ANALEPTICS

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INTRODUCTION

The term "analeptic" usually refers to a drug able to restore depressed medullary and other functions of the central nervous system (CNS). This definition is applicable to drugs of very different pharmacological groups. It includes not only substances which act by primary excitation of the CNS, but also substances which act by competition with depressants, or by opposing metabolic or circulatory disturbances in the CNS. From a pharmacological standpoint it is advisable to restrict the term "analeptic" to substances which stimulate the normal as well as the depressed CNS, presumably by the same elementary mechanism.

In recent years strong objections have been raised to the use of analeptics in the treatment of CNS depression, and supportive treatment without analeptics has been recommended (505, 506). This new approach has found many followers in all countries. On the other hand, the over-all rejection of analeptics has been criticized from a pharmacological point of view (275, 276, 394, 396, 552). Certain analeptics may have a place in the management of severe barbiturate intoxication; a new analeptic agent, bemegride, has recently found widespread use in this condition. From this it can be deduced that the need for active therapy, in addition to merely supportive measures, is still felt.

This rather confusing status of the treatment of barbiturate intoxication and

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of all other potential fields of analeptic therapy requires a critical analysis of the pharmacological background of the use of analeptics. It will not be surprising if such a critical survey indicates a restriction of the number of useful analeptic drugs and of the range of their usefulness. The widespread and overemphasized use of analeptics, irrespective of their chemical nature, in the past has not been supported by experimental data. The outspoken opponents of analeptic therapy frequently overlook the possibility of differences in mode of action of the various analeptics, and consider only the danger of overstimulation which is common to all analeptics. Other factors, especially the site and mode of action, obviously play a major role with respect to the usefulness or risk of a given analeptic. Therefore, the need for a careful differentiation of the actions of the different analeptics seems evident.

This article deals in detail only with the tetrazoles, picrotoxin, bemegride, the alkylated acid amides, and the centrally acting sympathomimetic amines. Some old and some newer agents of limited effectiveness are considered briefly in Section VI.

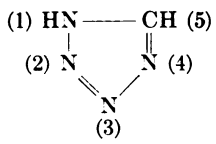
The most extensively studied analeptic is pentylenetetrazol. As a convulsant agent it exhibits some characteristic properties, because of which it has aroused considerable interest amongst neurophysiologists. Furthermore, pentylenetetrazol is used clinically not only as an analeptic but also as an EEG-activating agent in the diagnosis of epilepsy and as a convulsant in the therapy of schizophrenia. Most basic pharmacological problems concerning analeptic action have been studied with pentylenetetrazol. Hence pentylenetetrazol it reviewed most extensively.

Only one-third of the literature on which this review is based has been quoted in the text. In order to reduce the number of references, a selection has been made so that the reader may obtain the most significant information from the references listed.

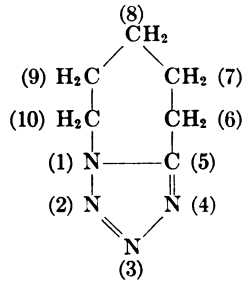
I. TETRAZOLES

A. Structure-action relationship

Pentylenetetrazol (1,5-pentamethylenetetrazole, Cardiazol, Metrazol) is the only one of the tetrazole derivatives which has been used therapeutically, although it is not the most active of this series of compounds. Good reviews of the early literature (326) and the chemistry of the tetrazole derivatives (42) are available.



Tetrazole



Pentylenetetrazol (PTZ)

Various derivatives of pentylenetetrazol have been studied (37, 240–244, 296, 297, 315, 316, 342, 576, 686), and their potencies have usually been estimated by the comparison of equieffective doses.

The introduction of a methyl group into the pentylenetetrazol molecule, especially in position 8, causes an increase in activity, *i.e.*, a reduction of the lethal, convulsant, and analeptic doses (240, 686); an isopropyl or tertiary butyl group in the same position is even more effective. Also, when tested against increasing amounts of barbital up to lethal doses, 7-methyl-pentylenetetrazole and especially 8-*iso*propyl-pentylenetetrazole are more potent than pentylenetetrazol in mice (287). A secondary butyl, a tertiary amyl or a cyclohexyl group, on the other hand, reduces or abolishes the stimulant action. The potency of 6-methyl-6,9-*iso*propyliden-pentamethylenetetrazole ("camphor-tetrazol") is very high (287, 342). It antagonizes lethal amounts of barbital more effectively than pentylenetetrazol (287). Various structural modifications, including the introduction of either a free or an esterified carboxyl group or the formation of quaternary compounds, result in more or less inactive substances (240, 297, 559).

1,5-Cyclohexamethylenetetrazole and 1,5-cycloheptamethylenetetrazole resemble pentylenetetrazol in their actions, whereas 1,5-cyclotetradecamethylenetetrazole is inactive (576). Compounds with smaller (tetra- or trimethylene) rings have low activity, which is increased by alkylation (686). In general terms, it thus appears that a certain number of carbon atoms is essential for significant activity of compounds of this group.

Unsubstituted tetrazole is devoid of significant pharmacological action, but alkylation in position 1 or 5 leads to compounds with both convulsant and analeptic properties, or to depressant substances. Optimal stimulant effects are obtained with a relatively large group substituted in position 1 and a small group in position 5. Reversal of the positions of the substituents causes decrease or even reversal of the stimulant action. 1-*Iso*butyl-5-methyl-, 1-cyclohexyl-5-methyl-, 1-cyclohexyl-5-ethyl-, and 1-cyclopentyl-5-methyltetrazole deserve special attention (241).

Alkylated 5-aminotetrazole derivatives cause convulsions and respiratory depression, but have no pronounced analeptic properties (242). The introduction of a methylene group between the tetrazole ring and the amino group increases the hypnotic and sedative action. Depending upon the nature of the substituents in position 1 or 5, convulsant or depressant compounds, or substances with mixed properties are obtained (243). Predominantly depressant drugs result from the substitution of a *m*-aminophenyl group (stronger in position 1 than 5), depending upon the size of the aliphatic chain substituted in the other position (244). 1-Aminoalkoxyphenyl-5-alkyl- and 5-aminoalkoxyphenyl-1-alkyl-tetrazoles also have a depressant action (711). Substituted 5-aminoethoxymethyltetrazoles are hypotensive by direct cardiac or vascular depression (123, 715).

As the foregoing results indicate, convulsant and the analeptic actions are not always associated. The association is greatest with the 1,5-dialkyl-tetrazoles and less so with the bicyclical derivatives, in which an increase of activity is combined with a diminished therapeutic index (240). In this respect the amino-

tetrazoles are the least suitable therapeutically, because their convulsant action is combined with depressant effects.

Pentylenetetrazol is readily soluble in both lipoids and water, but most of the active derivatives are water-insoluble. Inasmuch as none of the more active substances has been compared directly with pentylenetetrazol in treating poisoning with lethal amounts of barbiturates or other CNS depressants, it remains undetermined which of the derivatives is the most effective.

The great variability of action of the tetrazole derivatives is the more remarkable since substitutions are possible at only two atoms (1 and 5) of the tetrazole ring. The appearance of either stimulant or depressant or mixed actions demonstrates the close structural relationship between the stimulant and the depressant properties of the molecule, as is already known for other series of substances.

Some authors believe that the most significant property of pentylenetetrazol is its ability to form insoluble molecular combinations with phenol-like substances (407, 408). Others emphasize the proton-donor nature of the tetrazole ring and of those derivatives which are substituted in position 5, while the N-substituted derivatives are weak proton-acceptors (42, 314). When the UV-light absorption curves of 31 tetrazole derivatives were measured, certain structure-action relationships were found. The stimulant compounds showed slight or no absorption. Derivatives with depressant actions showed a high absorption. Essential for the stimulant action are substituents with a low resonance (such as alkyl groups) in positions 1 and 5 (596).

B. Pentylenetetrazol (PTZ)

1. Site of action. As in the study of other analeptic substances, the site of action of pentylenetetrazol (PTZ) has been localized by the analysis of its convulsant action.

a. Action on the spinal cord. Pentylenetetrazol acts on the whole CNS, including the spinal cord (57, 257). It causes an increase in reflex activity in the normal as well as the anesthetized spinal cord (57, 356, 377, 387, 603, 651, 672), and is able to elicit convulsions in spinal animals (57, 132, 270, 356, 387, 651), although in spinal preparations sensitivity is reduced (24, 86, 89, 224, 257, 270, 301, 588, 651). This might be due to the removal of supraspinal impulses or to the effect of surgical shock. However, acute spinal section results in little or no reduction of the response to various other agents (7, 158, 270, 651). It may thus be concluded that the sensitivity of the spinal cord is low for PTZ. On the other hand, unilateral supersensitivity of the spinal cord to PTZ is found after chronic lesions in the spinal cord on the same side, and in acute spinal preparations if the contralateral frontal lobe or contralateral hemisphere has been removed previously (156).

The study of the electrical activity of the cortex and the spinal cord in the intact animal has furnished further evidence of the low direct sensitivity of the spinal cord, and has suggested that the changes in the electrical activity of the spinal cord after PTZ are due to efferent impulses from supra-spinal centers (7, 86, 158). Since these experiments were carried out under anesthesia or curare,

the influence of these factors has to be considered. Anesthetics antagonize the action of PTZ more easily in the spinal than in the intact animal (270, 356, 481). The importance of afferent impulses for the convulsant action of PTZ on the spinal cord and the possibility of "functional deafferentation" by anesthetics and curare have been emphasized (7, 57, 528). It has been assumed, however, that activation of the motor neurons in spinal preparations may be initiated along pathways different from those of the intact animal (356). Whether the action of PTZ on the spinal cord is influenced by anesthetics in the same manner in intact as in spinal preparations is therefore still undecided.

Several observations suggest an action of PTZ on sites which differ from those of strychnine. In the intact animal the convulsant actions of PTZ and of strychnine are not synergistic (6, 7, 143, 254, 272), but they act synergistically in restoring spinal reflex activity under the influence of various anesthetic agents (387). The action of PTZ on the spinal cord is more easily antagonized by anesthetics than is that of strychnine (356). It has been claimed that PTZ acts mainly on the motor part of the reflex arc at a site associated with the terminations of the pyramidal tract, and that strychnine, on the other hand, acts predominantly dorsally on the sensory part of the reflex arc (387). This assumption is derived from the observation in the anesthetized intact cat that PTZ, in contrast to strychnine, has a stronger action on the cortically evoked flexor reflex than on the flexor reflex elicited by contralateral stimulation of the peroneal nerve. These experiments do not exclude the possibility that PTZ causes some supra-spinal effects on the pyramidal tract. Furthermore, there is more recent evidence that PTZ acts chiefly by stimulation of excitatory synapses, while strychnine acts by attenuating inhibitory systems (540).

