*Chapter 7*

# Ergot Alkaloids and Related Substances

P. B. Bradley and I. Briggs

*Medical Research Council Neuropharmacology Unit*
*The Medical School*
*University of Birmingham*
*Birmingham, England*

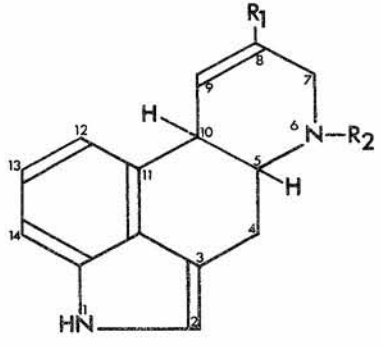
## 1. INTRODUCTION

Ergot has been called a treasure-house of drugs; possibly no other source of biological products has so many active constituents with such a wide spectrum of pharmacological properties, which has been further expanded by the production of derivatives with qualitatively new actions. Ergot consists of the sclerotia or resting stage produced by fungi of the genus *Claviceps*, most commonly *C. purpurea*, which is principally parasitic on the rye, *Secale cereale*. Many other varieties of ergot are known; over 50 species of *Claviceps* have been described, infesting over 600 recorded host species of the family Gramineae (grasses and cereals) (Bové, 1970). Although possible allusions to ergot are found in early records (see Bové, 1970), the earliest undisputable reference to ergot itself was made in 1582 by Lonicer, who described its use in midwifery. However, it was not widely accepted by physicians until the nineteenth century. The history and pharmacognosy of ergot have been extensively reviewed by Barger (1931) and by Bové (1970).

## II. CHEMISTRY OF ERGOT ALKALOIDS

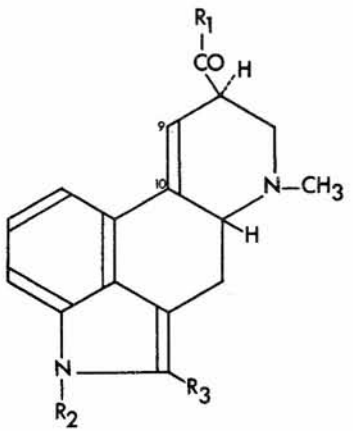
More than 40 different natural ergot alkaloids have been isolated from *Claviceps* species, which are the main sources of these drugs, and some are also found in a few other fungi (e.g., *Aspergillus* and *Agropyrum* spp.) and in a few species of the *Convolvulaceae* (for references, see Bové, 1970; Der Marderosian, 1967). The alkaloids to be described in this chapter are all derived from the ergolene ring system (Table I). The ergolene skeleton is formed from tryptophan and mevalonic acid; the first compound having the skeleton complete is agroclavine, which is a precursor of all the other natural alkaloids. The detailed biochemistry of this compound has been reviewed by Ramstad (1968), who pointed out that the pathways involved in ergot alkaloid biogenesis form a nearly continuous sequence of oxidative steps and speculated that these substances are the products of "detoxification" pathways. After agroclavine, elymoclavine is formed, and this in turn gives rise to lysergic acid, which has $\Delta_{9-10}$ instead of $\Delta_{8-9}$ (*cf.* Tables I and II). Subsidiary pathways lead to the formation of other clavine alkaloids, some with pharmacological activity. Synthetic clavine derivatives have recently been prepared which have potent and specific pharmacological properties.

**Table I. Clavine Alkaloids**




| Alkaloid | $R_1$ | $R_2$ |
|---|---|---|
| Ergolene | H | H |
| Agroclavine | $CH_3$ | $CH_3$ |
| Elymoclavine | $CH_2OH$ | $CH_3$ |

**Table II. Amine Alkaloids**



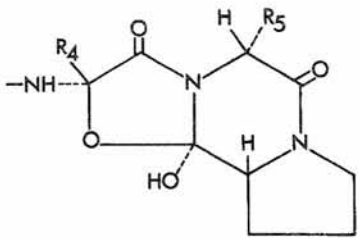

| Alkaloid | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| Lysergic acid | —OH | H | H |
| LSD-25 | $-N(C_2H_5)_2$ | H | H |
| BOL-148 | $-N(C_2H_5)_2$ | H | Br |
| Ergometrine | $-NH\cdot CH\cdot(CH_3)\cdot CH_2OH$ | H | H |
| Methylergometrine | $-NH\cdot CH\cdot(CH_2CH_3)\cdot CH_2OH$ | H | H |
| Methysergide | $-NH\cdot CH\cdot(CH_2CH_3)\cdot CH_2OH$ | $CH_3$ | H |

Lysergic acid is the basis for all of the drugs commonly referred to as ergot alkaloids. These drugs are most easily divided into the two series of optical isomers. Only the *l*-isomers are pharmacologically active; these generally have the suffix *-ine* and are derivatives of *d*-lysergic acid, whereas the inactive *d*-forms have the suffix *-inine*, are derived from *l*-lysergic acid, and are thought to be produced from the natural *l*-isomers during chemical manipulations. This isomerism of lysergic acid is due to an asymmetry at $C_8$. Another asymmetry at $C_5$ gives rise to the isolysergic acids, which are pharmacologically inactive derivatives. The pharmacologically active isomers have the R configuration at both $C_5$ and $C_8$.

In the natural ergot alkaloids, *d*-lysergic acid is combined with either an amine moiety or an oligopeptide moiety, the two groups of derivatives formed being the "amine" alkaloids (Table II) and the "amino acid" alkaloids of ergot (Table III), respectively. Other active groups of alkaloids are derived semisynthetically from the natural alkaloids; one group is made

**Table III. Amino Acid Alkaloids**

These derivatives are also based on the structure in Table II. $R_1$ is an oligopeptide with the general structure




$R_2$ and $R_3$ both = H. The different amino acid aklaloids vary in the groups at $R_4$ and $R_5$ in the oligopeptide moiety as shown in the table below.

| | $R_5$ | | |
|---|---|---|---|
| $R_4$ | $-CH_2 \cdot C_6H_5$ | $-CH(CH_3)_2$ | $-CH_2 \cdot CH(CH_3)_2$ |
| $-CH_3$ | Ergotamine | Ergovaline | Ergosine |
| $-CH_2 \cdot CH_3$ | Ergostine | Ergonine | Ergoptine |
| $-CH \cdot (CH_3)_2$ | Ergocristine | Ergocornine | Ergokryptine |

by dihydrogenation of the lysergic acid moiety at $C_9$ and $C_{10}$ to yield a series of analogues of the natural alkaloids. Another group consists of lysergic acid derivatives with synthetic substituents other than natural ones; these include derivatives of all three types of natural alkaloids.

*Terminology*: In this chapter, the term *ergot alkaloids* will be used to refer to the natural alkaloids (ergometrine and those in Table III); *ergot derivatives* include all the compounds, natural or synthetic, derived from ergot. Compounds other than natural ergot alkaloids will be referred to specifically. *Hydergine* is a mixture of equal amounts of dihydroergocornine, dihydroergocristine, and dihydroergokryptine, as the mesylates.

## III. PHARMACOLOGY

Many of the alkaloids derived from ergot have little or no pharmacological activity, but the active alkaloids and derivatives have extremely varied and complex effects, some of them being highly potent. No recent detailed review of the subject is available, but early work has been

described by Barger (1931), Rothlin (1947, 1957), Cerletti (1959), and Bové (1970).

Ergot alkaloids can affect the functions of many tissues by virtue of their ability to stimulate directly or to interfere with the actions of monoamines on smooth muscles, nerves, and metabolic processes. At present, it seems unlikely that a unified explanation of all the actions of these drugs can be formulated; the drugs are known to affect mechanisms involving norepinephrine (NorE), dopamine (DA), and 5-hydroxytryptamine (5-HT), and the diversity of the drug actions reflects the diversity of the physiological roles of these monoamines. Possibly other systems are also affected, but the main emphasis of pharmacological research into ergot derivatives has been on their interactions with monoaminergic mechanisms.

The pharmacology of the ergot derivatives is described in this chapter in two main sections, one covering peripheral actions and the other central actions. However, some overlapping is convenient; for example, both centrally and peripherally mediated actions on the cardiovascular system are placed in one section, since the effects of the drugs are frequently the resultant of both central and peripheral actions.

## A. Peripheral Actions of Ergot Alkaloids and Their Derivatives

### *1. Effects of Ergot Alkaloids and Derivatives on the Uterus*

*a. Direct Actions on the Uterus.* The abortifacient effects of ergot, the result of its stimulation of strong contractions of the uterus, have long been recognized, and the drug has been used medically for its oxytocic properties for over 400 years. Rothlin (1947, 1957) has described the direct actions of ergot derivatives on the uterus. Ergometrine is the most active; it is absorbed well, so it can be given orally to produce a rapid effect. In contrast, the amino acid alkaloids are ineffective orally and must be given by injection, ergotamine being the most active. Its onset of action is slow, and it is more toxic than ergometrine. Thus ergometrine and its congener methylergometrine are the oxytocics most often used clinically. The dihydrogenated ergot alkaloids have no uterotonic actions in experimental animals. LSD has about two-thirds of the potency of ergometrine on the rabbit uterus, while D-2-bromolysergic acid diethylamide (BOL) has no stimulant actions (Rothlin, 1957). Acetyldihydrolysergamine has been reported to have oxytocic activity comparable or superior to that of ergometrine, while its antiserotonin and antiadrenergic actions and its toxicity are relatively slight (Fregnan and Glässer, 1968). The stimulant actions of ergot derivatives are exerted via $\alpha$-adrenergic receptors on the uterus, and these

effects can be antagonized by $\alpha$-adrenergic blockers (Konzett, 1960; Brody and Diamond, 1967). The sensitivity of the uterus varies with its state of maturity and during ovarian cycles and gestation; it appears that the numbers and proportions of $\alpha$- and $\beta$-adrenergic receptors on the uterus change in different hormonal states (Miller and Marshall, 1965); in the uterus dominated by estrogen, $\alpha$-receptors predominate, while in the progesterone-dominated organ, $\beta$-receptors predominate (Brody and Diamond, 1967).

*b. Interactions of Ergot Derivatives and Catecholamines in the Uterus.* The excitatory action of epinephrine on rabbit uterus is antagonized by all of the natural and dihydrogenated alkaloids. Only slight differences in potency are found, with the dihydrogenated alkaloids generally having stronger and longer-lasting effects (Rothlin, 1947). The $\alpha$-receptor blocking actions of LSD on the uterus are weak (Rothlin, 1957).

The derivatives with predominantly $\alpha$-blocking actions (e.g., dihydroergotamine) can reverse adrenergic stimulation to relaxation (Miller, 1967). This phenomenon is explained by the selective blockade of the $\alpha$-adrenergic stimulant receptors, permitting activation of $\beta$-receptors to produce relaxation. Dihydroergotamine can block adrenergic inhibition of the rat uterus (Levy and Tozzi, 1963), and there may be some similarity between this action and that on the metabolic receptors involved in lipolysis and in the liver glucogenic response to sympathomimetic agents, which dihydroergotamine also blocks, apparently at a stage subsequent to the formation of cyclic AMP (Hornbrook and Brody, 1963) (cf. Sections IIIA4a and IIIA4b).

*c. Interactions of Ergot Derivatives and 5-HT in the Uterus.* The dihydrogenated alkaloids and some of the synthetic amide derivatives of lysergic acid are highly potent antagonists of 5-HT-induced contractions of the uterus. Rothlin (1957) and Cerletti and Doepfner (1958) made extensive comparative studies of synthetic lysergic acid derivatives and LSD. Only derivatives of *d*-lysergic acid were active; derivatives of *l*-lysergic acid and of *d*- and *l*-isolysergic acids had less than 1% of the activity of LSD. Methylation or acetylation of LSD in the 1-position or bromination in the 2-position increased anti-5-HT potency, while all other modifications of the LSD structure studied by these authors, including dihydrogenation and alteration of the substituents on the amide group, reduced potency. However, methysergide was later found to be four times as active as LSD (Fanchamps *et al.*, 1960), and methergoline is an extremely potent antagonist of 5-HT in the rat uterus, being 500 times more potent than methysergide (Beretta *et al.*, 1965). Certain clavine alkaloids also antagonize the actions of 5-HT on the rat uterus; the most potent derivative tested, 1-methylelymoclavine, is approximately as potent as methysergide in this respect (Yui and Takeo, 1964). Cerletti and Doepfner (1958) were unable to confirm the reports by Costa (1956) and Delay and Thuillier

(1956) that LSD in low doses appeared to facilitate contractions of the rat uterus due to 5-HT.

*d. Effects of Ergot Derivatives on Intestinal Responses to Catecholamines and Serotonin.* The actions of both $\alpha$- and $\beta$-adrenergic agonists on the intestine are inhibitory, and ergot alkaloids can block these actions (Rothlin, 1947). The derivatives with polypeptide side-chains (e.g., ergotamine, ergokryptine, dihydroergotamine, and dihydroergocornine) are potent antagonists of epinephrine's inhibitory effects on the rabbit isolated intestine, and are still active in the presence of hexamethonium and atropine, indicating that their actions are exerted directly on receptors on smooth muscle of the tissue, and not via intramural ganglia. The inhibitory action of epinephrine on pendular movements of the intestine is more readily blocked than the action on tonus. Furthermore, the actions of NorE are less readily blocked than are those of epinephrine (Rothlin *et al.*, 1954).

Catecholamines also have inhibitory actions on human isolated taenia coli and isolated jejunum, which, like rabbit intestine, appear to have both $\alpha$- and $\beta$-adrenergic inhibitory receptors. Hydergine blocks the actions of $\alpha$-adrenergic agonists but not the actions of $\beta$-adrenergic agonists on these preparations (Bucknell and Whitney, 1964; Whitney, 1965).

Erspamer (1966) has extensively reviewed the complex interactions of serotonin and lysergic acid derivatives on the intestine. In the limited space available here, this topic cannot be discussed fully; for further details, reference should be made to Erspamer's paper.

### 2. *Effects of Ergot Derivatives on the Cardiovascular System*

The effects of ergot derivatives on the vascular system are complex, and the net effect of a particular derivative on blood pressure may be the resultant of one or more of the following actions: (1) central effects influencing vascular tone and heart rate, mediated by alterations in tone in adrenergic nerves, by increases in activity in cholinergic sympathetic nerves, or by increases in vagal tone; (2) peripheral effects, including agonistic actions on catecholamine or serotonin receptors and antagonistic actions toward catecholamines or serotonin. In the interests of simplicity, both central and peripheral actions will be described together in this section.

*a. Effects on Systemic Blood Pressure.* Early work on the vasoactive effects of ergot derivatives has been reviewed by Rothlin (1947, 1957). In intact anesthetized animals, only ergotamine always causes a rise in blood pressure; ergosine in low doses also raises blood pressure, but in high doses causes a fall. The other natural alkaloids, the dihydrogenated alkaloids, LSD, and BOL all reduce blood pressure in intact animals, including cats and dogs. In the spinal cat, the effect of both natural and dihydrogenated

alkaloids and of LSD is an increase in blood pressure due to direct constrictor actions on blood vessels, the natural alkaloids being somewhat more active. In man and rats, LSD causes a slight rise in blood pressure (Rothlin, 1957; Salmoiraghi *et al.*, 1957), which in rats is enhanced by pithing or pretreatment with ganglionic blockers; the marked depressor action of BOL in rats is abolished by these treatments.

*b. Central Effects of Ergot Derivatives Mediated via Adrenergic Sympathetic Nerves.* The hypotensive effects of ergot alkaloids were attributed by Rothlin (1947) to a decreased sympathetic outflow from vasomotor "centers," resulting from either stimulation of inhibitory influences or inhibition of excitatory influences on the "centers." Konzett and Rothlin (1953) showed that the depressor effect of dihydrogenated alkaloids occurs only when at least the medulla oblongata and the spinal cord down to the seventh thoracic segment are intact. Downman (1972) recently reviewed the evidence on central vasomotor control; it appears that both pressor and depressor reflexes are controlled by an extensive system of neurons in the brain stem, diencephalon, and limbic cortex. In the brain stem are a pontomedullary pressor area and a medullary depressor area, each consisting of laterally situated neurons activating more medially placed efferent neurons, but it may be that these areas contain general sympathetic facilitatory and inhibitory mechanisms of which vasomotor components are only a part (Coote *et al.*, 1973). Vasodepression of medullary origin is probably due to inhibitory pathways acting on tonically active spinal segmental pressor reflexes, reducing the excitability of the spinal preganglionic neurons (Downman, 1972). The bulbospinal pathways involved appear to be noradrenergic (Chalmers and Wurtman, 1971; Coote and Macleod, 1972). In man, the central vasodilator actions of ergot derivatives are abolished by sympathectomy and appear to be due to a fall in sympathetic tone originating in the medulla and/or hypothalamus (Bluntschli and Goetz, 1948). There is evidence that stimulation of $\alpha$-adrenergic receptors in the lower brain stem results in hypotension and bradycardia (Bolme *et al.*, 1972; Share, 1973; Haeusler, 1973), and it thus seems possible that ergot derivatives act by stimulation of adrenergic receptors in this area, increasing the activity of the bulbospinal NorE pathways which inhibit the spinal preganglionic sympathetic neurons. An interaction with serotoninergic mechanisms controlling blood pressure (Ito and Schanberg, 1972) is also a possibility, although the precise location and function of the neurons with these receptors are still uncertain.

