(SKF 525-A) has been reported to be highly effective (*3*). Although no quantitative comparisons were made, the prolongation of anesthesia in mice with INH and Marsilid appeared to be of the same order as that of SKF 525-A. Dimercaprol and SKF 525-A have been reported to inhibit the rate of biotransformation of pentobarbital in the body (*2, 7*). This has not been determined with respect to the action of drugs reported here.

Although both INH and Marsilid, when administered simultaneously with or prior (4 hr) to pentobarbital, in both cases prolonged anesthesia, they do not appear to act in an entirely similar manner. Marsilid (250 mg/kg) caused a significant reduction (40 to 50 percent) in the dose of pentobarbital required to induce anesthesia in 50 percent of the animals (ED_{50}). With the same dose of INH, reduction of the ED_{50} was not significant (5 to 10 percent). This occurred even though at equivalent doses Marsilid is less toxic than INH. With a subanesthetic dose of pentobarbital (30 mg/kg), Marsilid (250 mg/kg) induced anesthesia while INH had no effect over a dose range of 50 to 400 mg/kg. Following recovery from pentobarbital (60 mg/kg) anesthesia, Marsilid (500 mg/kg) reinduced anesthesia, whereas INH (500 mg/kg) did not.

Also INH and 3-acetyl pyridine do not appear to act in an entirely parallel manner. Pentobarbital afforded protection against the toxicity of INH but did not protect against that of 3-acetyl pyridine. Nicotinamide did not protect against INH toxicity but did protect against that of 3-acetyl pyridine (*1*). The administration of nicotinamide or nicotinic acid did not result in any prolongation of anesthesia with pentobarbital.

Nicotinamide and pentobarbital do not appear to act antagonistically with respect to 3-acetyl pyridine. Protection by nicotinamide against the toxicity of 3-acetyl pyridine (*1*) did not appear to reduce the potentiating effect of the latter on pentobarbital anesthesia. Also, pentobarbital administration did not reduce the protective action of nicotinamide against 3-acetyl pyridine toxicity. However, nicotinamide metabolism has been implicated in the duration of action of barbiturates and in their metabolism (*8–10*).

Kaplan and Ciotti have observed an inhibition of diphosphopyridine nucleotidase activity by pentobarbital (*11*). The relationship of enzymatic transformations involving diphosphopyridine nucleotidases to the potentiation of barbiturate anesthesia and the observed toxicologic interrelationships is under investigation (*11*).

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22 December 1954.

Relationship of Hallucinogens to Adrenergic Cerebral Neurohumors

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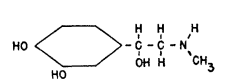
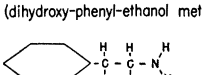
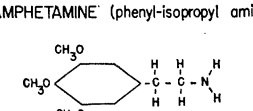
The study of cerebral synaptic transmission, by recording the postsynaptic electric response evoked by presynaptic stimulation, has demonstrated that an adrenergic synaptic transmission mechanism is present and capable of operating in the cat's brain. Marrazzi (*1*) has reviewed the evidence for this in a recent article in which he describes the use of the relatively simple transcallosal pathway connecting symmetrical points in the right and left optic cortex of the cat, thus making it possible to study one cortex when test stimuli are applied to the other. The electrocortical record so obtained indicates the activity at the terminal synapses by a surface positive wave corresponding to the inflow of impulses into the synapses and a surface negative wave indicating the outflow. In such a preparation, adrenaline, noradrenaline, and the so-called "adrenaline preservatives" cause a decrease in the surface negative wave generated by synaptic outflow without causing a change in the surface positive wave generated by the inflow—that is, a differential reduction in output or a synaptic inhibition.



ADRENALINE (dihydroxy-phenyl-ethanol methyl amine)



AMPHETAMINE (phenyl-isopropyl amine)



MESCALINE (trimethoxy-phenyl-ethyl amine)

Fig. 1. Types of phenylethyl amines producing mental effects.

Because of the structural similarity (Fig. 1) between adrenaline, which occasionally causes mental disturbances in man, amphetamine, which does so more often, and mescaline, which is a powerful hallucinogen, it was decided to compare the effects of the three on cerebral synaptic transmission. We had al-