Blume (57), on the other hand, located the site of action of PTZ in the sensory part of the reflex arc. His conclusions have been challenged (387), but have gained further support from the study of the effects of injections of PTZ into the sensory nucleus of the trigeminal nerve (256).

b. Action on higher centers. The whole area between the cortex and the brain stem is involved in the convulsive response to PTZ (224); when the brain is removed stepwise, the convulsant activity is diminished in proportion to the mass of brain removed (24, 257, 588). The changes in the type of convulsions observed during the gradual removal of the CNS, and the question of different origins of the clonic and tonic convulsions are still matters of controversy and will not be discussed here.

Generalized convulsive discharges were observed after the injection of PTZ into either the carotid or the vertebral artery (613). When the basilar artery was tied in the mid-region of the pons, the higher centers were found to be much more sensitive to PTZ than the centers located in the pons and medulla oblongata (354).

Some authors maintain that the sensitivity to PTZ is greatest in the higher centers and that the convulsions in the intact organism originate largely from the most sensitive areas (cortex or subcortex) (49). According to others, the convulsions caused by PTZ are the result of spatial and temporal summation, in

which all parts of the CNS are involved (256, 257). This, however, does not exclude the possibility that convulsions originate in specific areas, but that the convulsive impulses become effective on the motor neurons because of the increased irritability of *all* neurons. However, unilateral injection of PTZ into the common carotid artery, and its local application to the cortex demonstrate the existence of an independent mechanism responsible for the spread of PTZ convulsions (613).

Formerly, a subcortical (extrapyramidal) site of origin of PTZ convulsions was postulated (24, 101, 326). However, direct stimulation of the cortex of cats after pretreatment with subconvulsant doses of PTZ revealed an increased excitability of the cortex (160). The changes in the EEG, well known since the work of Fischer and Löwenbach (225, 326, 660), have often been interpreted as indicating a direct action of PTZ on the cortex. Since a better understanding of the influence of the subcortex on the cortex has been gained, renewed interest has been concentrated on possible subcortical actions of PTZ, particularly on the reticular formation of the brain stem and the arousal reaction (21, 472, 657, 659). In the latter region, interaction of PTZ with a neurohumoral transmitter has been proposed (339, 539). The "search and flight reaction" of rabbits after hypothalamic stimulation is not enhanced by PTZ (501).

Because of the interactions between the cortex and subcortex it is not possible to determine the primary site of action of PTZ by recording the electrical activity of the cortex. Even the simultaneous recording from both cortical and subcortical layers fails to provide consistent results (234, 427, 429, 532, 627).

The results of local application of PTZ to either cortical or subcortical structures (224, 464, 613, 689) do not answer the question of the origin of the PTZ convulsions under normal conditions. The same is valid for experiments in which subcortical structures (thalamus or reticular formation) have been destroyed (196, 517a). The latter experiments have shown only that there are some subcortical influences upon the systemic convulsions. Decortication has but a slight effect on the sensitivity to PTZ (257, 326, 651); this procedure usually results in a moderate increase in the dose necessary to produce convulsions. On the other hand, the sensitivity to PTZ as well as to other convulsive agents was found to be increased two to eight months after unilateral removal of the motor cortex, of the frontal lobe, or of the hemisphere (156).

Experiments on the isolated cortex indicate a cortical site of origin of PTZ convulsions (224, 536, 627). The sensitivity of the isolated cortex to PTZ is similar to that of the intact animal. The initial stimulation of the cortex spreads to the anterior horn cells via the pyramidal tract, as well as to the subcortical structures; the latter in turn influence the spinal cord and have a modifying action on the convulsions (689). The action on the subcortex involves both the extrapyramidal motor nuclei and the thalamus with its sensory relay stations and associative nuclei, while the diffuse projection system is involved to a lesser degree (627). This spread of excitation is due to facilitatory processes (224, 436) and may be enhanced by a direct action of PTZ on the activated neurons of lower regions.

The process of radiation may be increased by afferent impulses. The combination of subconvulsant doses of PTZ with photic or auditory stimulation causes reflex myoclonus and seizures (208). Specific sensory cortical areas, as well as the motor cortex, have been found to play a leading role in cortical radiation and in the myoclonic response to PTZ (336, 438, 481, 627).

c. Action on the autonomic nervous system. Actions of PTZ on the centers of the autonomic nervous system are detectable after subconvulsant, and pronounced after convulsant doses (212, 274). These actions are further enhanced when convulsions are suppressed by means of curare (259, 270, 519). The following responses have been observed: salivation, sweating, piloerection, exophthalmus, mydriasis, contraction of the nictitating membrane and of the spleen, inhibition of gastric and intestinal motility (or a slight increase in tone), bronchial dilatation, contraction (and inhibition) of the bladder, erection and ejaculation, hyperglycemia, increase in metabolic rate, hypothermia, action on the chromatophores, tachycardia or bradycardia (23, 59, 89, 202, 212, 233, 259, 271, 273, 274, 278, 326, 349, 416, 430, 464, 465, 514, 519, 542, 560, 610, 650). Both divisions of the autonomic nervous system are involved (89), but sympathetic activation predominates (210, 212, 273, 274, 278, 709). The preponderance of sympathetic effects is especially well demonstrated by organs with antagonistic autonomic innervation, such as the pupil (212) and intestine (273), and by the reaction of the skin of *Rana esculenta* (278), but less evidently by that of *R. pipiens* or *R. temporaria* (610, 650). In decapitated cats, PTZ is less effective than nikethamide on the spinal centers responsible for erection and ejaculation (270), which are believed to belong to the parasympathetic system. In intact mice ejaculation is produced by the synergistic action of a barbiturate and one of several stimulants, especially nikethamide (430, 432), but in this species the efferent pathways of ejaculation are probably predominantly sympathetic (430, 432, 435). The pulmonary edema caused by high, convulsant doses of PTZ (273, 555) is believed to be due partly to an action on sympathetic centers (349, 556). Pentylenetetrazol, like picrotoxin but unlike nikethamide and amphetamine, has an emetic action in pigeons (98).

The parasympathetic system seems to be involved only after the injection of convulsant doses of PTZ, but even then the action on the parasympathetic centers is masked by the sympathotonic effects (210, 212, 439, 709). Small doses inhibit the parasympathetic centers (212, 233).

Stimulation of peripheral ganglion cells and facilitation of synaptic transmission by PTZ have been demonstrated in perfused ganglion preparations (160); these actions have been suggested also by the responses to stimulation of the peripheral divisions of the cut vagus and splanchnic nerves (716, 717). With therapeutic doses of PTZ, the stimulant action on parasympathetic ganglion cells is said to surpass that on sympathetic ganglia (717). Since in the whole animal the activation of the sympathetic system predominates, the ganglionic actions of PTZ seem to be less important than its central actions.

Peripheral effects of PTZ seem hardly to be involved in the responses of the effector organs. Pentylenetetrazol usually has no action or only a weak inhibitory

action on smooth muscle (227, 288, 326). Elimination of autonomic responses by section (89, 212) of the appropriate nerves or central anesthesia (202, 273, 274, 561) indicates that the responses to PTZ are due to central stimulation. Convulsant doses of PTZ cause a prolonged increase in electric irritability of the hypothalamic sympathetic centers (210), and its direct injection into the hypothalamus causes stimulation of the autonomic nervous system (214, 464). Changes in the volleys conducted in the vagus nerve and in the sympathetic chain have also been demonstrated (517, 518).

The liberation of epinephrine from the adrenal medulla is partly responsible for the sympathomimetic responses to PTZ, but this is generally observed only after convulsant doses (210, 307, 489, 562).

The action of PTZ on peripheral ganglion cells is related to its effect on other synaptic and neuroeffector structures. Pentylenetetrazol antagonizes fatigue and reinforces contraction of indirectly stimulated frog muscle (186, 388, 530), and restores the respiration of curarized rabbits (359). Decurarization is observed also in frog, leech and cat muscles (174, 334, 388). The negative results of those investigators who failed to observe a decurarizing action of PTZ have been discussed by Huidobro (334). The drug increases the inhibitory effect of neostigmine on indirectly stimulated striated muscle of cats, and by itself inhibits, if the rate of stimulation is sufficiently high (334). Although these data are only suggestive of such, PTZ has to be classified as a depolarizing substance. The drug exhibits also certain veratrine-like action (179).

Miscellaneous observations, including its effects on leech and frog muscle and isolated organs, and its modifications of acetylcholine synthesis *in vitro* have suggested that PTZ acts *via* cholinergic mechanisms (96, 174, 312, 471, 543, 663). Although PTZ inhibits cholinesterase (312, 564, 663), the significance of this effect is doubtful (174, 602, 719). The reports concerning the action of atropine on PTZ-induced convulsions (224, 278, 439, 619, 707), as well as those on the effect of convulsions by PTZ and other agents on the acetylcholine content of the brain (171, 318, 658, 662) are contradictory. These experiments do not justify the conclusion that PTZ-induced central stimulation is due to a cholinergic mechanism. This does not exclude the possibility that PTZ, by its analeptic action, may restore the acetylcholine metabolism which has previously been depressed by anesthesia (318). Parasympathomimetic drugs, with the exception of the anticholinesterase agent di*iso*propylfluorophosphate and of pilocarpine (39, 258, 338, 516), may enhance the development of PTZ-induced convulsions (122, 192, 258, 289, 338, 564).

According to most authors (289, 351, 516, 619, 707), relatively high doses of epinephrine facilitate PTZ convulsions. This effect has not been observed consistently (484). Small doses appear to depress convulsions by eliciting reflexes from the carotid and aortic pressoreceptors (49, 213, 523, 714). No basis can be given for the facilitation of PTZ convulsions by large amounts of epinephrine. Vasomotor influences, an increased flow of PTZ into the brain, and a direct action of epinephrine on the central reticular system have to be considered (141, 289, 351). Pentylenetetrazol convulsions are inhibited by ergot alkaloids (557, 563, 571).