Schmitt and Fénard (1970) reported that low doses of dihydroergotamine, dihydroergotoxine, and ergotamine increased electrical activity in the splanchnic nerve, and reduced activity only in high doses. These workers concluded that hypotensive actions could not be related to inhibition of sympathetic tone. However, ergot derivatives appear to have

differential effects on tone in different parts of the vasculature. For example, dihydroergocornine, which induces a centrally mediated vasodilatation in most areas, causes a fall in blood flow in the splanchnic area (Bluntschli and Goetz, 1948; Freis *et al.*, 1949), indicating a rise in sympathetic tone, which the results of Schmitt and Fénard also indicate. Thus splanchnic nerve activity may be misleading as an indicator of general sympathetic tone, and data from sympathetic nerves supplying other areas are needed. The differential actions of these drugs on different areas may indicate an action on mechanisms integrating vasomotor control rather than on vasomotor reflexes themselves.

Ergot derivatives can affect vasomotor reflexes evoked by physiological or electrical stimuli; these drugs prevent both depressor responses to stimulation of the aortic (depressor) nerve and pressor responses to bilateral occlusion of the carotids (Rothlin, 1947; Fanchamps *et al.*, 1960). They also reduce the pressor responses to electrical stimulation of the vestibular nuclei and parvocellular reticular nuclei in the medulla (Kovalyov, 1967). The efferent pathway for these reflexes and possibly for the areas activated by Kovalyov (1967) is the bulbospinal NorE pathway (see above), which, when activated, causes a fall in sympathetic tone. The fact that these drugs inhibit both pressor and depressor responses is further evidence that the site of action is not on the reflex pathway itself, but on some mechanism which can affect the responsiveness of the vasomotor reflexes to afferent stimuli.

*c. Central Effects of Ergot Derivatives Mediated by Cholinergic Sympathetic Nerves.* Mellander and Nordenfelt (1970) found that, among other actions, dihydroergotamine usually dilated resistance vessels (which mainly correspond to arterioles) in skeletal muscle without much affecting vascular resistance in intestine or kidney. In skeletal muscle, NorE constricted resistance vessels, and the authors considered that the dilator responses to dihydroergotamine were related to a central action of the drug leading to a reduction of sympathetic constrictor fiber discharge, since denervation prevented the dilatation. There are two functionally separate central vasodilator mechanisms (Uvnäs, 1960) which are both effected via sympathetic nerves: (1) inhibition of vasoconstrictor tone and (2) initiation of vasodilator activity. The former is not blocked by atropine; it is associated with vasodepressor reflexes in the medulla, which can be affected by ergot derivatives, as has already been discussed. However, more recent evidence has also given support to the second possible explanation of the centrally mediated dilatation. Owen and Stuermer (1971) confirmed the results of Mellander and Nordenfelt (1970) in cats with intact innervation, while in denervated preparations dihydroergotamine was found to cause constriction in the muscle resistance vessels. Chu and Stuermer (1973) reported that in innervated preparations the dilator effect of the drug on

skeletal muscle resistance vessels was blocked by atropine but not by phenoxybenzamine, and was potentiated by eserine. After atropine, dihydroergotamine had a constrictor effect on resistance vessels similar to that seen in the denervated preparation. These authors conclude that the dilator effect of dihydroergotamine in cats is mediated centrally via cholinergic innervation of the muscle resistance vessels. It seems that only skeletal muscles receive sympathetic cholinergic vasodilator innervation (Mellander and Johansson, 1968), and it is therefore likely that vasodilator responses in most other organs and tissues are due to reduction of sympathetic constrictor tone.

The sympathetic vasodilator innervation of skeletal muscle can be activated by stimulation of several areas of the brain, including the hypothalamus, where it constitutes part of the mechanism of the coordinated defense reaction; the vasodilatation may be elicited as a relatively isolated response by stimulation of an area dorsal to the cerebral peduncles (Abrahams *et al.*, 1960, 1964). The results of Chu and Stuermer (1973) indicate that dihydroergotamine can activate this mechanism. Horeyseck *et al.* (1972) found that stimulation of the hypothalamic defense area elicited activity in about 10% of the single nerve fibers studied in the cat gastrocnemius soleus sympathetic innervation. These fibers showed no spontaneous activity and were not activated by baroreceptor reflexes. An investigation of the effects of dihydroergotamine on activity in these fibers would be of interest.

*d. Centrally Mediated Effects of Ergot Derivatives on Heart Rate.* The heart does not seem to be directly affected by ergot derivatives, but there is often a fall in pulse rate which appears to be centrally mediated via the vagal motor nuclei (Rothlin, 1947, 1957). This is supported by observations that intraventricular or intracisternal administration of NorE results in cardiac slowing which can be partly reduced by vagotomy. However, the fact that atropine is not wholly effective and that vagotomy is ineffective in some species indicates that reduction of sympathetic cardioaccelerator tone is an important component of the action (for references, see Bhargava *et al.*, 1972). Similar conclusions were reached in a study of dihydroergocornine in man (Freis *et al.*, 1949).

*e. Direct Agonistic Actions on Blood Vessels.* The potent vasoconstrictor effects (Rothlin, 1947, 1957) of these drugs are probably due mainly to direct stimulant actions on $\alpha$-adrenoceptors (Innes, 1962). This is one of the most undesirable effects of the natural alkaloids; they may cause marked constriction of veins and even of arteries as large as the aorta, which may seriously impair circulation. The deleterious consequences of this action will be dealt with in Section IVB.

The dihydrogenated alkaloids, ergometrine, and LSD have direct vaso-

constrictor effects weaker than those of the natural alkaloids (Rothlin, 1947, 1957; Ginzel and Kottegoda, 1953; Savini, 1956). The actions of LSD on some vessels are due to stimulation of 5-HT receptors and can be blocked by BOL (Dyer and Gant, 1973), which has no vasoconstrictor actions itself (Savini, 1956).

Mellander and Nordenfelt (1970) found that dihydroergotamine has a strong constrictor action on capacitance vessels (which mainly correspond to veins) in skin and skeletal muscle and on resistance vessels in skin, although centrally mediated dilatation obscures the direct constrictor action on muscle resistance vessels (see Section IIIA2C). Resistance vessels in intestine and kidney and precapillary sphincter vessels in skin, muscle, or intestine are little affected. The constrictor effects are blocked by phenoxybenzamine and are thought to be due mainly or entirely to a direct action on the vascular smooth muscle $\alpha$-adrenergic receptors (Chu and Stuermer, 1973). Owen and Stuermer (1972) reported the results of similar studies on Hydergine, which differs from ergotamine in that it appears to have little effect on resistance vessels, while it dilates precapillary sphincter vessels, which are not affected by dihydroergotamine (Mellander and Nordenfelt, 1970; Owen and Stuermer, 1971). Dihydroergotamine is about 50 times more potent than Hydergine in constricting capacitance vessels.

Methysergide was found by Fanchamps *et al.* (1960) to have no vasoconstrictor actions in the spinal cat, anesthetized intact dog, or perfused rabbit isolated hind leg. Saxena (1972) observed that both methysergide and ergotamine did have direct vasoconstrictor actions on the external carotid bed in dogs, increasing resistance and decreasing blood flow in doses which did not affect general blood pressure. It seems that these compounds have relatively selective actions on the external carotid circulation.

Aellig and Berde (1969) found that the direct effects of ergot alkaloids on vascular tone in anesthetized dogs were dependent on the preexistent tone; they observed an "inversion-point" phenomenon, in which many derivatives had amphoteric effects, causing vasoconstriction when the existing tone was low and vasodilatation when it was high. Ergotamine, dihydroergotamine, 1-methylergotamine, ergostine, dihydroergostine, and 1-methylergostine all showed this effect. No correlation was found between the degree of existing vasoconstriction represented by the "inversion point" and the potencies of the different alkaloids as vasoconstrictor agents or as $\alpha$-receptor blockers.

*f. Circulatory Actions in Man.* Bluntschli and Goetz (1948) studied the circulatory effects of ergot derivatives in man and found that ergotamine and dihydroergotamine have both direct constrictor actions and centrally mediated vasodilator actions. The dilator effects are abolished by sympathectomy, but whether they are due to a fall in adrenergic constrictor

outflow or to augmented cholinergic dilator outflow is not known. In fact, it is not yet certain whether cholinergic sympathetic vasodilator fibers exist in man, although Greenfield (1966) reviewed the evidence and considered that these fibers probably do exist in man. Dihydroergocornine has vasodilator actions which are also abolished by sympathectomy, but unlike ergotamine and dihydroergotamine it seems to have no direct constrictor effects (Bluntschli and Goetz, 1948). Freis *et al.* (1949) and Barcroft *et al.* (1951) found that the hypotensive actions of dihydroergocornine and of Hydergine in man seemed to be due to centrally mediated dilatation occurring mainly in the skin, and only slightly in muscle. The effects of dihydroergostine (DE-145) on the human calf have been compared with those of dihydroergotamine by Ulrich and Siggaard-Andersen (1972), using a plethysmographic method. DE-145 gave a significant rise in resting blood flow, possibly indicating a potent dilator effect on resistance vessels, but dihydroergotamine did not raise resting blood flow. A decrease in the limb volume indicated a constriction of capacitance vessels by dihydroergotamine, but DE-145 did not have this effect. It thus seems that in man the effect of DE-145 on muscle blood flow is mainly or wholly centrally mediated, and while dihydroergotamine has little effect on blood flow, it is possible that central vasodilator effects may be counterbalanced by direct constrictor actions.

*g. Antagonism of the Actions of Catecholamines by Ergot Derivatives.* The abilities of ergot derivatives to antagonize the actions of CAs vary considerably among different species and different test organs. The antagonist activities of the different alkaloids vary with respect to the different CAs.

With the exception of ergometrine, all the natural and dihydrogenated alkaloids cause "reversal" of the action of epinephrine on blood pressure (Rothlin, 1947). The reversal of epinephrine-induced pressor effects to depressor effects is due to blockade of $\alpha$-adrenergic vasoconstrictor actions, allowing latent $\beta$-adrenergic vasodilator actions to predominate (Levy and Ahlquist, 1961). The action of the natural alkaloids is itself of a biphasic nature; the antagonism of epinephrine pressor effects is seen first, and later a sensitization to epinephrine often occurs (Rothlin, 1947). The $\alpha$-adrenergic blocking actions of LSD and BOL are weak in comparison with those of the natural and dihydrogenated alkaloids (Ginzel and Kottegoda, 1953; Rothlin, 1957; Salmoiraghi *et al.*, 1957; Palmer and Burke, 1971), and LSD can potentiate epinephrine and NorE vasoconstriction in rabbit ear (Gaddum and Hameed, 1954; Savini, 1956) and human veins (Del Bianco *et al.*, 1972). Methysergide has little or no activity on cerebral vasoconstriction induced by NorE in monkeys (White *et al.*, 1971); neither LSD

nor methysergide affects NorE-induced venoconstriction in man (Del Bianco *et al.*, 1972). Nicergoline is a potent and highly specific blocker of the effects of epinephrine and of sympathetic nervous stimulation on vascular tone (Arcari *et al.*, 1968).

*h. Effects of Ergot Derivatives on the Actions of Serotonin.* Vasoconstriction induced by 5-HT in rabbit ear vessels is blocked by LSD, ergotamine, and dihydroergotamine (Gaddum and Hameed, 1954). Savini (1956) found that both 5-HT- and tryptamine-induced constrictions in rabbit ear were antagonized equally by LSD and ergometrine, while the actions of epinephrine and NorE were not affected. BOL had about one-tenth the activity of LSD against the action of 5-HT.

Methysergide prevented 5-HT-induced constriction of dog femoral arteries and the pressor actions of 5-HT in anesthetized dogs (Fanchamps *et al.*, 1960) and pithed rats (Beretta *et al.*, 1965). In rats, LSD and BOL were also effective antagonists of the cardiovascular effects of 5-HT, while their actions in cat and dogs were slight or variable (Salmoiraghi *et al.*, 1957), although LSD does antagonize 5-HT vasoconstriction in the cat's pulmonary circulation; ergotamine and dihydroergotamine were less effective (Gaddum *et al.*, 1953; Ginzel and Kottegoda, 1953). The cerebral vasoconstrictor effects of 5-HT in the monkey were specifically blocked by methysergide (Karlsberg *et al.*, 1963; White *et al.*, 1971). Methysergide, LSD, and methylergometrine had potent and specific actions against 5-HT induced constriction of human veins *in situ* (Del Bianco *et al.*, 1972).

*i. Migraine.* The therapeutic actions of certain of the ergot derivatives in migraine and in related conditions involving pain of vascular origin, like cluster headache, are probably related to their actions on blood vessels and/or vasomotor control. To explain the actions of the drugs, it is useful to consider briefly the etiology of migraine. The primary cause of migraine is uncertain (Sicuteri, 1967; Sicuteri *et al.*, 1973; Heyck, 1969; Anthony *et al.*, 1969; Dalessio, 1972), but it is generally agreed that in certain people there is an abnormality in the central control of the tone in some vascular beds, which generally includes a hyperreactivity of the reflexes controlling the carotid circulation. When these individuals are subjected to some types of stress, there is a strong vasoconstriction in the carotid beds causing a reduction of blood flow which is associated with the aura preceding a migraine attack. The formation of kinin due to ischemia is thought to initiate release of 5-HT from platelets and mast cells. Both 5-HT and bradykinin are vasoactive and pain-producing; consequently headache develops, due mainly to chemical stimulation of nociceptors. During migraine attacks, there is increased vascular sensitivity to the actions of 5-HT, NorE, and epinephrine; the emetic and vasoconstrictor effects of ergotamine and

methysergide and the psychotomimetic actions of LSD and psilocybin are also increased (Sicuteri *et al.*, 1973). These last observations appear to indicate a change in central 5-HT functions in migraine.

In the treatment of migraine, methysergide is generally used prophylactically in attempts to prevent or reduce the occurrence of headaches, whereas ergotamine can be used acutely to alleviate developing or existing headaches. The use, side-effects, contraindications, and possible mechanisms of action of these compounds have been reviewed by Dalessio (1972).

The prophylactic value of methysergide in the treatment of migraine has been attributed to several possible actions, and it may be that more than one of these contribute to its effectiveness. One action of methysergide may be to reduce the reactivity of the unstable vasomotor reflexes, preventing the initial vasoconstrictor response to stress, possibly by antagonism of 5-HT in the pons and medulla, where it appears to have a role in cardiovascular control (Ito and Schanberg, 1972). This is one possible explanation of the relative ineffectiveness of this drug as an acute treatment for migraine: once vasoconstriction started, an attack would not be prevented by inhibition of the initial cause. The drug may also reduce the vasodilator actions of 5-HT released from platelets (Anthony *et al.*, 1969; Hilton and Cumings, 1972) on arteriovenous anastomoses, although if the vasoconstriction phase is prevented there may be no release of 5-HT. Sicuteri (1967) pointed out that the ability of methysergide to prevent 5-HT-induced sensitization of pain receptors to bradykinin could partly explain why the drug is of little value after an attack starts; if methysergide is given before an experimental dose of 5-HT, sensitization to bradykinin is inhibited, but if it is given after 5-HT the pain receptors remain sensitized.

Another property of methysergide, which is also shared by ergotamine and methylergotamine, is the ability to prevent the normal aggregation response of platelets to 5-HT (Cumings and Hilton, 1971), which would presumably abolish or reduce the autoregenerative release of 5-HT from these cells.

The effectiveness of ergotamine and the other derivatives used in acute treatment of migraine appears to be due to their ability to cause vasoconstriction (Dalessio, 1972), particularly in the carotid vascular bed (Saxena, 1972), and it may be that in migraine these drugs act on dilated arteriovenous anastomoses in this area, thus restoring capillary circulation and permitting the removal of pain-producing agents from the affected areas.

