) Does reserpine pretreatment modify the action of general anesthetic agents upon the cardiovascular system? The hazard of reserpine is sought in its effects on the circulation because there is no evidence to implicate other physiological functions.

If these questions can be answered, there remains a further point of practical importance. What is the influence of pretreatment upon the therapeutic ratio of general anesthetics, *i.e.*, the ratio of the concentration required for surgical anesthesia and the concentration that causes dangerous circulatory depression?

Reserpine and Anesthetic Potency

Reserpine was shown to prolong sleeping time in mice and rats after injection of hexobarbital,[21, 84] pentobarbital,[105, 109] ethanol,[21] and tribromoethanol.[84] Induction time after injection of barbital was shortened [34, 35] and the anesthetic threshold for nitrous oxide (the partial pressure required to produce loss of righting reflexes) was lowered after reserpine pretreatment.[147] In most of these studies, the doses of reserpine were large (1 to 5 mg./kg.), and the anesthetic was tested shortly after a single, subcutaneous injection of reserpine, the longest interval being 24 hours.

The explanation for these effects of reserpine has been sought in the decrease in body temperature which follows large doses of reserpine in rodents at room temperature. The potency of barbiturates is known to be increased at low body temperatures,[105] presumably due to lowered rate of elimination.[64] However, increased anesthetic potency after reserpine was observed when the fall in body temperature was prevented by high ambient temperature [35] and also with anesthetics which are not eliminated by metabolic detoxification.[147]

The increased sleeping time after hexobarbital and the shortened induction time after barbital were shown not to be due to a more rapid uptake of barbiturate by the brain [34] or to a reduced rate of elimination.[21] Since reserpine alone does not produce anesthesia at any dose level, the effect is a true potentiation.

In only one study [35] has barbital induction time been measured over a prolonged period of treatment with a high dose of reserpine (0.3 mg./kg. per day). Induction time was at first shortened, then returned to normal after nine days, and was considerably prolonged after 14 days. Unfortunately, the results of this study are difficult to interpret because reserpine treatment was accompanied by severe adverse effects (diarrhea, anorexia, weight loss) which in themselves might alter the sensitivity to barbiturates in some unknown manner.

This investigation emphasizes the need for adequate controls comparing reserpine-treated with normal animals. If one desires to study the influence of reserpine upon physiological processes, it is important either to avoid toxic effects or to dissociate them from the therapeutic actions of the drug. It has been found that reserpine in large doses, as used in many laboratory investigations, often results in serious illness.[185] Toxic effects of this type are not a usual feature of clinical use of reserpine and are, to a considerable extent, avoidable in the laboratory by appropriate treatment schedules.

No systematic study of the potency of anesthetics after reserpine pretreatment in large animals or in man has been reported. In several publications,[66, 124, 171] the comment has been made that, after reserpine pretreatment, less than the usual dose of anesthetic was sufficient to produce anesthesia. This corresponds to our own laboratory experience, both with the parenteral use of sodium pentobarbital [96] and with administration of halothane.[53] In two clinical studies,[79, 166] undertaken to evaluate the use of reserpine as preanesthetic medication, there is no mention of a reduction in the required concentration of anesthetic.

More information concerning the influence of reserpine upon the potency of anesthetic agents is needed. Preferably, such studies should be conducted in primates or man, in whom the effects of reserpine alone can be better evaluated. They should be carried out after prolonged treatment with small doses of reserpine, in order to approximate clinical conditions and to minimize the adverse effects of reserpine administration.

Reserpine and the Circulatory Response to Anesthesia

The importance of the sympathetic nervous system in the maintenance of circulatory homeostasis during general anesthesia has recently been emphasized.[139, 140] In the light of the wide participation of the sympathetic system in the circulatory response to anesthesia, one would expect significant alterations to occur after reserpine. However, few studies have attempted to evaluate this relationship quantitatively.