2. Action on blood pressure. The value of PTZ as a central circulatory stimulant has been both emphasized and denied (326). This is not surprising in view of the usual difficulty in demonstrating the pressor action of centrally acting substances (284, 635). Anesthesia has been blamed as the principal reason for lack of pressor responses, and for the appearance even of depressor effects (53, 231, 520, 675, 709). However, some observations indicate that PTZ still has a pressor action when anesthesia causes circulatory failure (279, 326). It has long been known that the choice of anesthetic agent is important for demonstrating a particular drug effect (231, 326, 341). Consideration of possible sites and modes of action is necessary for a better understanding of these differences.

Parts of the CNS other than the medullary vasomotor center (206) are known to take part in the pressor response. Decerebration reduces the pressor action of PTZ (112, 255, 268). The injection of PTZ into the hypothalamus or into the lateral ventricle of cats raises the blood pressure and increases the pressor response to hypothalamic stimulation (214, 464, 701). Decapitation and spinal section are alleged to abolish the pressor effect (111, 231, 301, 326), but that is not the case after careful decapitation (228, 270). A direct vasoconstrictor action seems to be excluded by the negative results of perfusion experiments (132, 227, 288, 326).

In unanesthetized and curarized dogs the pressor action of PTZ is said to originate in the cortex (112). The evidence is based on the inhibitory action of barbiturates, of hydantoins, and of decerebration, but alone is not convincing. The observation that barbiturates depress the hypertension which is caused by electrical stimulation of the cortex, and PTZ restores it (111) suggests that vasopressor centers of the cortex respond to the latter drug. It has been suggested (488) that the pressor action is related to the epileptogenous action of PTZ on the cortex, although an independent action on the blood pressure has not been denied. This independent action is demonstrated in cases of severe barbiturate poisoning by the rise of blood pressure after high doses of PTZ without the appearance of cortical convulsion potentials (279). Cortical convulsion potentials after overdosage of PTZ may be accompanied by a fall of blood pressure.

A depressor response may also occur, and under some circumstances this may be due to stimulation of the vagal centers (259, 268, 288, 326, 452, 519). In many cases, however, the depressor action is not mediated by the vagus (89, 268, 282, 284, 301) and thus is due either to inhibition of sympathetic vasoconstrictor centers or to the activation of putative vasodilator fibers. Peripheral vasodilator actions [as have been postulated (301)] or depression of the heart hardly plays a role (288, 326). Ganglionic blocking agents like azamethonium bromide (Pendiomid) inhibit the depressor action less readily than the pressor action (220).

Results which have been obtained with injections of PTZ into the vertebral artery of cats suggest that the main sites of the depressor action are the depressor centers in the brain stem and medulla oblongata (282, 284). Injections into the vertebral artery cause pressor and depressor responses depending upon the experimental conditions. The importance of a labile dualistic regulatory system has thus been emphasized. The response to intravenous injections of PTZ de-

pends not only on the balance of this regulatory system but also on the activity of pressor centers which are not reached by injections into the vertebral arteries (especially the spinal centers). After intravenous injection of PTZ, therefore, the pressor response usually prevails.

In this complex system the choice of anesthetic and the depth of anesthesia are of special importance. Chloralose anesthesia leads to predominantly pressor responses after intravenous, intraventricular, or vertebral arterial injection of PTZ (219, 231, 268, 282, 701). The reverse is seen in response to injection into the vertebral arteries under barbiturate anesthesia. After intravenous injections the response of the blood pressure is not uniform and depends on the depth of anesthesia as well as on the dose of PTZ. Experiments in artificially respired cats and dogs which had received lethal amounts of barbiturates showed that PTZ in sufficiently high doses (50 to 600 mg/kg) causes a rise of blood pressure and restoration of the circulation (279). The effect of overdosage (650 to 1970 mg/kg), already mentioned, is perhaps due to a prevailing action on the depressor centers, or to reversal of the stimulating effect on the pressor centers. It is probable that Bailey *et al.* (27) who administered very large doses of PTZ (1 to 4 g/kg) observed only the depressor action; they therefore unjustly denied the possibility of a collapse-relieving action of PTZ, especially since they themselves observed a beneficial effect when smaller doses were given. Under deep barbiturate anesthesia the activation of pressor centers outside the brainstem and medulla is probably of special importance. But since barbiturates cause—in addition to the depression of the hypothalamic pressor centers—peripheral ganglionic block, the possibility remains that in severe barbiturate collapse PTZ acts also directly on the peripheral ganglia.

The action of convulsant doses is not uniform: convulsions may be accompanied by very pronounced pressor responses (212, 520, 709), or with a fall of blood pressure (23, 115, 212, 259, 260, 268, 439, 482, 520). The fall may be aggravated by peripheral factors such as muscle metabolites (259, 270).

The following observations suggest structural or organizational differences in the systems regulating the blood pressure in different species. The tendency to a depressor response is less pronounced in rabbits than in cats (288). Doses affecting the blood pressure are smaller in cats than in rabbits (220). Inhibition of the pressor response to PTZ by the ganglionic blocking substance, azamethonium bromide, is more easily obtained in cats than in rabbits, and more easily under chloralose than under urethane anesthesia (220). A complete blockade, however, cannot be achieved either in rabbits or in cats; increased amounts of PTZ are able to overcome it.

A direct action of PTZ on the carotid sinus has been excluded (713, 718), but there is much evidence that it enhances the carotid occlusion reflex (98, 209, 324, 683, 701) and reduces the inhibition of the vasomotor center caused by an increase of the pressure in the carotid sinus (523). (In these experiments it was not considered that the carotid occlusion reflex may consist of two components: one due to the lowered endosinual pressure, the other due to the anoxic state of the carotid body chemoreceptors after the clamping. Pentylenetetrazol, there-

fore, may or may not have a different action on these components.) On the other hand, PTZ has been said to enhance the depressor response to increased pressure within the carotid sinus (166). Carotid exclusion or section of the buffer nerves potentiates the pressor response to PTZ in cats and dogs (268, 523), but less so in rabbits (288, 635). These maneuvers have been found both to increase (282) and to reduce depressor responses to PTZ (212). The depression of the carotid sinus occlusion reflex by reserpine is not restored by PTZ (700). In carbon monoxide-poisoned cats, occlusion of the carotid artery causes a fall of blood pressure, which is prevented by PTZ (or by atropine, vagotomy, or nikethamide) (365). The severe reflex hypotension which is observed after veratrine or viscotoxin (mistletoe extract) is not always counteracted by PTZ (720).

Less important for the pressor response to PTZ, especially in subconvulsant doses, is the liberation of epinephrine from the adrenal medulla (112, 212, 301, 489, 523). Adrenergic blocking substances reduce the pressor response to PTZ (112, 519, 709).

Pressor responses to PTZ are favored by lowering of blood pressure (by anesthetics, bleeding, acetylcholine, adenylic acid) to an optimal level (89, 231, 268, 326), by hypoxia of the centers (282), and by accumulation of CO_2 in the blood (721). Anoxic paralysis of the centers, on the other hand, probably limits the effectiveness of PTZ, although the blood pressure still responds to oxygen (165). Carbon dioxide may have a more pronounced central vasoconstrictor action than PTZ and other analeptics (357), but this needs further study. Pentylenetetrazol increases the sensitivity of the pressor centers to CO_2 (675). In this respect it has been said to differ from other analeptic substances. By its stimulant action on respiration, PTZ causes a reduction of the CO_2 tension of blood and thus indirectly causes a decrease of the sensitivity of the pressor centers to itself. Furthermore, in the presence of an impaired respiration PTZ may improve O_2 supply to the centers and thus cause a fall in blood pressure, if the blood pressure has been increased by anoxia (61). In such experiments it is therefore necessary to administer artificial respiration in order to study the uncomplicated direct action of the drug on the vasomotor centers (268, 635).

A positive inotropic action of PTZ on the heart has not been found (231, 326); cardiac disturbances resulting from the administration of respiratory paralysants are improved by its respiratory action (232, 419).

The main therapeutic usefulness of PTZ is in the central vasomotor collapse due to anesthetic agents. Peripheral failure of the circulation is difficult to overcome, especially collapse due to histamine, peptones, nitrites, and surgery (268, 326, 499, 523). In rabbits, PTZ antagonizes partially the depression of the blood pressure occurring in anaphylaxis (415). After injection into the hypothalamus, it antagonizes the hypotensive action of acetylcholine, methacholine, and histamine (214).

The combined administration of PTZ and peripherally active sympathomimetic amines reveals a synergism according to some authors (166, 593), an additive or subadditive effect according to others (283, 330).

The literature dealing with the relative hemodynamic potencies of the various

analeptic substances is controversial (165, 209, 232, 326, 354, 357, 452, 519, 545, 633, 675, 683, 720). The reason is that few comparative experiments have been carried out under constant conditions on the same animal (219, 269, 281, 282, 284, 288). These have shown that the ratio of equipressor doses of some analeptics (PTZ, azoman, bemegride, picrotoxin, hexeton) on cats is identical with the ratio of convulsant doses. This parallelism does not apply to all analeptics; in equiconvulsant doses nikethamide (tested on rabbits) and caffeine (tested on cats) are more potent pressor substances than PTZ, whereas strychnine (tested on cats) is a weaker pressor agent. In cats vasodepressor actions of PTZ are less pronounced than those of certain other substances like nikethamide, caffeine, and hexeton (231, 269, 284, 354, 586).

3. Action on respiration. a. Mode and site of action. Stimulation of respiration in normal animals is observed after the administration of half the convulsant dose of PTZ (22, 66). During the convulsive phase it may cause "spastic apnea" by a very pronounced increase in inspiratory tone (590). This, predominantly initial, apnea has often been observed with PTZ (17, 89, 145, 206, 311, 724) as well as with other analeptic substances (311, 545, 724), although it is questionable whether the mode of action of all these substances is identical.

An exact localization of the site of respiratory action of PTZ has not yet been made. The respiratory effects of PTZ are not due to reflexes arising from the carotid body or aortic chemoreceptors (718, 724). The increase in respiratory rate is not due to an action on the nucleus of the tractus solitarius (313). An indirect action of PTZ *via* the higher centers may be deduced from experiments with intravertebral, intracarotid and intravenous injections in rabbits (354). It is usually not appreciated that PTZ, by acting on the cooling center, stimulates respiration in normal rabbits (panting) in order to lower the body temperature (271). The presence of a direct action of PTZ on the respiratory center can be concluded from the effectiveness of intracisternal injection (89, 206), from the persistence of the respiratory stimulant action in decerebrate anesthetized or unanesthetized cats (98, 145, 313, 459, 675), as well as from the increase of the response to electrical stimulation of the inspiratory center after injection of PTZ (145).