In view of the evidence of Sicuteri *et al.*, (1973) that there is a malfunction in the central control of pain thresholds which may be related to an abnormality in 5-HT functions in the CNS, the possibility must be

considered that the drugs act at least partly on the central 5-HT receptors concerned.

### 3. *Effects on the Peripheral Nervous System*

*a. Effects on the Release of NorE from Sympathetic Nerve Terminals.* When the sympathetic nerve supplying an organ is stimulated, the NorE released from the terminals is partly taken back into the terminals and partly lost into the blood or perfusion fluid. The amount of NorE escaping is increased by $\alpha$-receptor blocking agents. This effect was first explained as an overflow of NorE due to the blockade of postsynaptic receptors, which were thought to act as a "brake" on the diffusion of NorE away from the terminals, and later was ascribed to a blockade of NorE reuptake (for references, see Pacha and Salzmann, 1970).

Ergot derivatives have been and are being used in the study of this mechanism because of their $\alpha$-receptor blocking properties. The dihydrogenated ergot alkaloids, in particular dihydroergotamine and Hydergine, have been valuable in this respect, but some apparently discordant conclusions have been reached when ergotamine and methylergotamine were used. Salzmann and coworkers (see Pacha and Salzmann, 1970) compared the effects of ergotamine and phenoxybenzamine (PBZ) on release of NorE from cat spleen and on responses of cat nictitating membrane to nerve stimulation and to epinephrine, NorE, tyramine, and 5-HT. High doses of ergotamine caused contractions of the nictitating membrane and spleen by direct stimulation of $\alpha$-receptors, which PBZ blocked. Low doses of ergotamine potentiated the effects of sympathetic nerve stimulation and of the monoamines on the nictitating membrane and increased stimulation-induced NorE release from the spleen. The authors concluded that the effects of ergotamine were due to inhibition of reuptake of NorE in the absence of $\alpha$-receptor blockade. Pacha and Salzmann (1970) compared ergotamine, 1-methylergotamine, Hydergine, dihydroergotamine, and PBZ on stimulation-induced release of NorE from isolated cat spleen and found that the first two, which have little $\alpha$-receptor blocking activity, were roughly as potent as the other drugs with strong $\alpha$-blocking actions. The authors suggested that these results indicate that the increased NorE release was due to block of NorE reuptake, and not to block of feedback inhibition of release. Ergotamine does have some NorE-uptake blocking activity in cat spleen (Dengler *et al.*, 1961), but Starke and coworkers (see Starke, 1972) found that PBZ and dihydroergotamine enhanced stimulation-evoked release of NorE from rabbit heart in concentrations which did not affect NorE reuptake. The method of Pacha and Salzmann does not specifically determine uptake-blocking activities, and although the

two preparations, (i.e., cat spleen and rabbit heart) may not be comparable, it seems that blockade of NorE reuptake is at most only a minor component of the action of the $\alpha$-blocking drugs on NorE release.

More recent studies have supported an alternative hypothesis: rather than interfering with the reuptake of transmitter, the $\alpha$-blockers are now thought to increase the stimulation-induced release of NorE from sympathetic terminals by blocking an $\alpha$-receptor-mediated feedback inhibition of the release (Farnebo and Hamberger, 1971). The precise mechanism is still uncertain. Three possibilities have been proposed:

1. The release of NorE could be regulated by the state of activity of the effector cells; during high activity of the effectors, NorE release would be low, and vice versa. Häggendal (see Stjärne, 1973) compared the effects on NorE release of doses of ergotamine and of PBZ which produced similar degrees of sympathetic blockade in cat skeletal muscle. The release of NorE in the presence of ergotamine was much lower than in the presence of PBZ, and the difference in output was attributed by Häggendal to the stimulating action of ergotamine on the effector cells. He therefore favored the hypothesis of transsynaptic feedback inhibition of release, but apparently did not consider the possibility of stimulation of presynaptic $\alpha$-receptors by ergotamine, which in the light of later results seems to be as likely an explanation as postsynaptic stimulation. Furthermore, there are several examples of drug actions which do not support this hypothesis (Starke, 1972; McCulloch *et al.*, 1972): certain $\alpha$-receptor stimulants can reduce NorE release at concentrations lower than those affecting the effector cells, and $\alpha$-blockers can increase NorE release at concentrations which do not cause postsynaptic blockade.
2. It is possible that the release of prostaglandins $E_1$ and $E_2$ ($PGE_1$ and $PGE_2$) during sympathetic nerve activity results in local feedback inhibition of NorE release (see Stjärne, 1973; Bergström *et al.*, 1973). The release of NorE from cat spleen is reduced by exogenous PGEs, and PBZ blocks the output of $PGE_2$ from dog spleen, at the same time increasing the output of NorE (Davies *et al.*, 1968). It is not yet known whether the PGEs are liberated in response to NorE action on postsynaptic receptors or originate presynaptically in the sympathetic terminals.
3. The $\alpha$-receptors mediating the local feedback inhibition may be situated on the sympathetic terminals (see Stjärne, 1973; McCulloch *et al.*, 1972). Thus the NorE released during sympathetic nerve stimulation activates the $\alpha$-receptors on the terminals,

causing an autoinhibition of further release, which is disrupted by $\alpha$-blocking agents.

Stärne (1973) studied the possibility that the prostaglandin-mediated and the $\alpha$-adrenoceptor mechanisms might be coupled, postulating that locally formed PGE might be the chemical mediator of the control system triggered by $\alpha$-receptors. He found that inhibition of prostaglandin synthesis did not prevent the enhancement by phentolamine of stimulation-induced release of tritiated NorE or its depression by the $\alpha$-receptor stimulant methoxamine. The fact that substances acting on $\alpha$-receptors were still effective during severe depression of PG synthesis makes it unlikely that the $\alpha$-receptor feedback mechanism requires the mediation of PGE.

A similar type of feedback inhibition mediated by adrenergic receptors seems to operate on release of acetylcholine from postganglionic parasympathetic terminals in the heart (Starke, 1972) and from preganglionic sympathetic terminals (Nishi, 1970).

*b. Actions on Autonomic Ganglia.* De Groat and Volle (1966*a,b*) found that epinephrine or NorE injected intraarterially in the cat superior cervical ganglion had inhibitory actions on ganglionic transmission, which dihydroergotamine blocked, unmasking a facilitation which was also seen with isoprenaline alone. The facilitation could be blocked by $\beta$-adrenergic antagonists. Facilitation of ganglionic transmission was associated with ganglionic depolarization, and inhibition with hyperpolarization.

However, there seems to be no evidence that adrenergic blocking agents can affect ganglionic transmission, and it appears that catecholamines do not have a physiological modulatory role in ganglionic transmission, at least in the superior cervical ganglion of the cat. For a more detailed review of the topics in this section, see Willems (1972).

### *4. Metabolic Effects of Ergot Derivatives*

*a. Antagonism of Catecholamine-Induced Hyperglycemia.* A striking and somewhat paradoxical effect of some ergot derivatives is their ability to inhibit epinephrine-induced hyperglycemia. The paradox is in the fact that although the drugs in question are considered to be mainly $\alpha$-adrenergic receptor blockers, their action on this response is shared by $\beta$-blocking agents such as dichloroisoprenaline (Northrop and Parks, 1964), while other $\alpha$-blockers have only weak inhibitory effects (Harvey *et al.*, 1951). Harvey *et al.* reported a lack of correlation between the antihyperglycemic actions of ergot derivatives and their abilities to inhibit pressor responses to epinephrine. The mechanism of the effects was elucidated to some extent when it was found that ergotamine blocked the

epinephrine-induced formation of cyclic AMP in liver homogenates (Murad *et al.*, 1962) and the activation of liver phosphorylase by epinephrine (Hornbrook and Brody, 1963). Dihydroergotamine is also said to block the hyperglycemic action of cyclic AMP (Northrop and Parks, 1964), but this finding has been disputed (Gothelf and Ellis, 1972).

Chan and Ellis (1969) found that at low doses of dihydroergotamine the blockade of the epinephrine-induced increase in glucose output from liver slices seemed to be competitive, and cyclic AMP effects were not blocked. At the higher concentration needed to block both epinephrine and cyclic AMP effects, the blockade was noncompetitive. It thus seems that the drugs can act in two ways on the hyperglycemic response to epinephrine; with ergotamine and with low doses of dihydroergotamine a competitive block of adrenergic receptors prevents the activation of cyclic AMP, and higher doses of dihydroergotamine exert a noncompetitive action subsequent to the formation of cyclic AMP which prevents the activation of liver phosphorylase.

A large fraction of the hyperglycemic response to epinephrine in intact animals is due to the activation of a central mechanism influencing blood glucose levels, apparently mediated by neurons in the medulla oblongata which are sensitive to epinephrine (Rosenberg and DiStefano, 1962; Ezdinli *et al.*, 1968). Some of the *in vivo* actions of ergot derivatives may thus be due to interference with this mechanism. Those derivatives which have centrally mediated sympathomimetic effects induce hyperglycemia as part of the syndrome (Cerletti, 1959), and it seems possible that the derivatives which reduce central sympathetic tone (e.g., dihydroergotamine; *cf.* Section IIIA2b) may have an opposite effect.

*b. Actions of Ergot Derivatives on Lipid Metabolism.* The first reports of the ability of catecholamines to induce lipolysis in adipose tissue were closely followed by attempts to block this action, using ergot alkaloids, particularly ergotamine and dihydroergotamine, and other $\alpha$- and $\beta$-blocking agents, in order to define the receptors involved. Most of the work has been carried out on rats or dogs.

In rats, ergotamine can reduce the physiological mobilization of fat caused by fasting, but only if the adrenals are removed, possibly because in intact animals the lipolytic action of corticosteroids can overcome the blocking action of ergotamine. Dihydroergotamine is able to inhibit the release of free fatty acids (FFA) from adipose tissue caused by catecholamines and also by other agents including ACTH, theophylline, and dibutyryl cyclic AMP. Dihydroergotamine in low doses also has a lipolytic action of its own, causing increased accumulation of cyclic AMP, and its effect is potentiated in the presence of growth hormone and dexamethasone or of theophylline. In low doses, it can also potentiate the effect of

dibutyryl cyclic AMP (for references, see Himms-Hagen, 1970; Fain, 1973).

In dogs, ergotamine reduces the resting plasma levels of FFA and inhibits the epinephrine-induced rise in FFA, but not that caused by fasting (see Himms-Hagen, 1970). The lipolytic action of dihydroergotamine is greater than in rats. However, in isolated perfused dog adipose tissue, dihydroergotamine and phentolamine have no lipomobilizing effects of their own, but potentiated the release of FFA and glycerol following stimulation of the sympathetic innervation of the tissue. They reduce the latency of the onset of release and increase the output of FFA and glycerol, the effect being more marked at higher stimulation rates (Fredholm and Rosell, 1968). It thus appears that the lipolytic effect of low doses of dihydroergotamine may be due to blockade of an $\alpha$-adrenergic inhibitory influence on the lipolytic mechanism; this could be mediated by inhibitory $\alpha$-receptors either on the fat cells themselves (Himms-Hagen, 1970) or on the sympathetic terminals—if feedback inhibition of transmitter release were blocked, the increased release of NorE would cause increased lipolysis. A third possible explanation of the effects of dihydroergotamine on lipolysis is derived from its actions on adenyl cyclase and phosphodiesterase. Catecholamine-induced stimulation of adenyl cyclase is blocked by the drug, thus preventing the catecholamine-induced lipolysis mediated by increased cyclic AMP formation. The lipolytic action of dihydroergotamine and its potentiation of the lipolytic actions of other drugs are ascribed to inhibition of phosphodiesterase, thus decreasing the catabolism of cyclic AMP and elevating its levels (Fain, 1973; Iwangoff and Enz, 1972).

High doses of dihydroergotamine cause a "nonspecific" reduction of lipolysis induced by several agents, indicating an action subsequent to the formation of cyclic AMP (*cf.* its action on hyperglycemia responses). It has been suggested that the drug may act by inhibiting the lipase activated by cyclic AMP (Nakano *et al.*, 1969).

Obviously, the effects of ergot alkaloids on lipid metabolism are complex, and more detailed study is needed to establish which of the possible modes of action are involved.

## B. Central Effects of Ergot Derivatives

### *1. Introduction*

In the CNS, as in the periphery, ergot derivatives have a multiplicity of actions. Different alkaloids can have opposite actions, and some have different actions at different doses. Although it is probable that most or all

of the effects are due to interactions with monoaminergic neuron systems, the variety of possible interactions has generally made it much more difficult in the CNS than in the periphery to ascribe effects to a particular mode of action. Receptors for NorE, 5-HT, and DA have been reported to be either stimulated or blocked by ergot derivatives, and since often two or more neuron systems containing different monoamines innervate areas in which the drugs appear to act, the interpretation of experimental findings can be difficult.

Among the central actions of these compounds are effects on behavior, including psychotomimetic, excitatory, and sedative actions; on central autonomic control; on respiration; on thermoregulation; and on neuroendocrine control of prolactin and gonadotropin secretion. Many of the drugs have emetic actions exerted via the CNS.

The psychotomimetic effect of some of the lysergic acid derivatives is one their most prominent central actions; however, many derivatives are inactive in this respect, and often sedative effects are seen (Yui and Takeo, 1958; Isbell *et al.*, 1959; Isbell and Gorodetsky, 1965). The psychotomimetic effects of lysergic acid derivatives, and in particular of LSD, the most potent, have been the subject of many reviews (Evarts, 1957; Purpura, 1957; Rothlin, 1957; Cerletti, 1959; Eiduson *et al.*, 1964; Cohen, 1967; Hoffer and Osmond, 1967; Freedman, 1963, 1969; Brawley and Duffield, 1972; Aghajanian, 1972*a*). Only a relatively brief discussion is possible here, and further details of less recent studies may be found via these reviews.

The psychotomimetic actions of LSD and related agents are characterized in man by excitation, mood changes, perceptual disturbances, hallucinations (particularly visual ones), depersonalization, and behavior which has some similarities to "psychotic" behavior.

### 2. *Biochemical Effects of Psychotomimetic Lysergic Acid Derivatives*

The psychotomimetic properties of LSD can be related to certain of its biochemical effects. The principal change appears to be in the metabolism of 5-HT in the brain. Although high doses of LSD have usually been used in order to produce detectable changes, it has recently been shown that changes in 5-HT levels occur after doses as low as 25 $\mu$g/kg (King *et al.*, 1972). After LSD, the turnover rate of 5-HT is reduced (Lin *et al.*, 1969; Freedman *et al.*, 1970), and 5-HT synthesis from tryptophan is reduced, although total 5-HT synthesis is not changed (Shields and Eccleston, 1973). The fall in 5-HT synthesis is probably a consequence of reduced synthesis of 5-HTP from tryptophan (Carlsson and Lindqvist, 1972). The fraction of 5-HT affected by LSD is thought to represent a small functional pool which can be released by nerve impulses (Shields and Eccleston, 1973).

Katz and Kopin (1969) also found that LSD selectively inhibited the release of 5-HT induced by electrical stimulation of rat brain slices. Since the slices were from brain areas without 5-HT-containing cell bodies, this effect was probably due to an action on the 5-HT terminals. However, only high concentrations of LSD were effective.

In contrast with 5-HT, levels of NorE fall and NorE turnover is increased (Freedman, 1963). The rise in 5-HT levels occurs mainly in the pons and medulla, and the fall in NorE is most marked in the cerebral hemispheres (I. L. Martin, personal communication).

Using the fluorescence histochemical technique, Andén *et al.* (1968) found that in high doses LSD reduces the turnover of 5-HT and increases that of NorE in terminals containing the amines: the disappearance of 5-HT from terminals after inhibition of tryptophan hydroxylase is markedly retarded by LSD, while the disappearance of NorE after inhibition of tyrosine hydroxylase is accelerated.

### *3. Behavioral and Central Physiological Effects of Ergot Derivatives*

Many attempts have been made to identify relationships between the hallucinogenic effects of LSD and related drugs and other behavioral and physiological effects which are more susceptible to analysis.