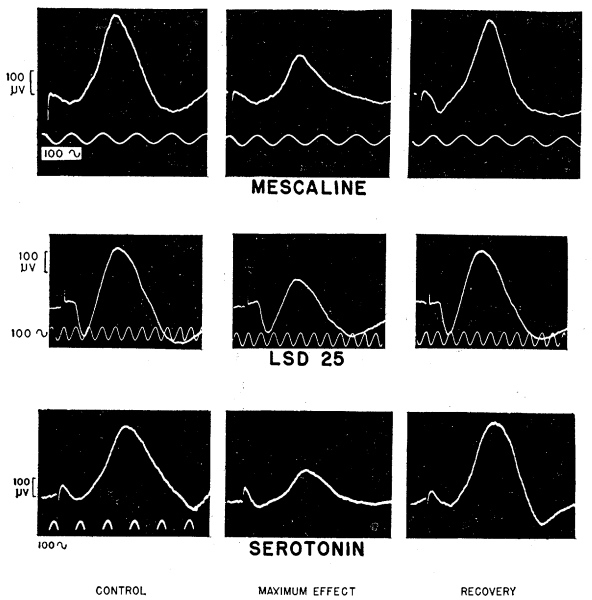


Fig. 2. Inhibition at cortical terminal synapses of transcallosal pathway in cat's brain. Potentials evoked in optic cortex of cat by electric stimulation of contralateral cortex. The drugs injected into carotid artery on recording side were mescaline, 15 mg/kg; lysergic acid diethylamide (LSD-25), 8 μg/kg; and serotonin, 1 μg/kg. Negativity is up. Sodium pentobarbital was used as the anesthesia.

ready shown that adrenaline and amphetamine, and other adrenalinelike compounds (*2*) produce cerebral synaptic inhibition in the cat. Figure 2 illustrates that the effects of mescaline on the synapses of the optic cortex of the cat are qualitatively identical with those of the other two members of the series. Thus, mescaline also produces a synaptic inhibition. It seems warranted to propose an empirical correlation between the synaptic inhibition and the disturbances in conduct observed on administration of mescaline to the unanesthetized cat and the marked hallucinations induced in man.

Additional similarities can be noted by comparing (Fig. 3) the chemical structures of adrenaline, adrenochrome—a possible breakdown product of adrenaline claimed to be capable of simulating schizophrenia (*3*)—and the very potent hallucinogen, lysergic acid diethylamide (LSD-25), as well as the chemical structure of serotonin, suggested by Woolley and Shaw (*4*) as the cerebral metabolite whose deficiency may be responsible for schizophrenia. The similarity between LSD-25 and serotonin is on the basis of the indole ring that they possess in common with adrenochrome, the possible metabolic product of adrenaline, through which the two series of hallucinogens examined are thereby linked.

The theoretical considerations advanced, as well as the suggestion that LSD-25 and serotonin might oppose each other's actions on the nervous system, made it logical to determine their effects on cerebral synaptic transmission in the brain of the cat, utilizing the preparation discussed earlier. Figure 2 demonstrates that LSD-25 has qualitatively the same synaptic inhibitory action as mescaline and adrenaline. The same is true of serotonin (Fig. 2), except that it is about 6 to 8 times as potent as LSD-25 and about 25 to 30 times as potent as adrenaline. Thus, the suggestion, arising from structural similarities, that all members of these series would produce cerebral synaptic inhibition is borne out, while a cerebral antagonism between LSD-25 and serotonin is not found. Competition among the members of these series can be expected, but, since serotonin is far more potent than the others in producing the same kind of synaptic action (inhibition), it would hardly be expected to offset the others, and its deficiency could not reasonably be expected to lead to the same type of effects as those exercised by LSD-25.

The high potency of serotonin, which is in the same range as that for acetylcholine (*1*) on these synapses, and its reported natural presence in the brain (*5*) make one speculate concerning the possible role it might play in the natural function of the nervous system, possibly as a humoral inhibitor. The synaptic inhibitory action of serotonin in the gamma doses used is unaccompanied by any significant change in circulation, as indicated by blood pressure. There is, therefore, little or no basis for assuming changes in cerebral blood flow sufficient to interfere with synaptic transmission. Furthermore, the synaptic effects of anoxia are quite delayed, while that of serotonin is achieved within 30 to 40 sec, reaching a maximum in about 1 min and receding by 3 min. It is clear from the cerebral action of serotonin, introduced into the circulation, that serotonin must pass the blood-brain barrier, although the comparative rate is not established.

The actions described here for one group of synapses are probably typical of more generalized effects, since they have also been recorded at a variety of synapses for adrenaline and adrenalinelike compounds (*1–2*) and in the ciliary ganglion for serotonin (*6*). With generalized synaptic inhibition, the resulting pattern of over-all activity would be a func-

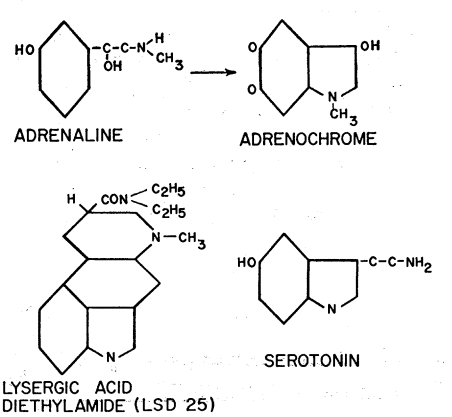


Fig. 3. Chemical structure of adrenaline, adrenochrome, lysergic acid diethylamide (LSD-25), and serotonin.

tion of the variations in synaptic thresholds. In this preliminary stage of correlation, an interpretation of hallucinations as stimulatory phenomena, rather than as derangements owing to partial inhibition, offers no real difficulty, since synaptic inhibition could readily result in release from normal restraining influences with consequent stimulation.