The respiratory action of PTZ seems to be at least partly due to a sensitization of the center to CO_2 (313). This probably takes place in the medullary respiratory center, although the cortex may contribute to the regulation of the respiration by CO_2. Cocaine, which stimulates by a supramedullary action (354), fails to sensitize to CO_2 (313). The synergistic action of CO_2 and of PTZ is part of a general synergism between CO_2 and convulsant substances (see 721 for further references). The increase in sensitivity of CO_2 cannot be the only mode of action of the analeptic substances, because section of the carotid chemoreceptor nerves and of the vagi abolishes the respiratory response to 2% CO_2, but not to injections of analeptic substances (313). Very high concentrations of CO_2 inhibit the respiratory and convulsant activity of PTZ (261, 422).

A number of investigators have studied the influence of PTZ and other analeptics on the volume and rate of respiration and on inspiration and expiration.

The contradictory results do not allow a differentiation of the actions of individual analeptics, but rather indicate a dependence on anesthesia and other experimental conditions.

b. Respiratory action under the influence of hypnotic and anesthetic substances. Stimulation of respiration by analeptics is relatively enhanced when the respiration is depressed by hypnotic or anesthetic substances (145, 326). It may persist when other analeptic effects are abolished (26, 701). When the sensitivity of the respiratory center to CO_2 has been decreased by anesthetic agents, it is restored by PTZ (313, 638). As the barbiturates may cause a shift of the regulation of respiration from the respiratory center to the carotid and aortic chemoreceptors, it is important that PTZ and picrotoxin enhance centrally the anoxic respiratory drive *via* the chemoreceptors, and that thereby they reduce the depressant action of breathing pure O_2 (458, 459, 638).

The therapeutic index, usually calculated as the ratio of the convulsant to the respiratory stimulant dose (occasionally as the ratio of the lethal to the respiratory stimulant dose), is modified by the choice of the anesthetic agent as well as by the depth of anesthesia. This index reflects mainly the different anticonvulsant activities of the different anesthetic agents (49, 168, 232, 237, 272, 311, 321, 341, 421, 452, 655, 687, 724). Thus, PTZ may have a higher therapeutic index under anesthesia with barbiturates or Avertin (solution of tribromoethanol in amylene hydrate) than under anesthesia with ether, chloralose, trichloroethylene, urethane, or chloral hydrate. It is well known that the sensitivity of the respiratory center to CO_2 is depressed more by some anesthetics than by others (691); it remains to be seen whether such a differential action of anesthetics applies also to stimulation of the respiratory center by analeptics.

Reversal of increasing depression of the respiratory center requires increasing amounts of analeptics; this increase is limited by the onset of convulsions or by the reversal of their stimulant action. The depressant actions of certain analeptics, therefore, may also reduce the therapeutic index (168). Usually no depressant action of PTZ has been observed (129, 168, 311, 459), contrary to the situation with other analeptics (hexeton, nikethamide, lobeline). In dogs under deep thiopental anesthesia, PTZ in amounts of 75 to 300 mg/kg had no depressant action, but stimulated the respiratory center (61). Contradictory results obtained with small doses of PTZ (491) are not convincing. The relation between the respiratory stimulant dose and the depth of anesthesia has been established for PTZ only with thiopental (61). The quotient "dose of PTZ/dose of thiopental" is a linear function of the dose of thiopental.

These experiments showed that PTZ has a stimulant action on respiration after respiratory depression has been produced by amounts of barbiturates up to lethal levels. However, the dose of the former must be high (17, 22, 61); small doses were unable to overcome respiratory arrest (491, 638, 705). It must be remembered that depression of respiration may lead to anoxia and thus to additional damage to the respiratory center. Some observations make clear the importance of anoxia to loss of the respiratory stimulant action of the analeptics in severe anesthetic respiratory depression (638). Several authors, however, have

observed increases in O_2 content of the blood following the administration of PTZ after the O_2 content had been lowered greatly by barbiturate anesthesia (17, 61, 136). The effectiveness of PTZ against hypoxia caused by central depressants has been established by other findings also (232, 454). However, the discrepancy between the analeptic-induced increase in O_2 consumption of the respiratory center and the availability of O_2 may constitute a danger. This has to be avoided by careful dosage, so that the stimulation of the respiratory center goes hand in hand with increasing oxygenation of the blood.

The comparison of PTZ with other analeptic substances (*e.g.*, picrotoxin, azoman, nikethamide, lobeline, icoral, ephedrine, strychnine) after pretreatment with barbiturates and other anesthetics has given results which are partly contradictory (33, 34, 126, 129, 163, 168, 311, 325, 326, 360, 452, 459, 551, 655, 705). This is at least partly due to the use of different anesthetic agents. However, in many cases it is also due to the fact that the whole range of effectiveness, up to the absolute limit of the analeptic substance, was not compared against increasing amounts of the anesthetics. Picrotoxin has been found superior to PTZ against several barbiturates (129, 459, 551), but not against barbital (34).

c. Respiratory action in poisoning with morphine. In experiments devised to study the respiratory action of analeptics, morphine has been the most frequently used respiratory depressant. Most of these experiments have been carried out in rabbits. Respiration which has been depressed partially by morphine is increased to some degree by all analeptic substances. This may be based on the particular mechanism of the respiratory depressant action of morphine (589). The latter probably does not produce direct paralysis of the respiratory center (188, 306). Rather morphine probably causes the elimination of vagal influences in the caudal half of the pons, which depresses expiration. It is, however, remarkable that when the respiratory center has been depressed by afferent stimulation of the vagus, it is not influenced by PTZ (309). The sensitivity of the respiratory center to PTZ, whether reduced by morphine or not, is increased by CO_2 (157).

The stimulation of respiration by PTZ has often been demonstrated in experimental morphine poisoning (66, 132, 311, 326, 421, 589, 594, 678, 724). Similar results have been obtained in man (292, 629, 630), and its action has been compared with that of other analeptics. No details are available concerning the doses effective at various levels of respiratory depression. The dose of PTZ which is effective against partial depression by morphine seems to correspond to that effective in respiratory depression by barbiturates and other anesthetics (66, 311, 421). However, the action of PTZ is said to decrease less with increasing depression caused by morphine than with increasing respiratory depression due to general anesthetics (589).

Inasmuch as morphine has a stimulant as well as a depressant action on the CNS, the antagonism between morphine and the analeptics is not pronounced as far as some other functions of the CNS are concerned. In most laboratory animals, morphine increases the convulsant action of PTZ and other analeptic

substances (306, 421, 587). Dihydromorphinone (hydromorphone) (306) and dihydrocodeinone (hydrocodone) (49) also lower the threshold for PTZ.

Because of the synergism between morphine and analeptics with respect to convulsions, the therapeutic index of the latter is distinctly smaller in morphine than in barbiturate or tribromoethanol poisoning (168, 311, 421, 545). Many authors have studied the differences in the therapeutic indices of PTZ and other analeptics (66, 311, 325, 326, 421, 452, 594, 724). An extensive reinvestigation with numerous analeptic substances (678) showed that the therapeutic indices of most of the analeptics varied within narrow limits (1.3 to 3.0).

Morphine does not kill most laboratory animals by respiratory depression, but by convulsions, which are not due to anoxia. Therefore one would expect anesthetics rather than analeptics to be life-saving. In experiments on mice (though with a very limited number of animals) a life-saving action of PTZ and other analeptics in morphine poisoning was not found (587). Contradictory results in experiments on cats (708) are probably due to the fact that these experiments were carried out using barbiturate anesthesia; under barbiturates, morphine has a predominantly depressant action, which could be counteracted by PTZ. On the other hand, PTZ is said to have a limited life-saving action in morphine-poisoned rabbits (93). In dogs the sleep after morphine is not interrupted by the administration of analeptics (306).

No conclusions drawn from the foregoing animal experiments can be applied directly to man, since in human beings death is mainly due to the depression of respiration. However, in man as in other animals there exists the risk of complications due to the synergistic convulsant action of morphine and PTZ (306).

d. Effects on the central action of local anesthetics. In contrast to the sequence of events after the administration of morphine, systemically administered local anesthetics cause convulsions followed by central paralysis. The convulsant action of cocaine and related substances is therefore potentially more serious than that of morphine both in animals and in man. Postconvulsive depression as well as spasm of the respiratory muscles and of the glottis may contribute to the impairment of the respiration by cocaine. Therefore, a therapeutic action of the analeptics is even more questionable than in morphine poisoning. Several studies have shown, in fact, that general anesthetics are better antagonists than analeptics of the central action of local anesthetic substances; the barbiturates apparently are the best.

Local anesthetics have also a direct depressant action on the respiratory and cardiovascular centers; the depression may be enhanced by barbiturates. One might expect an antagonistic action of the analeptic substances to the direct depressant actions of the local anesthetics. But there is no convincing evidence from the somewhat contradictory experiments of several authors (326, 511, 581, 722) that PTZ and other analeptics have a curative action against the respiratory depressant or lethal action of local anesthetics. High doses may even enhance the toxicity of local anesthetics (647). In combination with anesthesia, on the other hand, PTZ and other analeptics seem to afford some protective action against the poisonous effects of local anesthetics (155, 581).

The antihistaminic substances, which in general are related chemically to the

local anesthetics, similarly have both stimulant and depressant actions. According to the reviewer's experience they also are antagonized by barbiturates. Small doses of mepyramine are synergistic with tribromoethanol and antagonistic to PTZ, but larger doses are synergistic with PTZ and antagonistic to tribromoethanol (1). Pentylenetetrazol antagonizes the antielectroshock effect of Benadryl (diphenhydramine) (105).

e. Action on anoxia. Analeptics usually fail to improve anoxic paralysis of respiration, whether due to asphyxiation by occlusion of the trachea, low atmospheric pressure, respiration of low O_2 in helium or bleeding (55, 165, 380, 690). Only experiments in rats which breathed low O_2 in nitrogen under pentobarbital anesthesia gave positive results with several analeptics (55). One may ask whether the few positive results were not due to a reduction of the depth of anesthesia by the analeptics and thus to the elimination of one of the factors contributing to anoxia.