*a. Effects on Arousal and Sleep.* Cerletti (1959) showed that the psychotomimetic effects of different lysergic acid derivatives vary in parallel with a variety of sympathomimetic effects, including piloerection, tachycardia, hyperglycemia, and hyperthermia, and he considered that this pattern of central sympathetic stimulation is one of the major factors determining psychotomimetic properties. The active compounds also cause increased behavioral and reflex responses to sensory stimuli. Sensory thresholds are reduced, although primary sensory responses in specific cortical areas are not increased, and may be reduced. The EEG shows arousal patterns, and sleep is reduced. Habituation to repetitive stimuli is abolished; the control of attention by the filtering and integration of sensory input is impaired, and the functioning of all the senses is disturbed.

The increases in arousal levels and responsiveness to stimuli after LSD appear to be due to an action in the reticular formation of the lower brain stem, facilitating the input to this area from sensory collaterals (see Key, 1965*a,b*; Brawley and Duffield, 1972). The action does not appear to be on the sensory collaterals themselves, but on the processes regulating the level of significance of the information; these processes appear to be involved in sensory habituation, and when they are disrupted the filtering out of irrelevant stimuli fails, reducing sensory and arousal thresholds. The particular neurons which control these functions are not yet known with certainty, but

it seems probable that the serotonin-containing cells of the raphe at least impinge on the process. Treatment of animals with *p*-chlorophenylalanine (PCPA), which inhibits 5-HT synthesis, or surgical destruction of raphe neurons has some effects similar to those of LSD, including reduction of sleep (both slow-wave and REM), induction of continuous pontogeniculooccipital (PGO) spiking, inhibition of habituation, and increased irritability (for review, see Jouvet, 1972).

Studies of the interactions of LSD with drugs or treatments which alter brain monoamine levels have also provided evidence that the effects of LSD involve monoaminergic neurons. Pretreatment of rats or mice with reserpine or tetrabenazine, which deplete both 5-HT and catecholamines, or with PCPA, which depletes 5-HT relatively selectively, enhanced the sensitivity of the animals to LSD (Appel and Freedman, 1964; Appel *et al.*, 1970*a*; Gessner, 1970). Lesions in the midbrain raphe which selectively reduced brain 5-HT concentrations also enhanced the sensitivity of rats to subthreshold doses of LSD (Appel *et al.*, 1970*b*). Furthermore, treatment with 5-HTP has been found to reduce the tremorogenic effect of LSD in mice (Gessner, 1970). Although a single dose of $\alpha$-methyl-*p*-tyrosine (AMPT) apparently did not affect the action of LSD in rats (Appel *et al.*, 1970*a*), pretreatment with AMPT for 24 hr did attenuate the behavioral actions but not the hyperthermic actions of LSD in rabbits (Horita and Hamilton, 1973). It is possible that in the experiments of Appel *et al.* (1970*a*) the brain catecholamines were not effectively depleted. The administration of L-DOPA to AMPT-treated rabbits restored the behavioral actions of LSD (Horita and Hamilton, 1973). It thus appears that the actions of LSD are exerted in some way counter to the physiological functions of 5-HT, and possibly in synergism with those of NorE or DA.

It seems probable that many of the effects of LSD are due to impairment of the functional roles of the 5-HT-containing raphe neurons. Aghajanian and coworkers have shown that LSD administered intravenously or directly to raphe neurons by microiontophoresis causes a marked inhibition of the activity of these cells, which are also inhibited by iontophoretically applied 5-HT (Haigler and Aghajanian, 1972; Aghajanian *et al.*, 1972). This finding offers an explanation of the biochemical and histochemical observations described earlier that LSD reduces 5-HT turnover in the brain. The inhibition of the release of 5-HT from terminals in brain slices has already been described in Section IIIB2. Also, the postsynaptic actions of 5-HT released from the terminals of raphe and other 5-HT-containing neurons might be blocked by LSD. Evidence for a block of the excitatory actions of 5-HT by LSD has been obtained by Roberts and Straughan (1967), Boakes *et al.* (1970), and Couch (1970). Couch found that LSD

simultaneously blocked the excitations evoked synaptically by stimulation of a region which contains 5-HT cell bodies and the excitations evoked by iontophoretically applied 5-HT. Certain methylated tryptamine derivatives with LSD-like behavioral effects also selectively antagonized 5-HT excitations of neurons in the reticular formation of the pons and medulla (Bradley and Briggs, 1974). It thus seems that hallucinogens can reduce the activity of raphe neurons by a direct action, can reduce the release of 5-HT from neurons, and also can antagonize the postsynaptic excitatory actions of 5-HT. All these actions would lead to a reduction of the influence of raphe cells on other systems.

The reduction of both slow-wave sleep (SWS) and rapid eye movement (REM) sleep by LSD and by methysergide (Stern *et al.*, 1972; Tabushi and Himwich, 1971) is probably also closely related to these actions. The mechanisms of induction and maintenance of sleep are controlled at least partly by 5-HT- and NorE containing neurons; 5-HT seems to be associated primarily with the control of SWS and the "priming" of REM sleep, whereas the catecholamines appear to be involved in tonic mechanisms concerned with arousal and REM sleep (for review, see Jouvet, 1972).

SWS appears to be induced by an inhibitory influence of structures in the lower pons and medulla on more rostal activating areas. The inhibitory mechanisms seem to be situated in the caudal pontine and medullary reticular formation, the nucleus tractus solitarius (NTS), and the area postrema. The area postrema appears to act as a "gain control" regulating the NTS. It has been suggested (Koella, 1969; Bronzino, 1972; Bronzino *et al.*, 1972) that 5-HT, acting via the area postrema, can facilitate the excitability of the NTS; the most significant projections of the NTS are to the medullary reticular formation (Morest, 1967), which exerts a strong inhibitory influence on the EEG-desynchronizing mechanisms (Jouvet, 1972; Bolme *et al.*, 1972). The extensive projections of the raphe neurons to the midbrain and forebrain, including the locus coeruleus, hypothalamus, and hippocampus, also appear to be important in the control of sleep and arousal (Jouvet, 1972; Morgane and Stern, 1972; Mabry and Campbell, 1973).

Mechanisms in the pons and medulla are also involved in the regulation of REM sleep. The pontine raphe nuclei appear to have a "REM-sleep-priming"role, acting on the NorE-containing neurons of the locus coeruleus which maintain the state of REM sleep (Jouvet, 1972).

Clearly, these systems could be affected by LSD and methysergide at several points; the antagonism of 5-HT excitations of single neurons in the medulla and pons (Boakes *et al.*, 1970) and pontine raphe (Couch, 1970)

and the direct inhibitory action of LSD on midbrain raphe neurons (Aghajanian *et al.*, 1972) have already been described, while the area postrema, the NTS, and the locus coeruleus might also be involved in the effects of these drugs on sleep.

Another aspect of sleep which is affected by LSD and methysergide is the phenomenon of PGO spiking. These waves can be recorded from the pons, lateral geniculate nucleus, and occipital cortex and from certain other areas; they normally occur mainly in association with REM sleep episodes and are strongly correlated with the eye movements of this state. The PGO waves appear to be under the control of a noradrenergic "pacemaker" in the dorsolateral pontine tegmentum, probably the medial part of the locus coeruleus (Jovet, 1972). The PGO pacemaker appears to be subject to an inhibitory serotoninergic influence, since administration of PCPA, or lesions of the raphe, can induce PGO waves outside REM sleep which are suppressed by 5-HTP (Jouvet, 1972). LSD also induces PGO spikes outside REM sleep; this action is not shared by methysergide or BOL (Stern *et al.*, 1972; Monachon *et al.*, 1972). Reserpine induces PGO spiking during SWS and waking, and, somewhat paradoxically, LSD and methysergide counteract this effect of reserpine (Jouvet, 1972; Monachon *et al.*, 1972).

A reduction of the serotoninergic inhibitory influence on the pacemaker by LSD would account for its facilitatory action on PGO spiking, and this effect could be achieved by the mechanisms already discussed in relation to the sleep states. The contrasting effect of LSD in reducing PGO spikes in reserpinized animals is difficult to explain in the same terms. Possibly the mechanism depends on a balance of opposing influences which may be altered by LSD in opposite directions in reserpine-treated and nontreated animals.

Other actions of LSD and related compounds have been suggested to be related to their psychotomimetic properties. These include suggestions of stimulation of 5-HT receptors (Aghajanian, 1972*a,b,c*; Andén *et al.*, 1968; Berridge and Prince, 1973), stimulation of NorE receptors or potentiation of the actions of NorE (Costa and Zetler, 1959), and inhibition of the release of an unknown transmitter (Tebëcis and Di Maria, 1972: see Section IIIB3b; Ambache *et al.*, 1973). The first of these receives most support as an alternative to the hypothesis described above, that LSD antagonizes the functions of serotoninergic neurons. In some mammalian peripheral organs and in some invertebrate test organs, LSD can stimulate 5-HT receptors. Andén *et al.* (1968) suggested that a stimulant action on 5-HT receptors could explain the facilitatory action of LSD on spinal extensor reflexes in acutely spinal rats. This effect was like that following combined nialamide and 5-HTP treatment, which presumably was due to increased 5-HT levels in the spinal cord. At the same time, LSD reduced

the turnover of 5-HT in terminals. This was attributed to a hypothetical inhibitory feedback loop activated by direct stimulation of 5-HT receptors, which reduces the activity of the 5-HT-containing neurons. Further evidence for this has been described by Aghajanian (1972*c*), who also attributes the LSD-induced reduction of firing of raphe neurons to an inhibitory feedback circuit, although he has also shown a direct inhibitory action of LSD on raphe neurons (Aghajanian *et al.*, 1972; Haigler and Aghajanian, 1972). A possible link in a feedback loop is the nonfluorescing neuron group in the anterior pole of the median raphe nucleus and the linearis caudalis nucleus. Neurons in this group receive 5-HT-containing terminals from the raphe, and following intravenous administration of LSD the firing of these is accelerated. This action is suggested to be due to the mimicking of an excitatory action of 5-HT on postsynaptic receptors on these neurons, which leads to compensatory inhibition of the raphe neurons (Aghajanian, 1972*c*). However, a reciprocal innervation of the raphe neurons by the neurons of the linearis caudalis nucleus has not yet been identified. Furthermore, the action of 5-HT on the latter neurons is not known, but no neurons in other areas studied appear to be excited by both 5-HT and LSD. Even if LSD does mimic 5-HT excitations of these neurons, the results of a study of four methylated derivatives of tryptamine, which have some 5-HT-mimicking actions (Bradley and Briggs, 1974), indicate that their LSD-like psychotomimetic properties are not related to their potencies in mimicking 5-HT excitations. Without more evidence, it is not possible to decide whether the feedback hypothesis is correct. At present, one reasonable alternative explanation is that the increased firing of linearis caudalis neurons after intravenous LSD is a consequence of the direct inhibition of raphe neurons by the drug.

*b. Actions of Ergot Derivatives in the Lateral Geniculate Nucleus.* Because of the prominencé of visual disturbances and hallucinations among the subjective effects of psychotomimetics in man, there have been a large number of studies of the actions of these drugs in the visual system. The earlier studies on this problem have been reviewed by Brawley and Duffield (1972) and Tebēcis and Di Maria (1972). LSD given by intracarotid injection depresses the transmission of optic nerve impulses through the lateral geniculate nucleus (LGN). At present, the transmitter released from optic nerve terminals is unidentified, and the mechanism of action of LSD is unexplained. Tebēcis and Di Maria (1972) reinvestigated the effects of iontophoretically applied monoamines and LSD on spontaneous and evoked activity in the LGN of the cat. With low ejecting currents, 5-HT depressed spontaneous activity and orthodromic activation of LGN neurons by light or optic nerve stimulation, but affected firing evoked by ACh, glutamate, or aspartate, or by antidromic activation, only when

higher ejecting currents were used. The actions of LSD were similar to those of 5-HT but of longer duration. The authors supported the hypothesis that 5-HT and LSD either blocked the release of the optic nerve transmitter or prevented its access to receptors on the LGN neurons. Higher concentrations of both agents had direct depressant actions on the LGN neurons, which were suggested to be mediated by 5-HT receptors. Horn and McKay (1973) studied the effects of intravenous LSD (25–300 $\mu$g per cat) on LGN neurons and found that spontaneous activity was generally depressed, although some cells were excited, particularly by the lower doses tested; responses to photic stimuli delivered to the center and surround regions of the receptive fields were also depressed. The size and shape of receptive fields did not change. BOL did not have effects like those of LSD. The changes in spontaneous activity caused by LSD were not correlated with changes in the responses to stimuli, and it seems that at the doses used LSD had no direct uniform depressant effect on the neurons. An indirect depressant action mediated via the reticular formation was considered possible.

Although the significance of these effects for the psychotomimetic actions of LSD is uncertain, they offer a possible explanation of the decreased photosensitivity of the baboon *Papio papio* observed after administration of LSD and other lysergic acid derivatives, including nonpsychotomimetic ones (Walter *et al.*, 1971; Meldrum and Naquet, 1971; Vuillon-Cacciuttolo and Balzano, 1972). The reduction of photically evoked epileptic responses in these animals appeared to be related to a depression of evoked responses in the LGN and visual cortex. The effects were not related to the psychotomimetic potencies of the drugs.

*c. Actions on the Nigrostriatal DA System.* Stone (1973) found that 1–2 mg/kg agroclavine in rats caused sedation and stereotyped sniffing and gnawing, while higher doses (5–10 mg/kg) induced transient sedation followed by hypermotility, excitation, and aggression. He considered that the stereotyped movements were similar to those observed with drugs such as apomorphine which are thought to stimulate DA receptors in the basal ganglia, and suggested that agroclavine had a similar mode of action. Support for this idea was provided by Corrodi *et al.*, (1973), who compared ergocornine and 2-bromo-$\alpha$-ergokryptine (CB-154) with apomorphine in rats with unilateral lesions induced by 6-hydroxydopamine in the substantia nigra. All three drugs caused stereotyped sniffing and gnawing and rotation of the animals toward the unlesioned side. Pimozide, which blocks DA receptors, blocked these effects, and Corrodi *et al.* (1973) proposed that the drugs all act by stimulation of DA receptors. However, it seems difficult to reconcile a direct action of the ergot alkaloids on DA receptors with the observation of Corrodi *et al.* (1973) that after pretreatment with reserpine

and AMPT the effects of the two derivatives were greatly reduced, unlike those of apomorphine, which were increased by this pretreatment. The effects of the ergot alkaloids thus seem to be mediated at least partly by the release of DA from DA-containing neurons, or by a potentiation of the effect of DA. The action of DA on receptors has been suggested to be due to the activation of adenyl cyclase, leading to increased cyclic AMP formation (Kebabian and Greengard, 1971). The enzyme which catabolizes cyclic AMP, phosphodiesterase, has been found by Iwangoff and Enz (1972) to be strongly inhibited by dihydrogenated ergot alkaloids in homogenates of cat brain gray matter. This enzyme appears to be localized predominantly in dendrites, immediately adjacent to subsynaptic membranes, possibly indicating a role related to the action of transmitters (Florendo *et al.*, 1971). If the two derivatives used by Corrodi *et al.* (1973) also inhibit phosphodiesterase, then the retardation of the catabolism of cyclic AMP would potentiate the effects of stimulation of adenyl cyclase by DA. Corrodi *et al.* (1973) also found that NorE levels were reduced and 5-HT levels increased by the two derivatives, as with LSD (Andén *et al.*, 1968), and attributed these effects to block of NorE receptors and stimulation of 5-HT receptors, respectively. In view of the results of Corrodi *et al.* (1973), it is possible that some of the effects of lysergic acid derivatives on arousal (see Section IIIB3a) might be mediated by the nigrostriatal DA neurons, which may have a role in the control of behavioral arousal (Jouvet, 1972).

*d. Actions on Spinal Reflexes.* The facilitatory action of LSD on spinal extensor reflexes (Andén, *et al.*, 1968) has been described in Section IIIB3a. Andén *et al.* considered it to be due to stimulation of 5-HT receptors by LSD. Methysergide and BOL did not have effects like those of LSD.