A disturbance of adrenergic or related cerebral neurohumoral mechanisms appears to be implicated in the actions of the hallucinogens studied. The resulting imbalance in the reciprocal relationship (*1*) between adrenergic inhibition and cholinergic excitation in the most susceptible cerebral synapses might be an underlying mechanism in mental disturbance.

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18 November 1954.

Alkaloid Formation in Ergot Sclerotia

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In exploring the possibilities of producing ergot alkaloids by culturing *Claviceps purpurea,* it is desirable to know at what time in the life-cycle of the fungus the alkaloids normally make their appearance. To determine this fact, a plot of tetraploid Rosen rye (*1*) was inoculated on 5 and 6 June 1954 by spraying the flowers each day with a sugar-spore suspension (*2*). The spores were produced in shake cultures on a medium of 40-percent commercial sucrose in a potato broth prepared by boiling 400 g of sliced potatoes in sufficient water to produce 1 lit of broth when decanted (*3*). Spores produced in this manner are far superior in yield, percentage germination, and longevity in storage than spores produced in wheat cultures as previously described (*2*).

Samples were collected 8, 10, 12, 15, 17, 19, and 26 days after the inoculation of 6 June (Fig. 1 *A–G*). Each sample consisted of 200 or more heads cut at random from the plot. The heads were dried for 2 days at a temperature of 60° to 80° C. Many heads were dissected to secure all the sclerotia in each head. Figure 1 shows 10 representative sclerotia from each sample; the average weight of the sclerotia is given in the legend.

The "sclerotia" collected on the 8th day can hardly be called sclerotia. Most of them show only a little purple pigment, and this is usually at the base. A few have no purple pigment at all and these are often nothing more than the ovary of the rye flowers overgrown with mycelium. The surfaces of all "sclerotia" of this age, especially the upper surface of the older ones, are covered with conidia and conidiophores.

In most of the sclerotia collected on the 10th day (Fig. 1 *B*) the basal pigmented portion has enlarged so that it forms one-half or more of the whole structure. The upper, nearly nonpigmented portion is the asexual development, and it does not enlarge once the true sclerotium begins to grow. With rare exceptions, all sclerotia collected on the 12th day and after (samples *C* to *G*) are heavily pigmented.

The amount and nature of the alkaloids produced during the development of the fungus were determined. Dried, pulverized samples of *A* to *G* were extracted with ammoniacal alcohol. After removal of the alcohol, the alkaloids in the water layer were extracted at *p*H 8 into chloroform, then returned to aqueous maleic acid solution. The percentage of ergot alkaloids in these dried samples, determined colorimetrically by a modification of the Van Urk method (*4*) was as follows: *A* (0); *B* (0), *C* (0.005), *D*

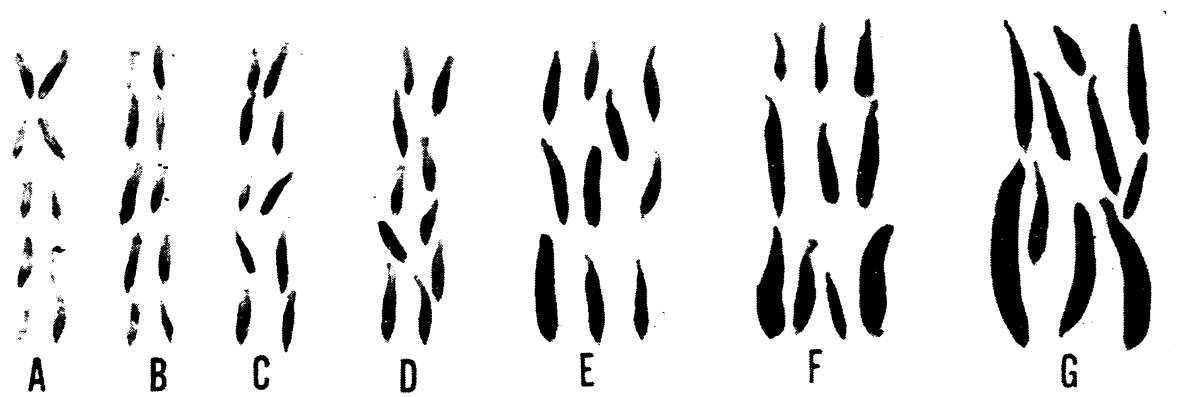

Fig. 1. Ergot sclerotia, natural size. The samples were collected on the following days after inoculation and have the average weights as noted: (*A*) 8th day, 4.9 mg per sclerotium; (*B*) 10th day, 6.2 mg; (*C*) 12th day, 7.3 mg; (*D*) 15th day, 10.2 mg; (*E*) 17th day, 23.2 mg; (*F*) 19th day, 38.0 mg; and (*G*) 26th day, 55.6 mg.