Some investigations have dealt with the prophylactic action of different analeptics in anoxia. In rabbits (692) PTZ had no consistent action in high altitude sickness produced in the low pressure chamber. Pentylenetetrazol in low doses reduced the mortality of mice subjected to low pressure; it increased the mortality in larger doses. Other analeptics gave similar or slightly different results (172, 173). The problem was reinvestigated by determining the resistance of mice to reduced atmospheric pressure at various intervals after the administration of various centrally stimulant or depressant substances (189). The action of these substances was found to be correlated with their action on body temperature; hypothermic substances (PTZ, *etc.*) increased the resistance to reduced atmospheric pressure, whereas hyperthermic substances (methamphetamine, *etc.*) decreased it. Nikethamide had a biphasic action on temperature and on resistance to hypoxia. It is well known that lowering of the body temperature increases the resistance to anoxia while increasing body temperature has the opposite effect. The prophylactic action of PTZ in anoxia is abolished when the body temperature is kept constant by an increase of the temperature of the surroundings (189). More recently, a biphasic effect of PTZ in mice, at first a decrease and after an hour an increase in the resistance to hypoxia, has been described (535), but in that study the possible role of the temperature effect was not examined. However, the time lag observed between the injection of PTZ and its protective effect in these experiments suggests that this effect depended on the lowering of body temperature. However, the somewhat similar action of amphetamine on the resistance to hypoxia remains inexplicable; other factors such as the vascular effects of the latter drug may have played a role in its protective action. Rats which were made hypothermic and depressed by the hypoxia and hypercapnia resulting from rebreathing air in a closed chamber, recovered more quickly after treatment with subconvulsant doses of PTZ or amphetamine, but not with nikethamide (646).

There is need for further analysis of the effects of PTZ and of other analeptics on hypoxia and anoxia. If the action of the analeptics is directed against the cause of hypoxia, as in the case of the respiratory depression by anesthetics, the

beneficial actions should prevail. The action on respiratory depression resulting from lack of availability of O_2 consists of opposite effects: increase in motility, metabolism, oxygen consumption, and body temperature on the one hand, and decrease of body temperature by a specific mechanism and perhaps some cardiovascular effects on the other hand. It has further to be considered that the respiratory stimulant and other excitatory actions of the analeptics are dependent on the presence of O_2 in brain tissue, as is their convulsant action (124, 165, 252, 575). Of practical importance is the fact that the convulsant action of analeptic substances may first be masked by anoxia and then unmasked by the subsequent administration of O_2.

There is no agreement on the value of analeptic substances in anoxia due to carbon monoxide poisoning. Schmidt (585) suggested the use of sedative substances instead of analeptics in order to reduce the oxygen consumption of the brain. In rabbits respired with 0.4% carbon monoxide, PTZ and other analeptics (nikethamide, caffeine, lobeline) lost their analeptic properties with increasing duration of exposure (486, 487). Twenty minutes after the beginning of the carbon monoxide inhalation, the rabbits responded to PTZ with a decrease of respiration and sometimes with circulatory failure. Botta (66), on the other hand, observed positive respiratory and vasopressor responses to PTZ (and to nikethamide and 3-ethoxy-4-hydroxybenzoic acid diethylamide), when apnea was caused by respiration with 30% coal gas for 10 to 15 min. It may be assumed that the analeptic substances are most active in the phase of recovery. Cats which had been exposed to 0.5% carbon monoxide recovered more quickly after the injection of PTZ or nikethamide (494), and the elimination of carbon monoxide in dogs was found to be increased by these substances (492, 654). When rabbits were exposed to carbon monoxide until their righting reflexes were abolished, the threshold for the convulsant action of PTZ was increased threefold (49).

An important clinical problem is the treatment of asphyxia neonatorum with analeptics. Experiments led to two arguments against their use. Some authors (165) found the analeptic substances to be ineffective against anoxia due to breathing in helium. Others, (428) studying the action of analeptic substances on newborn rabbits with or without pretreatment with pentobarbital, emphasized the closeness of the respiratory stimulant and the convulsant doses. One may raise the criticism that these experiments did not reproduce the conditions of asphyxia neonatorum and thus do not exclude the possibility that adequate doses of analeptics may be beneficial.

f. Action on respiratory paralysis due to curare. Kahlson and Peil (359) observed in 1937 that PTZ was able to antagonize the paralysis of respiration produced by curare in rabbits. In these experiments, PTZ seemed to abolish the respiratory paralysis either by a direct action on the motor endplates of the respiratory muscles or by emission of a greatly augmented discharge from the CNS, which was able to overcome the peripheral paralysis. Recent investigations have demonstrated the possibility of an antagonism between curare and PTZ at central synaptic sites. This has been found in the EEG of artificially respired

cats under light pentobarbital anesthesia after the injection of very large amounts of curare (467) as well as in the EEG of unanesthetized and spontaneously breathing rabbits (46). In the former experiments PTZ presumably acted directly against the barbiturate (which acts synergistically with curare); in the latter, an indirect action of PTZ *via* an improvement of respiration cannot be excluded. Large doses of curare do not prevent the appearance of cortical potentials after the injection of PTZ (660 for ref.). Pick and Unna reported that in frogs other analeptics (picrotoxin, strychnine) did not antagonize the cortical depression caused by curare (660 for ref.). The possibility of a direct central antagonism between PTZ and curare is of special interest because the peripheral antagonism on the motor endplate may provide a clue for the mechanism of the central action of PTZ (see I.B.1.c).

The respiratory depressant action of the magnesium ion in dogs and cats is antagonized slightly by PTZ (and by amphetamine, camphor, and lobeline) without any concomitant reduction of the muscular paralysis. The combination of the analeptics with neostigmine almost momentarily abolished the "anesthesia" caused by magnesium ion (65, 554).

4. Action of pentylenetetrazol on body temperature. Pentylenetetrazol has a hypothermic action, which has been demonstrated in dogs, rabbits, rats, mice, and guinea pigs (189, 271, 389, 508, 587a, 609a). The response of rabbits given PTZ (*i.e.*, panting, *etc.*) resembles that seen after increasing the room temperature. This suggests that the physiological factors of heat regulation are mobilized by an adjustment of the central regulatory mechanism to a lower temperature. When dogs are transferred into an incubator, those pretreated with PTZ show tachypnea at a lower rectal temperature than do untreated animals (36). Like picrotoxin, veratrine, santonin, aconitine, triazoles, aminopyrine, and megimide (bemegride), PTZ is thus a "hypothermic convulsant agent." The mode of action on temperature regulation is probably identical for all these substances. The importance of physical factors (increased heat elimination) for their hypothermic action in rabbits has probably wrongly been denied by some authors (271 for further ref.).

In dogs, paralyzed by a neuromuscular blocking agent, which have been given *convulsant* doses of PTZ, the hypothermic action is masked by a hyperthermic action, probably due to a centrally mediated release of epinephrine and norepinephrine. This is seen only at ambient temperatures above 23 to 25°C, whereas at lower temperatures the hypothermic action prevails (609a). Observations with other species indicate that *subconvulsant* doses of PTZ have a predominantly hypothermic action. Here again the hypothermic action of PTZ is favored if the ambient temperature is low. This particular aspect of the cooling effect of PTZ has been discussed by the author in connection with its supposed central mechanism (271).

The hypothermic action of these convulsants led to the postulation of a "cooling center," which was later localized in the hypothalamus (569). In contrast to this, the thermogenetic functions are regulated by a system which is less sharply defined. The "centralization" of the cooling mechanism was interpreted to indicate that heat loss involves a more complicated integrative mecha-

nism than heat production. This difference is also demonstrated by the differential action of anesthetics. The paralysis of the thermogenetic centers during anesthesia is not dependent on the nature of the anesthetic, but is correlated with depth (77 and 271 for ref.). The temperature-lowering action of the hypothermic convulsant agents, on the other hand, is selectively blocked by barbiturates in very small doses. Paraldehyde is less effective, and urethane and chloral hydrate have the weakest action (77, 389, 568). Ether and amylene hydrate act synergistically in this respect (271 for ref.). Since analeptics with hypothermic actions have the strongest awakening effect, especially against barbiturates, the hypothermic and the general analeptic effects seem somehow to be correlated (389). This mechanism has been classified by recent experiments, which showed that very strong local heating of the hypothalamus, *i.e.*, stimulation of the thermoreceptive structures, elicited a typical arousal reaction (685). But the parallelism between the hypothermic action and the antagonism against barbiturates is not complete. Megimide (bemegride), which has a stronger antibarbiturate action than PTZ, does not have a stronger hypothermic action (280, 510). Aminopyrine, the hypothermic action of which is most pronounced, antagonizes barbiturates but only to a small degree.

H. H. Meyer related the hypothermic action of the convulsant agents predominantly to a stimulant action on parasympathetic centers (661a for ref.), but this generalization does not apply to the action of PTZ (see I.B.1.c.). Furthermore, nikethamide, which raises the body temperature (271), is more effective than PTZ on the parasympathetic centers (278). During the fall of the body temperature after the administration of hypothermic convulsant agents a typical sympathetic response, hyperglycemia, is observed (567). There is some parallelism between the hypothermic and the hyperglycemic effect of different convulsants (80, 280, 510) Hyperglycemia after PTZ and picrotoxin, like their hypothermic action, is selectively inhibited by barbiturates (276, 570).

These interactions are more easily understood if one assumes that the hypothermic convulsant agents act on an integrative system of the CNS which is responsible for the so-called ergotropic functions of W. R. Hess (321a). Increased motor activity requires not only the supply of energy, in the form of blood sugar, but also protection from the accumulation of heat. The exceptional position of barbiturates within the group of hypnotics may be based on their action on this system (276).

In rabbits, PTZ increases the temperature of the brain. This action is inhibited by barbiturates and by curare (182). The question arises, therefore, whether the hypothermic action of PTZ is due to a direct stimulation of the cooling center or to an increase in the temperature of the surrounding brain tissue.

In deep barbiturate anesthesia the hypothermic action of PTZ is reversed. It restores the body temperature to normal when it has been lowered by the anesthesia. This effect is the consequence of restoring the normal functions of the CNS and is coupled with the awakening effect of PTZ (271, 395). There is, therefore, no hyperthermia above the normal level. (The possibility of excessive heat production due to massive doses is not taken into account.) The assumption of the Danish school of anesthesiologists that the use of analeptics causes

hyperthermia in barbiturate poisoning cannot hold for PTZ and similarly acting analeptics. Unfortunately the authors (505, 506) do not state which analeptics were used. Only the alkylated acid amides (271) and the sympathomimetic amines have a hyperthermic action. The fact that Geastimol (Neospiran, tetraethyl-phthalamide), which raises body temperature, is very much used in Scandinavia suggests that this substance was used in these studies reported. For other reasons as well, the analeptics in these groups are not suited for the treatment of barbiturate poisoning.