The effects of LSD, methysergide, and BOL on the bulbospinal influences on spinal reflexes have been discussed in a review by Anderson (1972). Administration of 5-HTP, tryptophan, or monoamine oxidase inhibitors to acutely spinalized rats causes a slowly developing but marked increase in monosynaptic spike size, a decrease in latency of the reflex, and spontaneous ventral root discharges, indicating increased excitability of $\alpha$-motoneurons. At the same time, the reflex response recorded from an adjacent dorsal root is depressed. LSD, methysergide, and BOL, and other structurally unrelated 5-HT antagonists, can rapidly reverse the facilitatory effect of 5-HTP but not the depression of the dorsal root reflex. The effects of 5-HTP are thought to be exerted via 5-HT-containing nerve terminals which appear to increase motoneuron excitability. This idea receives support from work of Barasi and Roberts (1973), who found that stimulation of the rat hindbrain in the region of the raphe facilitated the monosynaptic reflex and that the facilitation was potentiated by intravenous injection of

tryptophan. Both the facilitation and its potentiation by tryptophan were blocked by intravenous LSD or cinanserin. In other experiments, negative field potentials elicited in the motoneuron pool by dorsal root stimulation were increased in amplitude by iontophoretic application of 5-HT, and by hindbrain stimulation; iontophoretic application of methysergide or cinanserin prevented the effect of hindbrain stimulation on the size of the potential. The hindbrain stimulation was associated with depolarization of spinal motoneurons, and these workers proposed the existence of an excitatory 5-HT synapse in the ventral horn, possibly on the motoneurons. However, Anderson and coworkers (see Anderson, 1972) found that stimulation of the raphe region of the pons and medulla could cause either potentiation or inhibition of the monosynaptic reflex; only the depressant effects were reduced by LSD, methysergide, and BOL. This discrepancy may be due to species or dosage differences.

*e. Effects in the Cerebral Cortex.* The desynchronizing effects of certain ergot derivatives on the activity of the cerebral cortex are now generally thought to be caused indirectly by actions in other areas, especially the lower brain stem (see Evarts, 1957; Purpura, 1957; Brawley and Duffield, 1972; and Sections IIIB3a and IIIB3c of this chapter). However, direct actions of these drugs on the cortex have been described. Krnjević and Phillis (1963) found that LSD, ergometrine, methylergometrine, methysergide, and 12-hydroxyergometrine could all affect cortical single-unit activity when applied iontophoretically, but the specificity of the effects is uncertain. Roberts and Straughan (1967) found that lysergic acid derivatives (LSD, methysergide, and BOL) depressed neuronal firing rates and spike amplitudes, and also preferentially antagonized 5-HT excitatory effects on single neurons. LSD was the most potent of the three in this respect. Davidson *et al.* (1969) found that somatosensory evoked potentials in the cortex were reduced by NorE topically applied to the same cortical area. This inhibitory effect of NorE was antagonized by LSD and by agroclavine, also applied topically. Somatosensory evoked potentials in the cortex were found by Samanin *et al.* (1972) to be inhibited by stimulation of the midbrain raphe area in rats. LSD potentiated the inhibitory effect of raphe stimulation. This finding seems to support the hypothesis that LSD can either potentiate the actions of 5-HT released from raphe neuron terminals or activate 5-HT receptors directly.

*f. Emetic Actions of Ergot Derivatives.* Many of the ergot derivatives have emetic activity. Wang and coworkers (see Wang, 1965) found that the site of action of dihydroergotoxine was in a "chemoreceptive emetic trigger zone" situated in the area postrema. A mode of action involving blockade of $\alpha$-adrenergic receptors was suggested. Fuxe and Owman (1965) considered the monoamine-containing neurons of the area

postrema to be important in the emetic reflex, and the projection of the area postrema to the nucleus tractus solitarius (Morest, 1967) has been proposed as another link in the reflex.

*g. Effects on Respiration.* It was demonstrated very early that ergot derivatives can depress or stimulate respiration (Barger, 1931; Horita and Dille, 1954), but there has been little further study of these actions. However, recent studies on respiratory control may help to explain the effects, although only speculation is possible at present. Bolme and Fuxe (1973) have postulated that there is a central noradrenergic inhibitory influence on respiration and suggested that the locus coeruleus might have a pneumotaxic role mediated via neurons in the nucleus tractus solitarius (NTS). An alternative or additional mechanism has been proposed by Ylitalo *et al.* (1970), who suggested that 5-HT-containing neurons in the area postrema, projecting to the NTS, are also involved in respiratory depression. If the existence of these mechanisms is substantiated, then the ability of ergot derivatives to act on NorE or 5-HT receptors is a possible explanation of their effects on respiration. A study of their interactions with monoamines on the medullary neurons controlling respiration would be of interest.

*4. Effects of Ergot Derivatives on Neuroendocrine Functions.*

Certain of the ergot derivatives have been known for some time to affect processes regulating reproduction and lactation; recently, these actions have been the subject of a considerable amount of research, and the ergot drugs have proved to be useful tools in the investigation of the regulation of secretion and functions of prolactin, one of the hormones involved in the control of these processes.

*a. Control of Prolactin Secretion.* Meites and Clemens (1972) and Meites *et al.* (1972) have reviewed recent work on prolactin, including studies of the inhibitory actions of ergot derivatives on the secretion of this hormone, and as only a brief account it is possible here, these reviews should be consulted for further information.

The secretion of prolactin (P) from the anterior pituitary is controlled by the hypothalamus, which in mammals secretes a prolactin-release inhibiting factor (PIF) into the pituitary portal circulation. A prolactin releasing factor (PRF) is also thought to play a role. The secretion of PIF is regulated by hypothalamic monoaminergic neurons, in particular dopamine (DA) containing neurons with cell bodies in the arcuate nuclei projecting to the external layer of the median eminence (see McCann *et al.*, 1972; Porter *et al.*, 1972; Hökfelt and Fuxe, 1972*a,b*; Björklund *et al.*, 1973; Björklund and Nobin, 1973). Increased activity in these DA neurons induces increased

PIF secretion and a fall in pituitary P release. NorE also inhibits P release but is much less potent than DA, where as 5-HT appears to stimulate P release. The DA-containing neurons seem to form part of the feedback mechanism by which plasma P levels influence the rate of release of further P. The activity of the neurons varies during the ovarian cycle; it increases markedly when plasma P levels are high, for example, during lactation or early pregnancy (Hökfelt and Fuxe, 1972*a,b*). The functions of NorE and 5-HT in this system are less well understood, but they may include the maintenance of basal release of P and the control of diurnal variations in its secretion. The mechanisms inducing release of P are not at present understood; there is preliminary evidence in some species that thyrotropin releasing factor (TRF) has high P releasing activity and may serve to regulate release of both thyrotropin and prolactin.

The results of iontophoretic studies of the actions of monoamines on hypothalamic neurons are so far difficult to relate to this system.

*b. Inhibitory Effects of Ergot Derivatives on Prolactin Secretion.* The derivatives which cause reductions in secretion of P have diverse structures; compounds with variations in both the ring system and the side-chain are active, but slight alterations in structure can cause marked differences in potency. Among the active compounds are ergokryptine, ergocornine, their dihydrogenated derivatives, 2-bromo-$\alpha$-ergokryptine, ergometrine, ergotamine, LSD, agroclavine, elymoclavine, and other synthetic ergoline derivatives; inactive compounds include lysergic acid, ergocorninine, and compounds with substituents on $N_1$. Variations in the peptide side-chain of the compounds can cause differences in potency, so it appears that this part of the molecule influences the activity, but an elaborate side-chain is not essential, since agroclavine, for example, is active with only a methyl group in the corresponding position (for references, see Meites and Clemens, 1972).

The inhibitory action of these drugs on P release seems to be exerted in two ways: they act on the hypothalamus to increase synthesis and release of PIF, which then affects pituitary P release, and they also act directly on the pituitary, apparently blocking the P release mechanism without affecting P synthesis, since the number of P granules in the pituitary cells increases. The mechanisms of action underlying these effects are not clear, but it seems likely that the hypothalamic actions involve a stimulation of the DA receptors which increase PIF secretion (Hökfelt and Fuxe, 1972*a*) (*cf.* Section IIIB3c).

The direct actions on pituitary release of P are at present difficult to explain. It has not been possible to demonstrate the presence of monoamines in the hypophyseal portal blood, and infusions of monoamines into the anterior pituitary via the portal vessels have no effect on the

secretion of P or of LH or FSH (for references, see McCann *et al.*, 1972); it thus seems that monoamines in portal blood do not affect hypophyseal cells, but the presence of monoamines in many cells of the adenohypophysis (Björklund and Falck, 1969) leads to the suggestion that the effects of ergot derivatives may be related in some way to these cells.

*c. Effects of Ergot Derivatives Mediated by Inhibition of Prolactin Secretion.* Since the demonstration that ergot derivatives inhibit P release, they have been used in the study of the processes in which P has regulatory functions.

Certain ergot derivatives prevent the rapid increase in P secretion during proestrus, estrus, and metestrus and inhibit the involution of corpora lutea during the ovarian cycle; corpora lutea therefore accumulate in the ovaries. On the other hand, when given to rats in early pregnancy, the drugs prevent the rise in prolactin secretion which normally occurs at this time; the corpora lutea then undergo involution, thus terminating the secretion of progesterone by the ovaries and preventing normal implantation of the ova. The animals then return to the estrous state, and ovulation recurs, usually followed by pseudopregnancy. These drug effects in early pregnancy resemble those produced by surgical removal of active corpora lutea and can be counteracted by administration of progesterone or P. These effects indicate that P has a dual function with respect to rat corpora lutea: it is important for maintenance of active corpora and secretion of progesterone in early pregnancy, but in cyclic rats luteolysis is dependent on the action of P. Although the ergot derivatives suppress the normal changes in P secretion, the estrus cycle itself is not altered and ovulation is not blocked (Wuttke *et al.*, 1971); it thus seems that P is of slight importance in this respect.

Daily administration of ergot derivatives to rats during the second half of pregnancy does not terminate pregnancy, although the animals do lose weight, a significant part of this being a fall in mammary gland weight. After parturition, lactation is significantly impaired, as judged by the rate of weight gain of the pups (Shaar and Clemens, 1972). In women, 2-bromo-$\alpha$-ergokryptine (CB-154) is highly effective in preventing puerperal lactation and breast engorgement, by suppressing the increase in P levels in the postpartum period. The drug also stops nonpuerperal galactorrhea in patients with high serum P levels (Del Pozo *et al.*, 1972) and galactorrhea induced by psychotropic drugs (see Daughaday and Jacobs, 1972).

It has been suggested (Flückiger and Wagner, 1968) that the inhibitory actions of ergot derivatives on fertility and lactation are achieved by actions on more than one mechanism, since ergocornine and 2-bromo-$\alpha$-ergokryptine have differential actions on the two processes; the latter drug is significantly more selective in preventing pregnancy.

In rodents, some ergot derivatives cause an inhibition of the growth of mammary and pituitary tumors, which is probably mediated by their effect on P secretion. It has been suggested that this action may be clinically valuable in the treatment of mammary tumors in women, but in a trial of 2-bromo-$\alpha$-ergokryptine in 19 women with advanced tumors no objective remissions were observed (European Breast Cancer Group, 1972). However, Stoll (1972) did find regression of mammary tumors in several patients treated with a combination of L-DOPA and estrogen, which is also supposed to act by inhibition of P secretion. Further work in this field is obviously desirable; treatment at an earlier stage might prove more effective.

In nonmammalian vertebrates, P is the most important hormone in osmoregulation, but until recently there was little evidence of such a function in mammals. Richardson (1973) found that chronic administration of 2-bromo-$\alpha$-ergokryptine to rats reduced the incidence of spontaneous nephrosis, decreased urinary $Ca^{2+}$ and specific gravity, and increased the daily volume of urine as well as its *p*H and its $Na^+$ and $K^+$ content. He suggests that these findings support a possible role of P in the control of electrolyte and water balance in rats.

*d. Effects of Ergot Derivatives on Gonadotropin Secretion.* Relatively high doses of the derivatives which inhibit the release of P can also alter the secretion of LH and FSH (Meites *et al.*, 1972). The release of these hormones is regulated by a releasing hormone (one hormone appears to control both FSH and LH; Schally *et al.*, 1973), which is itself controlled by monoaminergic neurons in the median eminence. The work of some groups indicates that DA neurons in this area have a facilitatory role in FRF/LRF release, whereas others suggest that their role is inhibitory. Serotonin appears to have an inhibitory effect on gonadotropin release (for references, see McCann *et al.*, 1972; Hökfelt and Fuxe, 1972*a,b*).

Ergot derivatives do not affect spontaneous ovulation in adult rodents, but it has been found that ovulation induced in immature mice or rats by pregnant mare serum (PMS) gonadotropin is facilitated by 5-HT and inhibited by LSD, methysergide, ergocornine, and 2-bromo-$\alpha$-ergokryptine (see Brown, 1968; Hökfelt and Fuxe, 1972*a*). PMS-induced ovulation has been suggested as a model for the study of the neuroendocrine mechanisms controlling LH release during the critical period for ovulation. The actions of the ergot derivatives in this system are of uncertain mechanism, but it has been suggested that the effects are at least partly mediated indirectly by the increased activity of the tuberoinfundibular DA neurons resulting from the inhibition of P secretion. On the other hand, the inhibition of 5-HT synthesis by PCPA also inhibits PMS-induced ovulation, so the effects of

the drugs may thus be due to an antagonism of 5-HT or to reduced activity in a serotoninergic input to the hypothalamus.

Although the secretion of at least some other hypothalamic regulating hormones is also thought to be affected by the DA neurons in the median eminence, ergot derivatives do not seem to affect the production of other pituitary hormones, so far as is known. It thus seems that their main effect is on P secretion, and the effects on gonadotropins of high doses of the drugs are possibly due to feedback mechanisms influenced by P levels.

### 5. *Effects of Ergot Derivatives on Thermoregulation*

The effects of ergot derivatives on the regulation of body temperature depend on the type of alkaloid, the dose, the species, and especially in small animals, the ambient temperature. Shemano and Nickerson (1958) first established the importance of this factor and found that an inversion of the effect of drugs on body temperature usually occurred around a particular ambient temperature for each drug. Above this temperature hyperthermia occurred, and below it hypothermia. The inversion temperature for Hydergine, ergotamine, and LSD was 30°C, which is in the range of thermal neutrality for the rat. In this range, constant body temperature is maintained with minimal physiological control, and the observation that these drugs have an inversion temperature around 30°C suggests that in the rat the drugs induce poikilothermia by inhibition of the processes of thermoregulation in the CNS. In other species (cat, dog, and rabbit), LSD causes marked hyperthermia (Horita and Dille, 1954). Rothlin (1947, 1957) pointed out a parallelism between the hyperthermic responses to ergot derivatives and other central effects, including nausea, vomiting, and general excitation. This observation was extended by Cerletti (1959), who reported a parallelism between the pyretogenic effects of lysergic acid derivatives and the "central excitatory syndrome" (see Section IIIB3a), which itself paralleled the psychotogenic properties of the drugs in man. There is thus a relationship between the hyperthermic effects of the drugs in animals and their psychotomimetic effects in man, although a dissociation of the two effects is seen in, for example, BOL and 1-methylated derivatives of lysergic acid. Horita and Hamilton (1973) produced a pharmacological dissociation between the behavioral excitatory effects and the hyperthermic effects of LSD in rabbits by pretreating the animals with $\alpha$-methyl-*p*-tyrosine. This abolished the behavioral but not the hyperthermic effects of low doses of LSD. The latter effect thus did not appear to depend on catecholaminergic mechanisms.

The mechanisms controlling thermoregulation are at present poorly

understood. Both heat production and heat loss can be varied to accomplish body temperature changes; the control mechanisms have been suggested to be influenced by 5-HT, NorE, DA, ACh, and prostaglandins (for reviews, see Borison and Clark, 1967; Avery, 1972; Fuxe and Sjöqvist, 1972; Hellon, 1972; Lomax and Schönbaum, 1973).

In view of the known interactions of ergot derivatives with 5-HT, NorE, and DA neuron systems, it is not surprising that thermoregulation is disrupted by these drugs. As the roles of the monoamines in thermoregulation are still uncertain, it is not possible at present to identify the modes of actions of the drugs. Only LSD has been studied in any detail; it inhibits the 5-HT-containing neurons in the raphe which are activated when body temperature rises (Corrodi *et al.*, 1967; Simmonds, 1970; Weiss and Aghajanian, 1971), but so far the physiological role, if any, of the raphe neurons in thermoregulation is not known, and no conclusions can be drawn until both thermoregulatory control and the central actions of the drugs are better understood.

## IV. POISONING

Ergot alkaloids and their derivatives are highly toxic, and may cause acute or chronic poisoning. Acute poisonings by the ergot derivatives fall into two main types; one type results from attempts to procure abortion, another from the nonmedical abuse of LSD and related psychotomimetic ergot derivatives taken for their mental effects. Chronic poisoning by ergot alkaloids was formerly not uncommon; widespread epidemics occurred frequently during the Middle Ages (Barger, 1931; Bové 1970), due usually to ingestion of bread contaminated with ergot. This type of chronic poisoning is now rare, thanks to better quality control of grain and flour, but chronic poisoning by the pure alkaloids from ergot is not rare, as a result of the use of the drugs in migraine and obstetrics. Toxic effects may result either from repeated or prolonged ingestion of excessive doses of ergot derivatives or from normally therapeutic doses, apparently due to hypersensitivity to the drugs.