In a comprehensive investigation, Bagwell *et al.*[5, 6] compared hemodynamic responses to anesthesia in untreated dogs with those observed after pretreatment with reserpine, either 0.1 mg./kg. for two days or 0.03 mg./kg. daily for two weeks. In the dog, these large doses

of reserpine deplete myocardial stores of norepinephrine and suppress the effect of sympathetic stimulation on myocardial contractility,[15] heart rate,[171] and vasoconstriction in the femoral vascular bed.[177] The response to increasing concentrations of cyclopropane, ether, and halothane was measured. Reserpine pretreatment alone resulted in reduction of arterial pressure, myocardial contractile force, and heart rate, but not in change in cardiac output. With all anesthetics studied, arterial pressure, cardiac output, and myocardial contractile force were increasingly depressed with increasing inspired concentrations, both in normal and reserpine-pretreated dogs. Despite lower absolute values after reserpine, the slopes of the regression lines relating the hemodynamic effects to inspired concentrations of the anesthetics were not significantly different in the two groups of animals. Cardiovascular collapse failed to occur in the pretreated animals despite concentrations of the anesthetics as high as those administered to the controls.

These experiments assume greater significance when it is realized that control values for cardiovascular functions in unanesthetized dogs are almost always abnormally high. Brendel *et al.*,[17] in a careful, long-term investigation with trained dogs, found that cardiac output and heart rate in unanesthetized animals were always elevated under usual laboratory conditions presumably because of apprehension and excitement. Special precautions were necessary to obtain normal "resting" values. In the study of Bagwell *et al.*, the animals underwent preparatory operation 24 hours before the main experiment, a procedure which must have increased apprehension, probably to a greater degree in the controls than in the "tranquillized" group. This factor may have contributed to the observed differences.

Preliminary results of a study in dogs by Rusy *et al.*[148] support the conclusions of Bagwell and co-workers. Preparatory operation was done 14 days before the control studies. After induction of anesthesia with 225 mg. of thiopental, 25 per cent cyclopropane was administered for 45 minutes and hemodynamic studies were then carried out. After the control measurements, the animals were given reserpine in a dose of 0.01 mg./kg. per day for ten days, when the observations were repeated. Reserpine was then administered for five additional days at a dose of 0.02 mg./kg. per day, and measurements were again made before and during anesthesia. Thereafter, an additional single dose of 0.1 mg./kg. of reserpine was given and the final observations were made 24 hours later. In the five dogs studied, a dose-dependent decrease in arterial pressure, myocardial contractility, and heart rate after reserpine was found. There was no consistent change in cardiac output. No significant differences were found in the cardiovascular changes during thiopental-cyclopropane anesthesia before reserpine, or after any of the dose schedules employed. Cardiovascular collapse was not observed, even after the highest dose of reserpine. Rusy and associates concluded that reserpine pretreatment does not severely reduce the ability of the dog to compensate for the cardiovascular effects of thiopental-cyclopropane anesthesia.

Stump and Fleming[167] determined, in dogs, the average dose of thiopental, infused intravenously at a constant rate, which would produce a 50 mm. of mercury fall of blood pressure. After pretreatment with reserpine (0.1 mg./kg. for two days or 0.01 mg./kg. for ten days) the dose of thiopental required for this effect was reduced by one half. Prior administration of ouabain (35 μg./kg.) to the reserpine-treated dogs allowed the dose of thiopental to be raised not only to control levels, but even higher. This observation seems to implicate the heart as the main site of the depressant effect of thiopental.

In isolated myocardium, reserpine pretreatment did not cause reduction of contractile force. Papillary muscles from cats pretreated with reserpine (10 mg./kg. 24 hours before the experiment) developed the same tension as did control muscles.[28] In the isolated whole heart (heart-lung preparation of the dog) pretreatment with reserpine did not depress the contractility of the heart[15, 96] (judged by competence tests and ventricular function curves), although the variability in normal hearts was such that minor differences might have been missed.[15] These results show that size of catecholamine stores does not affect contractility of the denervated heart to a major degree and indicate that there can be only a small

spontaneous release of catecholamines, if any, in the absence of nerve activity. This conclusion is supported by the observation of Fawaz[51] that the coronary flow, oxygen consumption, and efficiency of the isolated heart are not influenced by reserpine treatment.