Analeptic effects of PTZ and other agents on cold-induced paralysis of the medullary centers are not pronounced; indeed, they are not able to stimulate respiration (247, 348), and their toxicity may be increased; the convulsive threshold is lowered and the tetanic component of the convulsions is enhanced (348). The pressor action of PTZ, nikethamide, and Vandid is reduced even more than the respiratory action (391).

It has often been shown that lowering the body temperature increases the tendency of the CNS to respond to analeptics with convulsions and tetanic discharges (385, 529, 643, 661 for further ref.). On the other hand, in cooled homeothermic animals the *intensity* of convulsions is reduced, and the duration of convulsions and the survival time are prolonged (426, 634, 643). This may explain why an increase in mortality is not always observed. The choice of convulsant agent, anesthetic, species, degree of cooling, and the mode of application are all of importance. The lethal activity of PTZ in cooled (as well as in hibernating) animals is usually unchanged (426, 529, 634). The decrease in the intensity of convulsions and the prolongation of survival time demonstrate that in the cold the reduced metabolic rate and the reduced energy requirements of the cells tend to balance the increased excitability. The prolonged duration of the PTZ-induced seizures may be due to a slowing of the detoxifying processes (521).

Below 20°C the spinal reflexes of homeothermic animals are eventually paralyzed. This action of cold has sometimes been compared with that of anesthesia, and with that of anoxia. The latter comparison has been criticized. Even the former is unable to explain satisfactorily the action of analeptics in hypothermic animals. It has been suggested that cooling causes partial depolarization of the cell membranes in the spinal cord combined with an intermediate instability, which is responsible for the tetanic phase (385). Since the analeptics seem to have a similar action, it is understandable that the action of analeptics is synergistic with rather than antagonistic to that of cooling.

The pressor action of sympathomimetic amines is not reduced in cooled animals (391). They have a pronounced analeptic action and a low toxicity in hibernating animals (529).

The action of the analeptic substances in *hyperthermia* is of interest with respect to their action in fever. Clinical observations indicate that in fever higher doses of analeptics are required and tolerated. The general tendency to convulsions, on the other hand, is high in fever and hyperthermia, especially in children. The convulsant as well as the lethal doses of several convulsants,

including PTZ, are reduced by an increase of the body temperature (77, 109). The high altitude-induced convulsions of mice are likewise facilitated by a rise in temperature (271 for ref.). These findings seem to be contradicted by the observation that an increase in temperature causes an increase of the threshold for electroshock in rats and depresses the sensitivity to PTZ and picrotoxin (643, 661). The increased threshold is accompanied by reduction of the duration of convulsions with an absolute and relative prolongation of the tonic phase. Warming of the cortex causes an increase in the frequency of locally evoked picrotoxin potentials and shortens the duration of the response (653). The effect of heat resembles that of anoxia. It thus appears that the increase in body temperature acts in two opposite ways: it increases the threshold for convulsions, and, on the other hand, it favors the initiation and spread of convulsions by an intensification of neuronal discharges. The latter effect in turn accelerates the onset of anoxia, which shortens the duration of convulsions. In the cold the threshold, intensity, and duration of convulsions seem to be affected in the opposite way.

The importance of the increase in metabolic rate in hyperthermia for the threshold or the intensity of seizure discharges has not been studied. Thyroid hormone lowers the convulsant dose of PTZ (205).

5. Antianesthetic action. As the analeptic substances stimulate all parts of the CNS, they might be expected to be most effective against general anesthetics. However, even the strongest analeptics do not possess the same antagonistic potency against all anesthetics; on the contrary, they have a certain specificity, especially against barbiturates. The mutual antagonism between analeptics and anesthetic agents makes it possible to overcome severe depression of the CNS by increasing the amounts of analeptic substances in relation to the depth of anesthesia. However, only a few analeptic substances are effective against poisoning with lethal amounts of anesthetics and hypnotics.

a. The antagonism between PTZ and the barbiturates. The antagonistic action of PTZ against the barbiturates was discovered by Tartler (326 for further ref.), and has since often been confirmed with various barbiturates in different species.[2] However, it is probable that PTZ is not able fully to antagonize the barbiturates in any of the stages of anesthesia (92). With increasing depth of anesthesia the antagonism becomes less and less complete. The awakening effect eventually is absent, even after convulsant doses of PTZ, although in light anesthesia nearly complete awakening can be obtained without convulsions. It is evident that with increasing depth of anesthesia, the centers for the righting and labyrinthine reflexes fail to respond to PTZ earlier than those responsible for convulsions (395). A detailed study showed that the various effects of PTZ were affected differently by an increase in the depth of anesthesia (431). The effects of PTZ on the CNS as a whole, therefore, cannot be regarded as a simple "mirror image" of the effects of barbiturates.

In spite of these considerations, PTZ has a life-saving action against lethal

[2] Only a few publications (449, 531) deal with species differences. Such differences should be studied in more detail, since some of the reports are contradictory.

doses of barbiturates (33, 34, 61, 68, 98, 169, 181, 218, 238, 239, 286, 371, 395, 431, 475, 704, 723). This antagonistic action of PTZ is most important in poisoning with long-acting barbiturates (barbital, phenobarbital). The effects of these substances are more difficult to counteract; they cause death not only by respiratory paralysis, as do the shorter-acting barbiturates (451), but also by secondary complications of the cardiovascular system and of the lungs (238, 239, 448, 453).

The most detailed analysis of the action of PTZ in lethal poisoning of rats with barbital was undertaken by Einhauser, using the isobolometric method (169). The LD50 of barbital was increased up to about 180% by a single dose of PTZ; fractional injections were not more effective. The life-saving effect of PTZ was markedly reduced if the dose of barbital was increased significantly above the LD100. The optimal dose of PTZ equalled about two-thirds of the dose of barbital. When using the "minimal lethal dose" (LD1) of barbital, the optimal dose of PTZ already surpassed its LD50 for normal rats. When the time interval between the injection of barbital and of PTZ was increased, the optimal dose of PTZ became smaller. It is remarkable, however, that at any time after poisoning with lethal amounts of barbital about the same percentage of the then surviving animals could be saved by PTZ.

The action of PTZ against phenobarbital is allegedly less pronounced than that against barbital (218); it elevated the LD50 of phenobarbital in mice to only 120% (431). The optimal dose of PTZ is approximately one-half its LD50 in normal mice. There are no exactly comparable experiments in mice indicating the maximal percentage increase of the LD50 of barbital produced by PTZ and establishing the required dose. In mice poisoned by the LD70 of barbital, the mortality was perceptibly decreased only when 2.5 times the LD50 of PTZ was administered (286). This suggests that the equieffective doses of PTZ against barbital are higher than those against phenobarbital.

The danger of overdosage of PTZ in barbiturate poisoning is relatively slight, since the antagonistic action of the barbiturates against PTZ is more complete than the inverse antagonism of the latter against the former (169, 395, 431, 704). The LD50 of PTZ may be increased 6.5 times in rats by barbital and 4 times in mice by phenobarbital (169, 431). This effect is related to the anticonvulsant action of the barbiturates. It is mainly the tonic phase of convulsions which is blocked (431). One might expect that on the basis of the decrease in the intensity of convulsions, barbiturates would increase the ratio of the convulsant to the lethal dose of PTZ. This has been described in the case of phenobarbital (431). Only a few experiments have dealt with the modification of the convulsant threshold dose of PTZ by increasing doses of barbiturates (49, 107, 108, 431). Subanesthetic doses of phenobarbital are more effectively antagonistic to PTZ than are equivalent doses of barbital (237, 619, 687). Increasing amounts of phenobarbital, however, cause about the same increase in the convulsant threshold dose of PTZ as do increasing amounts of barbital (107). In a certain range of dosage there is a synergism between the excitatory action of phenobarbital and the stimulant action of PTZ (264, 431). High doses of barbiturates

abolish the convulsant action of PTZ completely (27, 169, 218, 279, 286, 655). The precise relationship between the optimal analeptic, convulsant, and lethal doses of PTZ under the influence of increasing doses of barbiturates is not known.

A very pronounced effect of relatively small amounts of PTZ against lethal doses of the shorter-acting barbiturate pentobarbital, has been shown in mice and rabbits (33, 181, 371). These experiments also revealed the risk of delayed convulsions when the effect of the barbiturate has worn off, but this occurs only after very high doses of PTZ (704). When one gives increasing doses of pentobarbital, the convulsant threshold dose of PTZ is found to increase; when phenobarbital is given in a similar manner the convulsant threshold dose of PTZ increases slightly more rapidly (107). Experiments were undertaken to search for a pentobarbital-PTZ combination which could provide a certain protection against intended or accidental poisoning with this barbiturate (180). The oral administration of PTZ failed to reduce the lethal effect of simultaneously administered pentobarbital in dogs when the dose of PTZ given amounted to threefold the quantity of pentobarbital (694).

The appearance of delayed convulsions should be expected, especially after barbiturates of short action. It is the more remarkable that a single injection of a large amount of PTZ can antagonize a lethal dose of thiopental without causing convulsions (61). This indicates that the anticonvulsant action of barbiturates, including the short-acting members, is longer lasting than the anesthetic or hypnotic effects (118, 169, 285). An antagonism of PTZ to lethal doses of hexobarbital has been demonstrated only by the simultaneous infusion of hexobarbital and PTZ (129, 723). Such experiments do not take into account the problem of delayed convulsions. It has further been shown by these experiments that the antagonistic effect of PTZ against butallylonal (Pernocton) is less than that against hexobarbital (723). The low antagonistic action of butallylonal against lethal amounts of PTZ (237), on the other hand, shows that the mutual antagonism between these two substances is weak.

The life-saving action of PTZ against the short-acting barbiturates is mainly due to its respiratory stimulant effect. Additional effects, however, may be involved in the antagonism of PTZ to barbiturates of long duration of action. The sum of these stimulant actions results in a general reduction of the depth of anesthesia without immediate awakening and in a shortening of the duration of anesthesia. However, no experimental evidence is available to indicate whether the barbiturate blood level is affected by PTZ. Besides the stimulant action on respiration and circulation (136, 279), the following actions of PTZ in barbiturate poisoning have been demonstrated: activation of the sympathetic system (276) and restoration of heat regulation (271, 395), of swallowing (271), of vomiting (600), and of spinal reflexes (387). There have been no experimental investigations of the effect of PTZ on renal function in barbiturate poisoning.