### A. Acute Poisoning

#### *1. Nonpsychotomimetic Derivatives*

The symptoms of acute poisoning by ergot or ergot alkaloids include tingling, itching, and coldness of the skin, thirst, vomiting, diarrhea,

confusion, and coma. Hemorrhage from the uterus and abortion may occur in pregnant women, but fatal poisoning may ensue in these cases without abortion taking place. The natural alkaloids are much more toxic than their dihydrogenated analogues (Rothlin, 1947).

### 2. *Psychotomimetic Derivatives*

The use of LSD and related agents as psychedelics has continued in spite of strong governmental measures against their illicit use. The complications of LSD use have been classified by Cohen (for reference, see Connell, 1972) into psychotic disorders, nonpsychotic disorders, and neurological reactions. The "psychotic" side-effects of LSD consist of schizophrenic-type reactions indistinguishable from paranoid, schizoaffective, or catatonic types of schizophrenia; paranoia; delusions; prolonged or recurrent LSD-like states; and psychotic depressions. "Nonpsychotic" reactions include chronic anxiety and acute panic. Neurological side-effects include epileptiform convulsions and EEG abnormalities. Some workers have suggested that LSD can precipitate psychosis in people without previous apparent disorder (Smart and Bateman, 1967), but other evidence suggests that persistent adverse reactions to LSD occur in predisposed individuals (Hollister, 1972). Díaz and Huttunen (1971) found that in rats given low doses of LSD daily for 1 month brain serotonin levels and turnover were increased, in contrast to the reduced turnover after acute doses of LSD. This change was considered to be persistent since the animals were not killed until 18 hr after the last dose of LSD, and the authors suggested that behavioral alterations among chronic users of the drug might be associated with similar persistent metabolic effects of LSD.

In 1967, it was suggested that there was a higher incidence of congenital abnormalities in the offspring of LSD users, and it has been found that, *in vitro*, LSD causes chromosome breakages in cultured cells. The possibility of genetic damage by LSD has been the subject of several reviews. Jacobson and Berlin (1972) considered that their findings did indicate that LSD taking was associated with teratogenic effects, although the ingestion of other illicit drugs, the presence of diseases, and marginal maternal nutrition precluded any definite conclusion with regard to the effect of LSD itself. Similar conclusions were reached by Dishotsky *et al.* (1971), Nichols (1972), and Long (1972), who considered that pure LSD in moderate amounts does not damage chromosomes *in vivo*, does not cause detectable genetic damage, and is not teratogenic or carcinogenic in man. When chromosome damage was found, it appeared to be related to extraneous factors associated with drug abuse, such as hepatitis, virus infections, and malnutrition, and not to LSD alone. A distinction was drawn

between pure and illicit LSD: use of the latter did seem to be associated with increased incidence of malformations and spontaneous abortions.

Another effect of LSD which may be significant for its use in humans was recently reported by Voss *et al.* (1973). *In vitro*, LSD appears to interfere with immunoglobulin synthesis by preventing tryptophan incorporation into protein molecules, either by terminating the peptide chain or by taking the place of tryptophan in the chain. It was therefore suggested that LSD could significantly interfere with antibody production. Lysergic acid also has this effect.

## B. Chronic Poisoning

The symptoms of chronic ergotism have been described graphically in the historical monograph by Barger (1931). Chronic ergot poisoning, whether a consequence of overdosage or of hypersensitivity, appears in two forms; the more common is characterized principally by circulatory changes, the other by nervous symptoms including convulsions.

### *1. Gangrenous Ergotism*

In gangrenous ergotism, intense vasoconstriction of arteries and veins and probably of lymph vessels occurs; the pulse often disappears in affected limbs; and the feet, legs, and sometimes the hands become cold, pale, and numb. Painful muscle cramps occur, and in severe cases gangrene and amputation of the limbs may result from the lack of circulation. Besides the vasoconstriction, hypercoagulability of the blood appears to develop (Cranley *et al.*, 1963), and thrombosis results in complete occlusion of the smaller arteries. Internal organs, as well as the limbs, can be affected: angina is aggravated by coronary vasoconstriction, gangrene of the bowel may follow constriction of the arterial supply, and renal failure may result from spasm of the renal arteries. The constriction of the renal arteries (Fedotin and Hartmann, 1970) has been suggested by Lewis and Lee (1972) to be a possible triggering factor in the postpartum renal failure sometimes associated with ergometrine. The fall in blood pressure in the kidney due to renal arterial constriction is suggested to cause excessive renin secretion from the juxtaglomerular apparatus, resulting in renal failure.

Vascular sensitivity to the ergot alkaloids is greatly increased in fever, infections, liver disease, and diseases in which vascular disorders already exist.

### 2. *Convulsive Ergotism*

Convulsive ergotism is said to occur mainly in people with vitamin A deficiency (Barger, 1931), which has been suggested to cause an increased sensitivity of the CNS to the ergot alkaloids. The symptoms usually start with twitching and numbness in the hands and feet, drowsiness, dizziness, weakness, formication and itching of the skin, and diarrhea. The clonic and tonic convulsions which follow in severe cases are extremely painful, and fatalities were formerly common. Convulsions have also been observed after LSD (see Connell, 1972).

### 3. *Fibrotic Effects*

As a result of the long-term use of methysergide in the prophylaxis of migraine, another serious side-effect, inflammatory fibrosis, has been observed (Graham, 1967; Graham *et al.*, 1967). The fibrosis may develop in the retroperitoneal space, causing compression of arteries, veins, and lymphatic vessels, leading to ischemic and obstructive lesions; in the connective tissue of cardiac valves, causing heart murmurs; and in the pleura and lungs, causing chest pain and respiratory difficulties due to pleural thickening and friction. The etiology of these fibrotic processes has been discussed by Graham *et al.*, (1967), who drew attention to the similarity of these effects to those found in various forms of vascular disease, including ergotism. It is possible that the inflammatory and fibrotic lesions are secondary to vascular changes caused by methysergide, which can have many effects similar to those seen in ergotism (Curran *et al.*, 1967).

## C. Treatment of Poisoning

In general, the main methods of treatment involve withdrawal of the offending drug, if the drug is still being taken, and symptomatic measures to counteract the effects.

### 1. *Poisoning with Nonpsychotomimetic Ergot Alkaloids*

In cases where the main toxic effect is excessive vasoconstriction, the treatment is designed to maintain adequate circulation in affected areas. Vasodilator agents, $\alpha$-receptor blocking agents, heparin, and low molecular weight dextran are all considered useful. Ganglionic blockade and epidural anesthesia have also been used to reduce any nervous component of the vasoconstriction, but since the constrictor action of the ergot alkaloids is

directly on the vessels (see Section IIIA2e), the value of these treatments is questionable.

### 2. *Psychotomimetic Agents*

In the treatment of LSD intoxication, sedation and symptomatic relief are the primary objectives: oral or intravenously administered phenothiazines, benzodiazepines, or short-acting barbiturates are effective (Isbell and Logan, 1957; Taylor *et al.*, 1970; Hasse *et al.*, 1971). In cases of illicit drug use, the situation is complicated by the possibility that the drug taken by the patient might not be LSD, or might be contaminated by other agents. In particular, the effects of anticholinergic agents are aggravated by phenothiazines, so since the psychotoxic symptoms of poisoning with anticholinergics can be difficult to distinguish from those of LSD, benzodiazepines or barbiturates are preferred to the phenothiazines by some practitioners for treatment of hallucinogen abuse (Taylor *et al.*, 1970).

## V. CONCLUSIONS

Although the present state of knowledge of the pharmacology of the ergot alkaloids and their derivatives is wide and complex, the field is by no means exhausted. The spectrum of effects is still being extended by discoveries of new properties, and the more detailed study of well-known actions is leading to a better understanding of their mechanisms. However, many aspects of the subject are controversial, and further research is needed to clarify the apparently conflicting findings. In view of the established importance and possible future value of these compounds both in clinical practice and in research, a more complete understanding of their actions is of great importance.

## VI. REFERENCES

Abrahams, V. C., Hilton, S. M., and Zbrożyna, A. W., 1960, Active muscle vasodilation produced by stimulation of the brain stem: Its significance in the defence reaction, *J. Physiol.* (*Lond.*) **154**:491.

Abrahams, V. C., Hilton, S. M., and Zbrożyna, A. W., 1964, The role of active muscle vasodilation in the altering stage of the defence reaction, *J. Physiol.* (*Lond.*) **171**:189.

Aellig, W. H., and Berde, B., 1969, Studies of the effect of natural and synthetic polypeptide type ergot compounds on a peripheral vascular bed, *Brit. J. Pharmacol.* **36**:561.

Aghajanian, G. K., 1972*a*, LSD and CNS transmission, *Ann. Rev. Pharmacol.* **12**:157.

Aghajanian, G. K., 1972*b*, Influence of drugs on the firing of serotonin-containing neurons in brain, *Fed. Proc.* **31**:91.

Aghajanian, G. K., 1972*c*, Chemical feedback regulation of serotonin-containing neurons in brain, *Ann. N.Y. Acad. Sci.* **193**:86.

Aghajanian, G. K., Haigler, H. J., and Bloom, F. E., 1972, Lysergic acid diethylamide and serotonin: Direct actions on serotonin-containing neurons in rat brain, *Life Sci.* **11**:615 (Part I).

Ambache, N., Dunk, L. P., Verney, J., and Aboo Zar, M., 1973, An inhibition of postganglionic motor transmission in the mammalian vas deferens by D-lysergic acid diethylamide, *J. Physiol. (Lond.)* **231**:251.

Andén, N.-E., Corrodi, H., Fuxe, K., and Hökfelt, T., 1968, Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide, *Brit. J. Pharmacol.* **34**:1.

Anderson, E. G., 1972, Bulbospinal serotonin-containing neurons and motor control, *Fed. Proc.* **31**:107.

Anthony, M., Hinterberger, H., and Lance, J. W., 1969, The possible relationship of serotonin to the migraine syndrome, *Res. Clin. Stud. Headache* **2**:29.

Appel, J. B., and Freedman, D. X., 1964, Chemically-induced alterations in the behavioral effects of LSD-25, *Biochem. Pharmacol.* **13**:861.

Appel, J. B., Lovell, R. A., and Freedman, D. X., 1970*a*, Alterations in the behavioral effects of LSD by pretreatment with *p*-chlorophenylalanine and $\alpha$-methyl-*p*-tyrosine, *Psychopharmacologia (Berl.)* **18**:387.

Appel, J. B., Sheard, M. H., and Freedman, D. X., 1970*b*, Alterations in the behavioral effects of LSD by midbrain raphe lesions, *Commun. Behav. Biol.* **5**:237.

Arcari, G., Dorigotti, L., Fregnan, G. B., and Glässer, A. H., 1968, Vasodilating and alpha-receptor blocking activity of a new ergoline derivative, *Brit. J. Pharmacol.* **34**:700P.

Avery, D. D., 1972, Thermoregulatory effects of intrahypothalamic injections of adrenergic and cholinergic substances at different environmental temperatures, *J. Physiol. (Lond.)* **220**:257.

Barasi, S., and Roberts, M. H. T., 1973, The action of 5-hydroxytryptamine antagonists and precursors on bulbospinal facilitation of spinal reflexes, *Brain Res.* **52**:385.

Barcroft, H., Konzett, H., and Swan, H. J. C., 1951, Observations on the action of the hydrogenated alkaloids of the ergotoxine group on the circulation in man, *J. Physiol. (Lond.)* **112**:273.

Barger, G., 1931, *Ergot and Ergotism*, Gurney and Jackson, London.

Beretta, C., Ferrini, R., and Glässer, A. H., 1965, 1-Methyl-8$\beta$-carbobenzyloxy-aminomethyl-10$\alpha$-ergoline, a potent and long-lasting 5-hydroxytryptamine antagonist, *Nature (Lond.)* **207**:421.

Bergström, S., Farnebo, L.-O., and Fuxe, K., 1973, Effect of prostaglandin $E_2$ on central and peripheral catecholamine neurons, *Europ. J. Pharmacol.* **21**:362.

Berridge, M. J., and Prince W. T., 1973, Mode of action of hallucinogenic molecules, *Nature New Biol.* **243**:283.

Bhargava, K. P., Mishra, N., and Tangri, K. K., 1972, An analysis of central adrenoceptors for control of cardiovascular function, *Brit. J. Pharmacol.* **45**:596.

Björklund, A., and Falck, B., 1969, Histochemical characterization of a tryptamine-like substance stored in cells of the mammalian adenohypophysis, *Acta Physiol. Scand.* **77**:475.

Björklund, A., and Nobin, A., 1973, Fluorescence histochemical and microspectrofluorometric mapping of dopamine and noradrenaline cell groups in the rat diencephalon, *Brain Res.* **51**:193.

Björklund, A., Moore, R. Y., Nobin, A., and Stenevi, U., 1973, The organisation of tuberohypophyseal and reticulo-infundibular catecholamine neuron systems in the rat brain, *Brain Res.* **51**:171.

Bluntschli, H. J., and Goetz, R. H., 1948, The effect of ergot derivatives on the circulation in man with special reference to two new hydrogenated compounds (dihydroergotamine and dihydroergocornine), *Am. Heart J.* **35**:873.

Boakes, R. J., Bradley, P. B., Briggs, I., and Dray, A., 1970, Antagonism of 5-hydroxytryptamine by LSD 25 in the central nervous system: A possible neuronal basis for the actions of LSD 25, *Brit. J. Pharmacol.* **40**:202.

Bolme, P., and Fuxe, K., 1973, Pharmacological studies on a possible role of central noradrenaline neurons in respiratory control, *J. Pharm. Pharmacol.* **25**:351.

Bolme, P., Fuxe, K., and Lidbrink, P., 1972, On the function of central catecholamine neurons—Their role in cardiovascular and arousal mechanisms, *Res. Commun. Chem. Pathol. Pharmacol.* **4**:657.

Borison, H. L., and Clark, W. G., 1967, Drug actions on thermoregulatory mechanisms, *Advan. Pharmacol.* **5**:129.

Bové, F. J., 1970, *The Story of Ergot*, Karger, Basel.

Bradley, P. B., and Briggs, I., 1974, Further studies on the mode of action of psychotomimetic drugs: Antagonism of the excitatory actions of serotonin by methylated derivatives of tryptamine, *Brit. J. Pharmacol.* **50**:345–354.

Brawley, P., and Duffield, J. C., 1972, The pharmacology of hallucinogens, *Pharmol. Rev.* **24**:31.

Brody, T. M., and Diamond, J., 1967, Blockade of the biochemical correlates of contraction and relaxation in uterine and intestinal smooth muscle, *Ann. N.Y. Acad. Sci.* **139**:772.

Bronzino, J. D., 1972, Evoked response study of postulated neural circuit associated with sleep–waking process, *Life Sci.* **11**:419 (Part I).

Bronzino, J. D., Morgane, P. J., and Stern, W. C., 1972, EEG synchronization following application of serotonin to area postrema, *Am. J. Physiol.* **223**:376.

Brown, P. S., 1968, The effect of drugs on induced ovulation, *J. Reprod. Fertil. Suppl.* **4**:61.

Bucknell, A., and Whitney, B., 1964, A preliminary investigation of the pharmacology of the human isolated taenia coli preparation, *Brit. J. Pharmacol.* **23**:164.

Carlsson, A., and Lindqvist, M., 1972, The effect of L-tryptophan and some psychotropic drugs on the formation of 5-hydroxytryptophan in the mouse brain *in vivo*, *J. Neural Trans.* **33**:23.

Cerletti, A., 1959, in: *Neuropsychopharmacology*, Proceedings of the First International Congress of Neuropsychopharmacology (P. B. Bradley, P. Deniker, and C. Radouco-Thomas, eds.) pp. 117–123, Elsevier, Amsterdam.

Cerletti, A., and Doepfner, W., 1958, Comparative study on the serotonin antagonism of amide derivatives of lysergic acid and of ergot alkaloids, *J. Pharmacol. Exptl. Therap.* **122**:124.

Chalmers, J. P., and Wurtman, R. J., 1971, Participation of central noradrenergic neurons in arterial baroreceptor reflexes in the rabbit, *Circ. Res.* **28**:480.