The sensitivity of the isolated dog heart to the depressant effect of anesthetic agents is not increased after administration of reserpine. Pretreatment of dogs with 0.3 mg./kg. reserpine, given 24 hours before setting up the heart-lung preparation, did not affect the dose-response relationship of the negative inotropic effect of pentobarbital.[100] Likewise, after treatment with 0.1 mg./kg. of reserpine for two successive days, no increased sensitivity to halothane was observed.[52] Chronic denervation of the heart with consequent catecholamine depletion also did not alter the sensitivity of the heart *in situ* to the administration of halothane.[125]

In the intact animal, on the other hand, lowered myocardial contractility after reserpine treatment was observed[5, 148] (although not resulting in lowering of cardiac output). This effect of reserpine may well be due to interference with the positive inotropic effect of sympathetic activity normally present.[53a, 147a, 151a]

The myocardial response to administration of anesthetic agents after pretreatment with reserpine depends upon several factors: (1) the direct depressant effect of the anesthetic upon the heart,[139] (2) the degree of reflex sympathetic activity elicited by the anesthetic,[140] and (3) the impairment of sympathetic transmission by reserpine. The experiments of Brewster *et al.*[18] and of Price and co-workers[141, 142] have demonstrated a significant role of the sympathetic nervous system in the response to ether and to cyclopropane. Recently, the importance of the sympathetic response during injection of thiopental has been pointed out.[12] After blockade of the sympathetic spinal outflow, myocardial contractility after a single dose of 5 mg./kg. thiopental was more severely impaired than in the normal control.

This role of the sympathetic nervous system during the response to thiopental is reflected in the marked increase in sensitivity after reserpine pretreatment observed by Stump and Fleming.[167] However, the experiments with the inhalation anesthetics[5, 6, 148] do not indicate an important alteration after catecholamine-depleting doses of reserpine. The reason for this discrepancy is not entirely clear. Several factors which may jointly be responsible for the observed result will be discussed later.

In summary, there is little evidence that circulatory homeostasis in inhalation anesthesia is severely impaired even after pretreatment with large doses of reserpine. It should not be overlooked, however, that some factors important in clinical anesthesia, such as the effects of preanesthetic medication and the role of postural changes, have not been examined.

Clinical Reports

Several reports[39, 41, 47, 120, 160, 165, 166] have described or predicted circulatory depression of an alarming degree during anesthesia and surgery in patients on reserpine therapy. Unfortunately, it is difficult to assess the significance of these reports. Some are single case studies[120, 160]; in others,[39, 165] the incidence and degree of circulatory depression are noted, but no control series was studied. In general, the dosage of reserpine is not reported. Furthermore, in all of these publications, the criteria for circulatory depression are vague: fall of blood pressure in percentage[165] or by an arbitrary change of 40 mm. of mercury,[39] or decline in heart rate below 60 or 70 beats per minute[39] are the parameters used. It should be noted that, as all authors emphasize, postanesthetic recovery was uneventful and no deaths have been reported. Anesthetists generally have adopted the rule that reserpine medication must be discontinued at least ten days prior to elective surgery.

In a more recent study, a dissenting voice has been raised. Munson and Jenicek[120] found no increased incidence of untoward circulatory reactions to all types of anesthesia and surgery in patients receiving reserpine (unspecified dose) as compared to a group in whom reserpine had been discontinued at least 8 days before operation. The authors point out that the difficulties may not necessarily be related to reserpine therapy but rather to the type of patient likely to receive reserpine. In these reports, fall in blood pressure, when en-

served after pretreatment with 0.1 mg./kg. reserpine for two days. Thus, it appears that the nervous homeostatic mechanisms are backed up by a considerable "autoregulatory" capacity of vascular smooth muscle itself, apparent even after pharmacological denervation by reserpine.

In the heart, the sympathetic "denervation" appears to be of little importance under these conditions. Heart rate becomes a limiting factor for cardiac output only at extreme values.[95] Under normal conditions, the magnitude of venous return, rather than myocardial contractility, is the major determinant of cardiac output. In this connection it should be remembered that the cost of cardiac work (in terms of coronary flow and myocardial oxygen consumption) is much greater for pressure than for volume work.[151] Anesthetic agents depress the ability of the heart to overcome high arterial resistance much more severely than its ability to increase output.[1] Thus, the reduction of peripheral resistance by reserpine may significantly ease the load on the heart, especially in a patient with hypertension.

A consideration of all these factors may well account for the observed minimal differences in the effects of anesthetic agents in the reserpine-pretreated as compared to the normal dog. Under the conditions of these experiments, no special circulatory stress was imposed upon the animals. However, the effect of the reserpine-induced impairment of the sympathetic nervous system may well become manifest only when a major neurogenic compensatory reaction is required. Such situations arise during clinical anesthesia; for example, with change in position and with rapid loss of circulating blood volume. In the animal experiments reported above,[157] the bleeding rate was adjusted to about 2 ml./kg. per minute. Different results might have been obtained with more rapid blood loss.