Cortical potentials of cats or dogs, even when fully depressed by phenobarbital or barbital, are reactivated by PTZ (136, 159, 279). Negative results (94) apparently were due to inadequate doses. The degree of possible reactivation depends on the depth of anesthesia. In light anesthesia the EEG pattern is

changed from the spindle, slow-wave activity (sleep pattern) to a low-voltage, high-frequency activity. The effect of PTZ has been interpreted as a result of increases in amplitude and frequency, which in turn are considered consequences of increased synchronization and recruiting, decrease of threshold, development of repetitive activity, and increase of spread of activity (160, 207, 613, 660, 680). The PTZ effect is manifested also in deep barbiturate anesthesia by an intensification of the activity of the sensory and motor cortex following stimulation of the sciatic nerve; in light anesthesia by an increase in both amplitude and frequency of the "barbiturate bursts" of the cortex (660); also, in deep anesthesia as an increase in the number and amplitude of unit spikes recorded from the thalamus with microelectrodes (680), as a decrease in latency of the photic response at various levels of the optic system following their increase by a barbiturate (353), and as abolition of the slow barbiturate waves in the human EEG (373).

It remains to be considered to what degree the action of PTZ on the reticular activating system is involved in the reactivation of the EEG when it is depressed by barbiturates. Barbiturates depress the activating, and stimulate the recruiting system; PTZ shifts the balance of these two systems in the opposite direction (659). In "encéphale isolé" preparations under light pentobarbital anesthesia, intraventricular injections of PTZ transform the spindle, slow-wave activity into a low-voltage, high-frequency activity. This effect is mediated by the ascending reticular system (657). After higher doses of pentobarbital the reactivation is incomplete, and with increasing intraventricular doses of PTZ convulsions appear finally without being preceded by the arousal pattern. The action of intravenous injections of PTZ in deep anesthesia seems, therefore, to be the result of the general activating effect of PTZ rather than of selective action on the activating system. It has further to be considered that the predominantly synchronizing action of PTZ on the cortex opposes the desynchronizing effect of the reticular system (502).

In order to explain the life-saving action of PTZ against the long-acting barbiturates, one has to consider all those actions (other than its action on respiration) which can prevent secondary damage of the cardiovascular system: *i.e.*, the action of the vasomotor center, the increase in muscular tone, the appearance of spontaneous movements, the restoration of heat regulation and of sympathetic tone, the increase in respiratory movements which prevent hypostasis and atelectasis, and the shortening of the duration of anesthesia. The publications of the Scandinavian anesthesiologists (505, 506) led to the widespread opinion that the circulatory signs are but the consequence of anoxemia. Analeptics were said to be of no value and even to be harmful because they are believed to increase the oxygen consumption without having significant respiratory stimulant action in barbiturate intoxication. But this view disregards many of the experimental facts. Unfortunately there are no experimental studies on the influence of artificial respiration on the lethal action of long-acting barbiturates. Experiments with shorter-acting barbiturates are not conclusive, because they have been shown to cause cardiovascular failure only under extraordinary

conditions, *i.e.*, when 6 to 7 times the lethal amount of aprobarbital (372), or over 4 times the lethal amount of pentobarbital was given under artificial respiration (413). In these experiments analeptics raised the lethal dose of pentobarbital only by a factor of 1.4 (bemegride) or 2.0 (picrotoxin). Artificial respiration was more effective; it raised the lethal dose up to the point where cardiovascular failure appeared, and was not able to prevent such. [According to the reviewer's recent experiments, the lethal dose of thiopental is raised more in dogs by a combination of artificial respiration and suitable analeptics (*e.g.*, bemegride) than by either of these two measures alone.] The mechanism of circulatory failure after extremely high doses of short-acting barbiturates is probably not identical with the mechanism of the secondary circulatory failure after lower doses of the long-acting barbiturates.

Peripherally acting cardiovascular-stimulant drugs are said to enhance the life-saving effect of artificial respiration in barbiturate poisoning (413). But there is no agreement about the value of the combination of PTZ with peripherally acting cardiovascular-stimulant drugs (33, 169, 238, 239, 419).

Only a few publications deal with the gradual decline of the effectiveness of PTZ as observed as the depth of anesthesia is increased. Koll (387) assumed this effect to be due to a discrepancy between the large number of anesthetized neurons and the small number of neurons responding to PTZ. As the postulated specific action of PTZ on the motor neurons of the reflex arc has been challenged (256), the hypothesis cannot yet be accepted as proved. Another hypothesis is based on the development of primarily depressant effects of PTZ. Most authors believe PTZ to have a pure stimulant action (*e.g.*, 236, 704, 723). An important argument in favor of this view is that large amounts of PTZ are tolerated in barbiturate poisoning without any preconvulsant depressant effects (704). The observation of Mousel and Essex (491) that very small doses of PTZ prolong thiopental anesthesia is difficult to interpret and, because of the wide scatter of results, difficult to accept. A depressant action of PTZ was also found by Carlsson and Theander (91, 92), who measured the nitrous oxide threshold in animals under barbiturate anesthesia. This action, however, seems to be postconvulsant, since the authors mentioned slight convulsions and since they found also that an increased dose of barbiturate abolished the depressant effects of PTZ. The same authors have found also that PTZ lowers the nitrous oxide pressure required to obtain a certain degree of depression in normal guinea pigs. But according to the reviewer's recent experiments, it has to be considered that this effect may be due to the lowering of the body temperature by PTZ, and not to a real depressant effect of PTZ. Bemegride and picrotoxin act similarly, but not nikethamide, which raises temperature. Some findings, however, indicate that in extreme cases of barbiturate poisoning, when the limit of the effectiveness of PTZ is nearly reached, massive doses of PTZ cause depression of the CNS without the appearance of preceding convulsions (27, 169, 218, 279, 655).

The relationship of the antianesthetic action of PTZ to its convulsant action has been interpreted in various ways. The question is whether there is a quantitative rather than a qualitative difference between the analeptic and the convul-

sant actions. Each action is influenced differently by certain drugs (cocaine, γ-chlorocyclohexane) or by increasing amounts of barbiturate (317, 401, 657). It has also been found that an analeptic effect can be demonstrated in barbiturate poisoning as long as convulsions can be elicited (286, 704). It may be true that on certain motor neurons the analeptic action is an intermediate step to the convulsant action, but the phenomenon of analepsis certainly comprises more than just motor phenomena. Convulsions, on the other hand, include neurophysiological processes which are not inherent in analepsis.

Arguments which have recently been put forward against the use of analeptics in poisoning with hypnotics (505, 506) are based on the convulsant action of the analeptics, which is said to cause a secondary lack of O_2 in the brain due to the discrepancy between supply and consumption of O_2 (585, 586). What is evidently disregarded is the fact that the aim of therapy is the restoration of the activity of the CNS to a normal level, rather than the production of convulsions. Furthermore, it is not clear to what degree convulsions cause cerebral anoxia. The increased O_2 consumption of the brain during convulsions has to be regarded as proved (12, 133, 134, 136, 203, 469). However, during convulsions the increased O_2 consumption is accompanied by an increase in cerebral blood flow (136, 203, 326, 351, 526, 585, 586). The latter effect is absent only after repeated injections of high doses of PTZ (203). These observations also disprove the old concept that PTZ-induced convulsions are due to vasoconstriction (144, 167) as well as older reports of a long-lasting decrease of central blood flow with slight PTZ convulsions (416); such conclusions were due to misinterpretations (439). The cerebral blood flow is dependent only partly on the systemic blood pressure (136, 160, 191, 326, 520). The postconvulsant reduction in O_2 consumption and decrease of blood flow as seen in light anesthesia (585, 586) have been compared with anoxia due to hemorrhage. However, the authors failed to demonstrate the transition from convulsions to anoxic depression; in that case a critical increase in the arteriovenous O_2 difference should have been detected (136). Furthermore, the decrease of blood flow and O_2 consumption have not been observed after injection of convulsant doses of PTZ (or of picrotoxin or bemegride) in cases of severe barbiturate poisoning (136).

The mechanism of postconvulsive depression thus remains in question. In addition to the exhaustion of the CNS, the following possibilities have to be considered: a diminution of the blood flow under special conditions (203), anoxemia due to the increased O_2 consumption of the muscles and to the tetanic fixation of the respiratory muscles (327, 394), the relation to the "spreading depression" (414, 676), and the relation to catatonic reactions (253, 379, 651). The difference between the minimal convulsant and the lethal dose, as well as the tendency to cause secondary depression varies from analeptic to analeptic (56, 200, 272, 280, 325, 326, 704). These facts emphasize the importance of the specific action as well as the site of action of the analeptics. The controversial results obtained in studies of the histopathological changes observed after convulsions and of the functional after-effects do not allow any definite conclusions concerning the possibility of

anoxic damage of the brain following repeated shock treatment, and will not be discussed here. Pentylenetetrazol in subconvulsant doses even reduces the recovery time for maximal electroshock seizures in rats (642).

Slight convulsions do not abolish the life-saving action of PTZ (239, 286, 395), but in the event of violent convulsions, the therapeutic effect is reduced (169). Convulsions should therefore be avoided in clinical cases by careful intravenous injections (310, 355, 394).

Finally, the question of whether the increase in metabolism of the brain produced by analeptics is harmful or not is a quantitative problem. Since barbiturates lower the O_2 consumption of the brain, a return to normal under the influence of analeptics should do no harm, since this effect is accompanied by a restoration of the reduced cerebral blood flow. This has recently been demonstrated after injections of PTZ, picrotoxin, or bemegride into dogs under deep barbital anesthesia (136). According to experiments on perfused heads of dogs, the increase of the O_2 consumption under PTZ seems not to be caused by alterations of the blood flow (293).

b. Other anesthetics, hypnotics, and sedatives. The action of PTZ against other anesthetics, hypnotics, and sedatives has been studied much less extensively than its antagonism to barbiturates. In general, the antagonism appears to be weaker than that against barbiturates.

Paraldehyde: The mutual antagonism is relatively strong (237, 326, 330), but probably weaker than against barbiturates. Pentylenetetrazol reduces the mortality of rats after a dose of paraldehyde which is 50% above the LD100 (237), and paraldehyde antagonizes PTZ at up to three times the lethal dose of the latter (236, 237, 263, 687).

Chloral hydrate: The mutual antagonism is weaker (33, 237, 389), probably because delayed lethal convulsions appear after the end of the short action of chloral hydrate (326). Small doses of PTZ, which are tolerated without delayed convulsions, antagonize chloral hydrate in rats up to its LD90.