Chan, P. S., and Ellis, S., 1969, Dihydroergotamine antagonism of glucose release by rabbit liver slices induced by catecholamines, glucagon and 3′,5′-AMP, *Fed. Proc.* **28**:742.

Chu, D., and Stuermer, E., 1973, Studies on the mechanism of action of dihydroergotamine (DHE) on the vascular bed of cat skeletal muscle, *Brit. J. Pharmacol.* **48**:331P.

Cohen, S., 1967, Psychotomimetic agents, *Ann. Rev. Pharmacol.* **7**:301.

Connell, P. H., 1972, Hallucinogens, in: *Side Effects of Drugs*, Vol. VII (L. Meyler and A. Herxheimer, eds.) pp. 38–50, Excerpta Medica, Amsterdam.

Coote, J. H., and Macleod, V.H., 1972, The possibility that noradrenaline is a sympathoinhibitory transmitter in the spinal cord, *J. Physiol. (Lond.)* **225**:44P.

Coote, J. H., Hilton, S. M., and Zbrożyna, A. W., 1973, The pontomedullary area integrating the defence reaction in the cat and its influence on muscle blood flow, *J. Physiol. (Lond.)* **229**:257.

Corrodi, H., Fuxe, K., and Hökfelt, T., 1967, A possible role played by central monoamine neurons in thermo-regulation, *Acta Physiol. Scand.* **71**:224.

Corrodi, H., Fuke, K., Hökfelt, T., Lidbrink, P., and Ungerstedt, U., 1973, Effect of ergot drugs on central catecholamine neurons: Evidence for a stimulation of central dopamine neurons, *J. Pharm. Pharmacol.* **25**:409.

Costa, E., 1956, Effects of hallucinogenic and tranquilizing drugs on serotonin evoked uterine contractions, *Proc. Soc. Exptl. Biol. Med* **91**:39.

Costa, E., and Zetler, G., 1959, Interactions between epinephrine and some psychotomimetic drugs, *J. Pharmacol. Exptl. Therap.* **125**:230.

Couch, J. R., 1970, Responses of neurons in the raphe nuclei to serotonin, norepinephrine and acetylcholine and their correlation with an excitatory synaptic input, *Brain Res.* **19**:137.

Cranley, J. J., Krause, R. J., Strasser, E. S., and Hafner, C. D., 1963, Impending gangrene of four extremities secondary to ergotism, *New Engl. J. Med.* **269**:727.

Cumings, J. N., and Hilton, B. P., 1971, Effects of methysergide on platelets incubated with reserpine, *Brit. J. Pharmacol.* **42**:611.

Curran, D. A., Hinterberger, H., and Lance, J. W., 1967, Methysergide, *Res. Clin. Stud. Headache* **1**:74.

Dalessio, D. J., 1972, *Wolff's Headache and Other Head Pain*, 3rd ed., Oxford University Press, New York.

Daughaday, W. H., and Jacobs, L. S., 1972, Human prolactin, *Ergeb. Physiol.* **67**:169.

Davidson, N., Edwardson, J. A., and Schwab, D. I., 1969, Agroclavine antagonises depression induced by noradrenaline in the cerebral cortex of the rat, *Nature (Lond.)* **223**:1166.

Davies, B. N., Horton, E. W., and Withrington, P. G., 1968, The occurrence of prostaglandin $E_2$ in splenic venous blood of the dog following splenic nerve stimulation, *Brit. J. Pharmacol.* **32**:127.

de Groat, W. C., and Volle, R. L., 1966*a*, The actions of the catecholamines on transmission in the superior cervical ganglion of the cat, *J. Pharmacol. Exptl. Therap.* **154**:1.

de Groat, W. C., and Volle, R. L., 1966*b*, Interactions between the catecholamines and ganglionic stimulating agents in sympathetic ganglia, *J. Pharmacol. Exptl. Therap.* **154**:200.

Delay, J., and Thuillier, J., 1956, Dualité d'action du diéthylamide de l'acid lysergique sur la contraction utérine provoquée par la 5-hydroxytryptamine (sérotonine), *Compt. Rend. Soc. Biol.* **150**:1335.

Del Bianco, P. L., Franchi, G., Fanciullacci, M., and Sicuteri, F., 1972, Clinical pharmacology of 5-hydroxytryptamine and catecholamines venomotor receptors, *Arch. Int. Pharmacodyn. Therap.* **196**: Suppl. 113.

Del Pozo, E., Brun del Re, R., Varga, L., and Friesen, H., 1972, The inhibition of prolactin secretion in man by CB154 (2-bromo-alpha-ergocryptine), *J. Clin. Endocrinol. Metab.* **35**:768.

Dengler, H. J., Spiegel, H. E., and Titus, E. O., 1961, Effects of drugs on uptake of isotopic norepinephrine by cat tissues, *Nature (Lond.)* **191**:816.

Der Marderosian, A., 1967, Hallucinogenic indole compounds from higher plants, *Lloydia* **30**:23.

Díaz, J.-L., and Huttunen, M. O., 1971, Persistent increase in brain serotonin turnover after chronic administration of LSD in the rat, *Science* **174**:62.

Dishotsky, N. I., Loughman, W. D., Mogar, R. E., and Lipscomb, W. R., 1971, LSD and genetic damage, *Science* **172**:431.

Downman, C. B. B., 1972, The vasomotor centre, in: *Modern Trends in Physiology* (C. B. B. Downman, ed.) pp. 292–308, Butterworth, London.

Dyer, D. C., and Gant, D. W., 1973, Vasoconstriction produced by hallucinogens on isolated human and sheep umbilical vasculature, *J. Pharmacol. Exptl. Therap.* **184**:366.

Eiduson, S., Geller, E., Yuwiler, A., and Eiduson, B. T., 1964, *Biochemistry and Behavior*, Van Nostrand, Princeton, N.J.

Erspamer, V., 1966, Peripheral physiological and pharmacological actions of indolealkylamines, *Handbook Exptl. Pharmacol.* **19**:245.

European Breast Cancer Group, 1972, Clinical trial of 2-Br-$\alpha$-ergocryptine (CB 154) in advanced breast cancer, *Europ. J. Cancer* **8**:155.

Evarts, E. V., 1957, A review of the neurophysiological effects of lysergic acid diethylamide (LSD) and other psychotomimetic agents, *Ann. N.Y. Acad. Sci.* **66**:479.

Ezdinli, E. Z., Rouliah, J., Owens, G., and Sokal, J. E., 1968, Effect of high spinal cord section on epinephrine hyperglycemia, *Am. J. Physiol.* **214**:1019.

Fain, J. N., 1973, Biochemical aspects of drug and hormone action on adipose tissue, *Pharmacol. Rev.* **25**:67.

Fanchamps, A., Doepfner, W., Weidmann, H., and Cerletti, A., 1960, Pharmakologische Charakterisierung von Deseril, einem Serotonin-Antagonisten, *Schweiz. Med. Wschr.* **90**:1040.

Farnebo, L.-O., and Hamberger, B., 1971, Drug-induced changes in the release of [$^3$H]-noradrenaline from field stimulated rat iris, *Brit. J. Pharmacol.* **43**:97.

Fedotin, M. S., and Hartmann, C., 1970, Ergotamine poisoning producing renal arterial spasm, *New Engl. J. Med.* **283**:518.

Florendo, N. T., Barrnett, R. J., and Greengard, P., 1971, Cyclic 3′,5′-nucleotide phosphodiesterase: Cytochemical localization in cerebral cortex, *Science* **173**:745.

Flückiger, E., and Wagner, H. R., 1968, 2-Br-$\alpha$-ergokryptin: Beeinflussung von Fertilität und Laktation bei der Ratte, *Experientia* **24**:1130.

Fredholm, B., and Rosell, S., 1968, Effects of adrenergic blocking agents on lipid mobilization from canine subcutaneous adipose tissue after sympathetic nerve stimulation, *J. Pharmacol. Exptl. Therap.* **159**:1.

Freedman, D. X., 1963, Psychotomimetic drugs and brain biogenic amines, *Am. J. Psychiat.* **119**:843.

Freedman, D. X., 1969, The psychopharmacology of hallucinogenic agents, *Ann. Rev. Med.* **20**:409.

Freedman, D. X., Gottlieb, R., and Lovell, R. A., 1970, Psychotomimetic drugs and brain 5-hydroxytryptamine metabolism, *Biochem. Pharmacol.* **19**:1181.

Fregnan, G. B., and Glässer, A. H., 1968, Structure–activity relationship of various acyl derivatives of 6-methyl-8$\beta$-aminomethyl-10$\alpha$-ergoline (dihydrolysergamine), *Experientia* **24**:150.

Freis, E. D., Stanton, J. R., Litter, J., Culbertson, J. W., Halperin, M. H., Moister, F. C., and Wilkins, R. W., 1949, The hemodynamic effects of hypotensive drugs in man. II. Dihydroergocornine, *J. Clin. Invest.* **28**:1387.

Fuxe, K., and Owman, C., 1965, Cellular localization of monoamines in the area postrema of certain mammals, *J. Comp. Neurol.* **125**:337.

Fuxe, K., and Sjöqvist, F., 1972, Hypothermic effect of apomorphine in the mouse, *J. Pharm. Pharmacol.* **24**:702.

Gaddum, J. H., and Hameed, K. A., 1954, Drugs which antagonize 5-hydroxytryptamine. *Brit. J. Pharmacol.* **9**:240.

Gaddum, J. H., Hebb, C. O., Silver, A., and Swan, A. A. B., 1953, 5-Hydroxytryptamine: Pharmacological action and destruction in perfused lungs, *Quart. J. Exptl. Physiol.* **38**:255.

Gessner, P. K., 1970, Pharmacological studies of 5-methoxy-*N,N*-dimethyltryptamine, LSD and other hallucinogens, in: *Psychotomimetic Drugs* (D. H. Efron, ed.) pp. 105–118, Raven Press, New York.

Ginzel, K. H., and Kottegoda, S. R., 1953, A study of the vascular actions of 5-hydroxytryptamine, tryptamine, adrenaline and noradrenaline, *Quart. J. Exptl. Physiol.* **38**:225.

Gothelf, B., and Ellis, S., 1972, Effect of dihydroergotamine (DHE) on liver glycogenolysis and hyperglycemia induced by epinephrine, glucagon and cyclic AMP (cAMP) in the rat, in: *Fifth International Congress of Pharmacology*, San Francisco, p. 86 (abst.).

Graham, J. R., 1967, Methysergide, *Practitioner* **198**:302.

Graham, J. R., Suby, H. I., Le Compte, P. M., and Sadowsky, N. L., 1967, Inflammatory fibrosis associated with methysergide therapy, *Res. Clin. Stud. Headache* **1**:123.

Greenfield, A. D. M., 1966, Survey of the evidence for active neurogenic vasodilatation in man, *Fed. Proc.* **25**:1607.

Haefely, W. E., 1969, Effects of catecholamines in the cat superior cervical ganglion and their postulated rôle as physiological modulators of ganglionic transmission, *Prog. Brain Res.* **31**:61.

Haeusler, G., 1973, Activation of the central pathway of the baroreceptor reflex, a possible mechanism of the hypotensive action of Clonidine, *Naunyn-Schmiedeberg's Arch. Pharmakol.* **278**:231.

Haigler, H. J., and Aghajanian, G. K., 1972, Mescaline and LSD: Direct and indirect effects on serotonin-containing neurons in brain, *Europ. J. Pharmacol.* **21**:53.

Harvey, S. C., Wang, C.-Y., and Nickerson, M., 1951, Blockade of epinephrine-induced hyperglycemia, *J. Pharmacol. Exptl. Therap.* **104**:363.

Hasse, H. E., Scheifgen, W., and Schönhöfer, P. S., 1971, Notfallsituationen bei jugendlichen Drogenkonsumenten, *Deutsch. Med. Wschr.* **96**:449.

Hellon, R., 1972, Central transmitters and thermoregulation, in: *Essays on Temperature Regulation* (J. Bligh and R. E. Moore, eds.) pp. 71–85, North-Holland, Amsterdam.

Heyck, H., 1969, Pathogenesis of migraine, *Res. Clin. Stud. Headache* **2**:1.

Hilton, B. P., and Cumings, J. N., 1972, 5-Hydroxytryptamine levels and platelet aggregation responses in subjects with acute migraine headache, *J. Neurol. Neurosurg. Psychiat.* **35**:505.

Himms-Hagen, J., 1970, Adrenergic receptors for metabolic responses in adipose tissue, *Fed. Proc.* **29**:1388.

Hoffer, A., and Osmond, H., 1967, *The Hallucinogens*, Academic Press, New York.

Hökfelt, T., and Fuxe, K., 1972*a*, On the morphology and the neuroendocrine role of the hypothalamic catecholamine neurons, in: *Brain–Endocrine Interaction. Median Eminence: Structure and Function* (K. M. Knigge, D. E. Scott, and A. Weindl, eds.) pp. 181–223, Karger, Basel.

Hökfelt, T., and Fuxe, K., 1972*b*, Effects of prolactin and ergot alkaloids on the tuberoinfundibular dopamine (DA) neurons, *Neuroendocrinology* **9**:100.

Hollister, L. E., 1972, Psychiatric syndromes due to drugs, in: *Drug-Induced Diseases*, Vol. 4 (L. Meyler and H. M. Peck, eds.) pp. 561–570, Excerpta Medica, Amsterdam.

Horeyseck, G., Jänig, W., Kirchner, F., and Thämer, V., 1972, Electrophysiological studies on the hindlimb vasodilators on anesthesized cats, *Pflügers Arch.* **332**: Suppl. R64.

Horita, A., and Dille, J. M., 1954, Pyretogenic effect of lysergic acid diethylamide, *Science* **120**:1100.

Horita, A., and Hamilton, A. E., 1973, The effects of DL-α-methyltyrosine and L-DOPA on the hyperthermic and behavioral actions of LSD in rabbits, *Neuropharmacology*, **12**:471.

Horn, G., and McKay, J. M., 1973, Effects of lysergic acid diethylamide on the spontaneous activity and visual receptive fields of cells in the lateral geniculate nucleus of the cat, *Exptl. Brain. Res.* **17**:271.

Hornbrook, K. R., 1970, Adrenergic receptors for metabolic responses in the liver, *Fed. Proc.* **29**:1381.

Hornbrook, K. R., and Brody, T. M., 1963, Phosphorylase activity in rat liver and skeletal muscle after catecholamines, *Biochem. Pharmacol.* **12**:1407.

Innes, I. R., 1962, Identification of the smooth muscle excitatory receptors for ergot alkaloids, *Brit. J. Pharmacol.* **19**:120.

Isbell, H., and Gorodetsky, C. W., 1966, Effect of alkaloids of ololiuqui in man, *Psychopharmacologia (Berl.)* **8**:331.

Isbell, H., and Logan, C. R., 1957, Studies on the diethylamide of lysergic acid. II. Effects of chlorpromazine, azacyclonol and reserpine on the intensity of the LSD-reaction, *A.M.A. Arch. Neurol. Psychiat.* **77**:350.

Isbell, H., Miner, E. J., and Logan, C. R., 1959, Relationships of psychotomimetic to antiserotonin potencies of congeners of lysergic acid diethylamide (LSD-25), *Psychopharmacologia (Berl.)* **1**:20.

Ito, A., and Schanberg, S. M., 1972, Central nervous system mechanisms responsible for blood pressure elevation induced by *p*-chlorphenylalanine, *J. Pharmacol. Exptl. Therap.* **181**:65.

Iwangoff, P., and Enz, A., 1972, The influence of various dihydroergotamine analogues on cyclic adenosine-3′,5′-monophosphate phosphodiesterase in the grey matter of cat brain *in vitro*, *Agents and Actions* **2**:223.

Jacobson, C. B., and Berlin, C. M., 1972, Possible reproductive detriment in LSD users, *J.A.M.A.* **222**:1367.

Jouvet, M., 1972, The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle, *Ergeb. Physiol.* **64**:166.

Karlsberg, P., Elliott, H. W., and Adams, J. E., 1963, Effect of various pharmacologic agents on cerebral arteries, *Neurology* **13**:772.

Katz, R. I., and Kopin, I. J., 1969, Effect of D-LSD and related compounds on release of norepinephrine-$H^3$ and serotonin-$H^3$ evoked from brain slices by electrical stimulation, *Pharmacol. Res. Commun.* **1**:54.

Kebabian, J. W., and Greengard, P., 1971, Dopamine-sensitive adenyl cyclase: Possible role in synaptic transmission, *Science* **174**:1346.