The time factor may be of great importance for circulatory compensatory reactions after catecholamine depletion. Burnstock and Holman [27] showed an increased latency period between nerve stimulation and contractile response after reserpine pretreatment. Thus, the vasoconstrictor response to sympathetic stimulation, after doses of reserpine causing incomplete block, might be of an equal magnitude but develop more slowly than normally. If, however, complete blockade does exist, the myogenic, "autoregulatory" mechanism of the vascular bed,[59] persisting after catecholamine depletion, may be expected to function more slowly than neurogenic reactions. Consequently, circulatory depression following rapid intravenous injection of thiopental might be more marked than that accompanying slowly increasing concentrations of anesthetics, administered via the lungs. (See section—Reserpine and the Circulatory Response to Anesthesia.)

Although the degree of catecholamine depletion in many of the experimental studies cited was probably more severe than that commonly produced under clinical conditions, it is likely that various degrees of depletion and sympathetic blockade will be encountered in man. It has been suggested that the degree of depletion may be estimated by testing preoperatively the response of a patient to a dose of ephedrine.[41] The choice of ephedrine for this purpose appears less than ideal, since, as shown above (table 1), ephedrine is classified as an amine with partly direct and partly indirect action. Recent data in man showed that the response to ephedrine is not a reliable prognostic test.[75] It would seem more appropriate to use tyramine which acts indirectly, *i.e.*, entirely by release of endogenous catecholamines.[111, 111a] It must also be remembered that use of a single dose is not an adequate test.[112] In order to distinguish between a low sensitivity to the drug and a depression of the maximal response (the latter indicating depletion), the dose-response relationship must be explored by giving several doses. It appears questionable whether any such drug test will prove useful. Perhaps the response of blood pressure and heart rate to a Valsalva or tilt table maneuver might provide more valuable information on the functional state of the circulation after reserpine.

Reserpine pretreatment with catecholamine depletion, and the resulting sympathetic depression, is only one of the many variables which affect the circulatory status of patients about to undergo anesthesia. It seems therefore that it would be more useful to evaluate the situation as a whole rather than to focus on reserpine medication alone. If it were

possible to construct a distribution curve of circulatory status and probable anesthetic risk in a typical population, many patients receiving reserpine might well fall within the normal range. Furthermore, the reserpine-treated group, even if it fell into the high risk category, might well have been in this category before reserpine therapy was instituted. In fact, lowering the blood pressure with reserpine might decrease anesthetic risk in some patients.

The main conclusion to be drawn from this presentation is that patients on reserpine medication present few problems that are fundamentally new and that would not be encountered in other patients. A special vulnerability may exist to sudden circulatory stresses and to sudden loss of blood volume. The former may be responsible for the increased sensitivity to thiopental injection found experimentally. Special care with the use of intravenous anesthetics is probably advisable in these patients. The possibility that the response to some sympathomimetic amines may be diminished because of tissue depletion of endogenous catecholamines, can easily be dealt with by selection of the proper drug. Directly acting sympathomimetic amines should be used when necessary in these patients.

Information resulting from attenuation or elimination of sympathetic cardiovascular influences by means of drugs (ganglionic and adrenergic blocking agents) and from acute denervation by surgical means or local anesthetics, has accorded to the sympathetic nervous system a dominant role in the preservation of circulatory homeostasis, particularly during anesthesia. Consequently, when the impairment of sympathetic impulse transmission by reserpine was recognized, diminution of circulatory reserve by reserpine was expected. Although blockade of the effects of electrical stimulation after reserpine has been demonstrated, the impairment of circulatory reserve under clinical conditions and in the laboratory is less than expected and less than that resulting from sympathetic blockade by other means. The reason for this discrepancy cannot be discerned at the moment. It is possible that the blockade of the sympathetic nervous system by reserpine is less complete for physiological impulse traffic than it is for massive electrical stimulation under experimental conditions. Or, the role of the sympathetic nervous system in control of circulation may be less important than concluded from the experiments cited above. The answers to these questions will be of considerable importance for our understanding of the circulation and of the autonomic nervous system. Concerning the implications of reserpine medication for anesthesia, these findings lead to the conclusion that discontinuation of reserpine therapy before anesthesia and surgery is not mandatory, since the danger of circulatory depression does not appear to be excessive and can be controlled by careful anesthetic management.

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