Key, B. J., 1965*a*, Effect of lysergic acid diethylamide on potentials evoked in the specific sensory pathways, *Brit. Med. Bull.* **21**:30.

Key, B. J., 1965*b*, The effects of drugs in relation to the afferent collateral system of the brain stem, *Electroenceph. Clin. Neurophysiol.* **18**:670.

King, A. R., Seymour, K. A., and Martin, I. L., 1972, Reversal learning enhanced by LSD 25: Correlation with levels of brain amines, *Psychopharmacologia (Ber.)* **26**: Suppl. 121.

Koella, W. P., 1969, Neurohumoral aspects of sleep control, *Biol. Psychiat.* **1**:161.

Konzett, H., 1960, Specific antagonism of dibenamine to ergometrine, in: *Adrenergic Mechanisms*, CIBA Foundation Symposium (J. R. Vane, G. E. W. Wolstenholme, and M. O'Connor, eds.) pp. 463–465, J. & A. Churchill, London.

Konzett, H., and Rothlin, E., 1953, Investigations on the hypotensive effect of the hydrogenated ergot alkaloids, *Brit. J. Pharmacol.* **8**:201.

Kovalyov, G. V., 1967, Localization and characteristics of the influence of some neurotropic drugs on the bulbar vasomotor centre, *Prog. Brain Res.* **20**:187.

Krnjević, K., and Phillis, J. W., 1963, Actions of certain amines on cerebral cortical neurones, *Brit. J. Pharmacol.* **20**:471.

Levy, B., and Ahlquist, R. P., 1961, An analysis of adrenergic blocking activity, *J. Pharmacol. Exptl. Therap.* **133**:202.

Levy, B., and Tozzi, S., 1963, The adrenergic receptive mechanism of the rat uterus, *J. Pharmacol. Exptl. Therap.* **142**:178.

Lewis, P. J., and Lee, M. R., 1972, Renin release in the rabbit produced by ergometrine infusion, *Brit. J. Exptl. Pathol.* **53**:150.

Libet, B., 1970, Generation of slow inhibitory and excitatory postsynaptic potentials, *Fed. Proc.* **29**:1945.

Lin, R. C., Ngai, S. H., and Costa, E., 1969, Lysergic acid diethylamide: Role in conversion of plasma tryptophan to brain serotonin (5-hydroxytryptamine), *Science* **166**:237.

Lomax, P., and Schönbaum, E. (eds.), 1973, *The Pharmacology of Thermoregulation*, Karger, Basel.

Long, S. Y., 1972, Does LSD induce chromosomal damage and malformations? A review of the literature, *Teratology* **6**:75.

Mabry, P. O., and Campbell, B. A., 1973, Serotonergic inhibition of catecholamine-induced behavioral arousal, *Brain Res.* **49**:381.

McCann, S. M., Kalra, P. S., Donoso, A. O., Bishop, W., Schneider, H. P. G., Fawcett, C. P., and Krulich, L., 1972, The role of monoamines in the control of gonado-tropin and prolactin secretion, in: *Brain-Endocrine Interaction. Median Eminence: Structure and Function* (K. M. Knigge, D. E. Scott, and A. Weindl, eds.) pp. 224–235, Karger, Basel.

McCulloch, M. W., Rand, M. J., and Story, D. F., 1972, Inhibition of $^3$H-noradrenaline release from sympathetic nerves of guinea-pig atria by a presynaptic $\alpha$-adrenoceptor mechanism, *Brit. J. Pharmacol.* **46**:523.

Meites, J., and Clemens, J. A., 1972, Hypothalamic control of prolactin secretion, *Vitam. Horm.* **30**:165.

Meites, J., Lu, K. H,. Wuttke, W., Welsch, C. W., Nagasawa, H., and Quadri, S. K., 1972, Recent studies on functions and control of prolactin secretion in rats, *Rec. Prog. Horm. Res.* **28**:471.

Meldrum, B. S., and Naquet, R., 1971, Effects of psilocybin, dimethyltryptamine, mescaline and various lysergic acid derivatives on the EEG and on photically induced epilepsy in the baboon (*Papio papio*), *Electroenceph. Clin. Neurophysiol.* **31**:563.

Mellander, S., and Johansson, B., 1968, Control of resistance, exchange and capacitance functions in the peripheral circulation, *Pharmacol. Rev.* **20**:117.

Mellander, S., and Nordenfelt, I., 1970, Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation, *Clin. Sci.* **39**:183.

Miller, J. W., 1967, Adrenergic receptors in the myometrium, *Ann. N.Y. Acad. Sci.* **139**:788.

Miller, M. D., and Marshall, J. M., 1965, Uterine response to nerve stimulation; relation to hormonal status and catecholamines, *Am. J. Physiol.* **209**:859.

Monachon, M.-A., Burkard, W. P., Jalfre, M., and Haefely, W., 1972, Blockade of central 5-hydroxytryptamine receptors by methiothepin, *Naunyn-Schmiedeberg's Arch. Pharmakol.* **274**:192.

Morest, D. K., 1967, Experimental study of the projections of the nucleus of the tractus solitarius and the area postrema of the cat, *J. Comp. Neurol.* **130**:277.

Morgane, P. J., and Stern, W. C., 1972, Relationship of sleep to neuroanatomical circuits, biochemistry and behavior, *Ann. N.Y. Acad. Sci.* **193**:95.

Murad, F., Chi, Y.-M., Rall, T. W., and Sutherland, E. W., 1962, Adenyl cyclase III: The effect of catecholamines and choline esters on the formation of adenosine 3′,5′-phosphate by preparations from cardiac muscle and liver, *J. Biol. Chem.* **237**:1233.

Nakano, J., Ishii, T., Oliver, R. D., and Gin, A. C., 1969, Effect of dihydroergotamine and propranolol on dibutyryl cyclic 3′,5′-AMP-induced lipolysis in isolated rat fat cells, *Proc. Soc. Exptl. Biol. Med.* **132**:150.

Nichols, W. W., 1972, The relationship of chromosome aberrations to drugs, in: *Drug-Induced Diseases*, Vol. 4 (L. Meyler and H. M. Peck, eds.) pp. 60–80, Excerpta Medica, Amsterdam.

Nishi, S,. 1970, Cholinergic and adrenergic receptors at sympathetic preganglionic nerve terminals, *Fed. Proc.* **29**:1957.

Northrop, G., and Parks, R. E., Jr., 1964, The effects of adrenergic blocking agents and theophylline on 3′,5′-AMP–induced hyperglycemia, *J. Pharmacol. Exptl. Therap.* **145**:87.

Owen, D. A. A., and Stuermer, E., 1971, Effect of dihydroergotamine (DHG) on the capacitance, resistance and precapillary sphincter vessels of denervated cat skeletal muscle, *Brit. J. Pharmacol.* **42**:655.

Owen, D. A. A., and Stuermer, E., 1972, The effects of Hydergine on acutely denervated cat skeletal muscle vasculature, *Nauyn-Schmiedeberg's Arch. Pharmakol.* **272**:395.

Pacha, W., and Salzmann, R., 1970, Inhibition of the re-uptake of neuronally liberated noradrenaline and $\alpha$-receptor blocking action of some ergot alkaloids, *Brit. J. Pharmacol.* **38**:439.

Palmer, G. C., and Burks, T. F., 1971, Central and peripheral adrenergic blocking actions of LSD and BOL, *Europ. J. Pharmacol.* **16**:113.

Porter, J. C., Kamberi, I. A., and Ondo, J. G., 1972, Role of biogenic amines and cerebrospinal fluid in the neurovascular transmittal of hypophysiotrophic substances, in: *Brain–Endocrine Interaction. Median Eminence: Structure and Function* (K. M. Knigge, D. E. Scott, and A. Weindl, eds.) pp. 245–253, Karger, Basel.

Purpura, D. P., 1957, Experimental analysis of the inhibitory action of lysergic acid diethylamide on cortical dendritic activity, *Ann. N.Y. Acad. Sci.* **66**:515.

Ramstad, E., 1968, Chemistry of alkaloid formation in ergot, *Lloydia* **31**:327.

Richardson, B. P., 1973, Evidence for a physiological role of prolactin in osmoregulation in the rat after its inhibition by 2-bromo-$\alpha$-ergokryptine, *Brit. J. Pharmacol.* **47**:623.

Roberts, M. H. T., and Straughan, D. W., 1967, Excitation and depression of cortical neurones by 5-hydroxytryptamine, *J. Physiol. (Lond.)* **193**:269.

Rosenberg, F. J., and DiStefano, V., 1962, A central nervous system component of epinephrine hyperglycemia, *Am. J. Physiol.* **203**:782.

Rothlin, E., 1947, The pharmacology of the natural and dihydrogenated alkaloids of ergot, *Bull. Schweiz. Akad. Med. Wiss.* **2**:249.

Rothlin, E., 1957, Pharmacology of lysergic acid diethylamide and some of its related compounds, *J. Pharm. Pharmacol.* **9**:569.

Rothlin, E., Konzett, H., and Cerletti, A., 1954, The antagonism of ergot alkaloids towards the inhibitory response of the isolated rabbit intestine to epinephrine and norepinephrine, *J. Pharmacol. Exptl. Therap.* **112**:185.

Salmoiraghi, G. C., McCubbin, J. W., and Page, I. H., 1957, Effects of *d*-lysergic acid diethylamide and its brom derivative on cardiovascular responses to serotonin and on arterial pressure, *J. Pharmacol. Exptl. Therap.* **119**:240.

Samanin, R., Valzelli, L., and Gumulka, W., 1972, Inhibitory effect of midbrain raphe stimulation on cortical evoked potentials in rats, *Psychopharmacologia (Berl.)* **24**:373.

Savini, E. C., 1956, The antagonism between 5-hydroxytryptamine and certain derivatives of lysergic acid, *Brit. J. Pharmacol.* **11**:313.

Saxena, P. R., 1972, The effects of antimigraine drugs on the vascular responses by 5-hydroxytryptamine and related biogenic substances on the external carotid bed of dogs: Possible pharmacological implications to their antimigraine action, *Headache* **12**:44.

Schally, A. V., Arimura, A., and Kastin, A. J., 1973, Hypothalamic regulatory hormones, *Science* **179**:341.

Schmitt, H., and Fénard, S., 1970, Effects des alcaloïdes de l'ergot de seigle sur les centres vasomoteurs et leur inhibition par la clonidine, *Compt. Rend. Soc. Biol.* **164**:1006.

Shaar, C. J., and Clemens, J. A., 1972, Inhibition of lactation and prolactin secretion in rats by ergot alkaloids, *Endocrinology* **90**:285.

Share, N. N., 1973, "Alpha" and "beta" adrenergic receptors in the medullary vasomotor center of the cat, *Arch. Int. Pharmacodyn. Therap.* **202**:362.

Shemano, I., and Nickerson, M., 1958, Effect of ambient temperature on thermal responses to drugs, *Can. J. Biochem. Physiol.* **36**:1243.

Shields, P. J., and Eccleston, D., 1973, Evidence for the synthesis and storage of 5-hydroxytryptamine in two separate pools in the brain, *J. Neurochem.* **20**:881.

Sicuteri, F., 1967, Vasoneuractive substances and their implication in vascular pain, *Res. Clin. Stud. Headache* **1**:6.

Sicuteri, F., Buffoni, F., Anselmi, B., and Del Bianco, P. L., 1972, An enzyme (MAO) defect on the platelets in migraine, *Res. Clin. Stud. Headache* **3**:245.

Sicuteri, F., Anselmi, B., and Del Bianco, P. L., 1973, 5-Hydroxytryptamine supersensitivity as a new theory of headache and central pain: A clinical pharmacological approach with *p*-chlorophenylalanine, *Psychopharmacologia (Berl.)* **29**:347.

Simmonds, M. A., 1970, Effect of environmental temperature on the turnover of 5-hydroxytryptamine in various areas of rat brain, *J. Physiol. (Lond.)* **211**:93.

Smart, R. G., and Bateman, K., 1967, Unfavourable reactions on LSD: A review and analysis of the available case reports, *Can. Med. Ass. J.* **97**:1214.

Starke, K., 1972, Alpha sympathomimetic inhibition of adrenergic and cholinergic transmission in the rabbit heart, *Naunyn-Schmiedeberg's Arch. Pharmakol.* **274**:18.

Stern, W. C., Morgane, P. J., and Bronzino, J. D., 1972, LSD: Effects on sleep patterns and spiking activity in the lateral geniculate nucleus, *Brain Res.* **41**:199.

Stjärne, L., 1973, Alpha-adrenoceptor mediated feedback control of sympathetic neurotransmitter secretion in guinea-pig vas deferens, *Nature New Biol.* **241**:190.

Stoll, B. A., 1972, Brain catecholamines and breast cancer: A hypothesis, *Lancet* **1**:431.

Stone, T. W., 1973, Studies on the central nervous system effects of agroclavine, an ergot alkaloid, *Arch. Int. Pharmacodyn. Therap.* **202**:62.

Tabushi, K., and Himwich, H. E., 1971, Electroencephalographic study of the effects of methysergide on sleep in the rabbit, *Electroenceph. Clin. Neurophysiol.* **31**:491.

Taylor, R. L., Maurer, J. I., and Tinklenberg, J. R., 1970, Management of "bad trips" in an evolving drug scene, *J.A.M.A.* **213**:422.

Tebēcis, A. K., and Di Maria, A., 1972, A re-evaluation of the mode of action of 5-hydroxytryptamine on lateral geniculate neurones: Comparison with catecholamines and LSD, *Exptl. Brain. Res.* **14**:480.

Ulrich, J., and Siggaard-Andersen, J., 1972, Vascular effects of dihydrogenated ergot alkaloids: Comparative effects of dihydroergostine and dihydroergotamine on the blood flow and the capacitance vessels in the human calf studied by plethysmography, *Angiology* **22**:622.

Uvnäs, B., 1960, Central cardiovascular control, in: *Handbook of Physiology*, Section 1: *Neurophysiology*, Vol. II (J. Field, ed.) pp. 1131–1162, American Physiological Society, Washington, D.C.

Voss, E. W., Jr., Babb, J. E., Metzel, P., and Winkelhake, J. L., 1973, *In vitro* effect of *d*-lysergic acid diethylamide on immunoglobulin synthesis, *Biochem. Biophys. Res. Commun.* **50**:950.

Vuillon-Cacciuttolo, G., and Balzano, E., 1972, Action de quatre dérivés de l'ergot sur la photosensibilité de l'E.E.G. du *Papio papio*, *J. Pharmacol.* (*Paris*) **3**:31.

Walter, S., Balzano, E., Vuillon-Cacciuttolo, G., and Naquet, R., 1971, Effets comportementaux et électrographiques du diéthylamide de l'acide D-lysergique (LSD-25) sur le *Papio papio* photosensible, *Electroenceph. Clin. Neurophysiol.* **30**:294.

Wang, S. C., 1965, Emetic and antiemetic drugs, in: *Physiological Pharmacology*, Vol. 2 (W. S. Root and F. G. Hofmann, eds.) pp. 255–328, Academic Press, London.

Weiss, B. L., and Aghajanian, G. K., 1971, Activation of brain serotonin metabolism by heat: Role of midbrain raphe neurons, *Brain Res.* **26**:37.

White, R. P., Heaton, J. A., and Denton, I. C., 1971, Pharmacological comparison of prostaglandin $F_{2\alpha}$, serotonin and norepinephrine on cerebrovascular tone of monkey, *Europ. J. Pharmacol.* **15**:300.

Whitney, B., 1965, A preliminary investigation of the pharmacology of longitudinal muscle strips from human isolated jejunum, *J. Pharm. Pharmacol.* **17**:465.

Willems, J. L., 1972, On the pharmacology of autonomic ganglia, *Arch. Int. Pharmacodyn. Therap.* **196**: Suppl. 244.

Wuttke, W., Cassell, E. and Meites, J., 1971, Effects of ergocornine on serum prolactin and LH, and on hypothalamic contents of PIF and LRF, *Endocrinology*, **88**:737.

Ylitalo, P., Tammisto, T., and Pohto, P., 1970, Effect of anaesthesia on the behaviour of exogenous 5HT in area postrema of rat and mouse brain studied by fluorescence microscopy, *Ann. Med. Exptl. Fenn.* **48**:94.

Yui, T., and Takeo, Y., 1958, Neuropharmacological studies on a new series of ergot alkaloids, *Jap. J. Pharmacol.* **7**:157.

Yui, T., and Takeo, Y., 1964, Increase in anti-5HT activity by 1-methylation of clavine-type ergot alkaloids, *Jap. J. Pharmacol.* **14**:107.