Chloralose: The antagonistic action of PTZ is weak and has not been demonstrated for lethal doses of chloralose (159, 164, 273, 321). In chloralose anesthesia, PTZ readily causes twitching, as well as spikes and waves in the EEG (159). This agrees well with the stimulant component of chloralose. Chloralose nevertheless increases the lethal dose of PTZ by a factor of 2 (273) or 3.5 to 5 (164).

Urethane and related compounds: The antagonism between urethane and PTZ is weak in both directions, although an analeptic effect of PTZ is not absent (26, 217, 218, 235, 237, 277). The antagonism is weaker than between PTZ and chloral hydrate. Ethynylcyclohexanol carbamate (Valamin) is not strongly antagonized by PTZ (280), but it has a strong anticonvulsant activity (639). Respiratory depression by propinylcyclohexanol carbamate is antagonized by PTZ (100).

Ethanol: The presence of a mutual antagonism has repeatedly been demonstrated (321, 468, 702, 703), but it has not been studied in the range of lethal doses. Pentylenetetrazol has been said to sedate excited alcoholics, possibly by the stimulation of the depressed inhibitory centers of the cortex (392).

Other alcohols: Pentylenetetrazol has no life-saving action against β-chlorovinylethylethynyl carbinol (371). There is little evidence of an antagonistic action of PTZ (480) against methylpentynol (ethylethynylmethyl carbinol).

Bromethol (tribromoethanol solution USP XVI, Avertin): The demonstration of any antagonistic action of PTZ is complicated by the appearance of delayed convulsions (237, 285, 326, 375, 421). This has been attributed to an inhibition of the breakdown of PTZ in the liver (237, 263). Recent investigations, however, indicate that the delayed convulsions are due to a discrepancy between the durations of the actions of PTZ and of bromethol (285). Many experiments have shown an analeptic effect of PTZ against bromethol, but do not allow any conclusion as to a life-saving action of PTZ (168, 262, 285, 326). The simultaneous infusion of bromethol and PTZ into cats caused a doubling of the lethal dose of bromethol (326), but this experiment disregarded the problem of possible after-effects of PTZ. The life of rabbits which had received lethal amounts of bromethol rectally was prolonged 4 to 10 times; the late deaths may have been due to the injurious effect of bromethol on the intestine (33).

Volatile anesthetics: Pentylenetetrazol is a weak antagonist to ethyl ether; conversely, ethyl ether causes but a weak inhibition of the convulsant activity of PTZ (49, 158, 341, 479), as seen in the EEG as well as in the whole animal. Pentylenetetrazol, on the other hand, inhibits the excitation due to ether (495).

Nitrous oxide (91, 92) and trichloroethylene (341) are scarcely influenced by PTZ.

Antiepileptics: As very little is known about the action of PTZ against these substances, they cannot be discussed in detail. The inverse antagonism, however, has frequently been used as a screening test for anticonvulsant activity, and as a test of antiepileptic potency.

With the exception of phenobarbital, trimethadione (troxidone, tridione) is the only antiepileptic substance against which the antagonistic action of PTZ has been tested (177, 434, 660). There is a strong reciprocal antagonism between PTZ and trimethadione in the EEG and in spinal reflexes. The antagonism between these two substances with respect to their general toxicity, however, seems to be more unidirectional from trimethadione to PTZ (434).

Mephenesin: Mephenesin, which acts specifically against strychnine, antagonizes only the tonic phase of PTZ convulsions (106). Pentylenetetrazol and other analeptics, with the exception of 1-n-butylamino-3-toluidino-2-propanol, fail to antagonize mephenesin-induced paralysis (43). There is, however, a reciprocal antagonism between PTZ and 1-(*o*-toluoxy)-2,3-bis-(2,2,2-trichloro-1-hydroxyethoxy)-propane (549).

Anti-Parkinsonian or antinicotinic substances: Trihexyphenidyl (benzhexol, Artane), caramiphen (Panparnit), and the phenothiazine derivatives, diethazine (Diparcol), chlorpromazine, ethopropazine (Parsidol), and mepazine (Pacatal). This group of substances is of particular interest because of its action on the reticular activating center and because both PTZ and strychnine have been said to act on the same centers (21, 657). But while these substances have central antinicotinic but hardly an antistrychnine action, only diethazine and ethopropazine

are effective against PTZ convulsions (29, 70, 391). The anti-PTZ action of some phenothiazine derivatives is independent of their antinicotinic potency as well as of their blocking action against the arousal reaction (29). Barbital, on the other hand, acts synergistically with chlorpromazine, so that the antagonism of barbital against PTZ is increased, while the antagonism of PTZ against barbital is reduced (287). Chlorpromazine abolishes the pressor response to PTZ (391). An antagonism of PTZ toward chlorpromazine has been demonstrated in the "stress reaction" of *Betta splendens* (669).

Reserpine: In contrast to other sedative agents, reserpine does not protect rats against PTZ-induced convulsions (668), and even facilitates the tonic phase of the convulsions in mice (47, 104). 5-Hydroxytryptamine does not antagonize the facilitating action of reserpine, nor does it elicit tonic convulsions when combined with PTZ (48). The facilitating action of reserpine is counteracted by trimethadione and phenacemide (47) as well as by iproniazid (320, 378).

Anesthetic steroid hormones: There is a mutual antagonism between PTZ and anesthesia produced by steroids (progesterone, hydrocortisone, desoxycortone acetate, hydroxydione *etc.*) (323, 601, 684). Desoxycortone acetate and cortisone have been found by others (423) to be ineffective against PTZ-induced convulsions.

Alkylphosphate anticholinesterase agents: The paralysis of the central control of respiration resulting from high doses of Paraoxon (diethyl-4-nitrophenyl phosphate) was reported to be reversed by PTZ, but not by 2-PAM (pyridine-2-aldoxime methiodide), a specific enzyme-reactivating compound (578).

c. General remarks. One of the most important reasons for the differences in the action of PTZ against the different anesthetics and hypnotics may be that the latter groups of drugs have different primary sites of action within the higher regions of the CNS. The analeptic potency of PTZ on the spinal cord apparently is identical against various anesthetics (387). Specific differences in the action of PTZ against various anesthetics have been demonstrated in the electrocorticogram as well as in centers of the brainstem responsible for the righting reflex, the blood sugar level or blood pressure regulation, and cooling effects. By this criterion, the various anesthetics might be assumed to act differently on the centers which regulate the righting reflex and other responses listed. Pick's (530a) subdivision of the anesthetics into those which act on the cortex and those which act on the brainstem seems inadequate to explain the differences in the awakening (*i.e.*, restoring of the righting reflexes) efficacy of PTZ. Moreover, some of the substances which are (in contrast to barbiturates) supposed to act on the cortex are relatively effectively antagonized by PTZ (*e.g.*, paraldehyde, chloral hydrate) whereas others supposedly of the same group (*e.g.*, ethyl ether, chloralose, urethane) very poorly. Recently it was observed that the righting reflexes of the labyrinthectomized cat (which are dependent on a cortical response) were restored by PTZ more effectively when the anesthetic was paraldehyde or chloral hydrate than after barbiturates (583); this is not consistent with Pick's (530a) hypothesis. No differences in the action of various anesthetics on the activating

center have been described (21). This should be studied in more detail in connection with the problem of analepsis.

It is also possible that the real reason for the varying efficacy of the antagonistic action of PTZ does not lie in the varying affinities of different anesthetics for different levels of the brain but in their varying affinities for certain specific structures or chemical groupings within the various levels.

6. Mode of action. It is not yet possible to provide a coherent theory of the elementary processes involved in the antagonistic action of PTZ. Pentylenetetrazol fails to increase the respiration or glycolysis of isolated brain tissue *in vitro* but rather, like the barbiturates, lowers it (138, 367, 446, 455, 470, 611, 695, 710).

A possibility to be considered is that the primary site of action of PTZ is the cell membrane and that PTZ, by influencing the initiation and the conduction of excitation, restores to normal the membrane stabilizing effect of anesthetics. The effect of high doses of PTZ on the permeability of the cell membranes of the frog muscle (632) and frog skin (331) has been studied; however, the effects in these structures do not differ from those of anesthetic substances. Changes in the permeability of the brain induced by PTZ convulsions (425, 626) as well as movements of electrolytes (632, 641) are caused by the convulsant action of PTZ rather than by its analeptic effect. Furthermore, the distribution of sodium and potassium seems to be influenced in a similar manner both by anesthetics and by PTZ (403). An action of PTZ on carbonic anhydrase, an enzyme which may be involved in the movements of electrolytes, has been both described (366, 664) and denied (403). Other biochemical hypotheses, including the influence of convulsions on phosphate metabolism, will not be discussed here, because they hardly contribute to a better understanding of the antianesthetic properties of PTZ.

Although PTZ readily penetrates into all peripheral organs (150), its peripheral effects are negligible (326), even in peripheral nerve fibers (660). The action of PTZ thus differs from that of the anesthetic substances in being totally dependent on the complex structure of the CNS and on functional mechanisms which are nonexistent in most non-nervous organs, such as processes of facilitation and summation, and the ability to discharge spontaneously (18). These phenomena are typical of synaptic structures and nerve cells, which are undoubtedly the site of action of PTZ (160, 179, 540).

Further electrophysiological studies may lead to elimination of the mechanism of the action of PTZ against anesthetics and other CNS depressants. Up to now such studies allow no clear interpretation of such a distinct action as the antagonism of PTZ against barbiturates. In spinal cats, PTZ does not antagonize the depressant effect of pentobarbital on the recovery process of the monosynaptic pathway, whereas it strongly antagonizes that of trimethadione (177). This difference suggests a localization of the action of PTZ, since trimethadione presumably affects synaptic recovery by acting at a presynaptic site without a primary depressant effect on the synaptic transmission, whereas the effect of pentobarbital on synaptic recovery probably depends on the synaptic depression which is observed coincidently. Under pentobarbital, PTZ increases only polysynaptic

activity. Another point of interest with respect to the localization of the action of PTZ is that it does not influence the depression of the post-tetanic potentiation produced by diphenylhydantoin (phenytoin, Dilantin), which is known to have little protective action against PTZ convulsions in contrast to the strong effect of trimethadione (176a for further ref.).

It may be objected that these studies do not take into account the influence of supraspinal factors on spinal reflexes, and that the results may not be transferable to nervous structures other than the spinal reflex arc. Studies of the "cycle of cortical excitability" seem to indicate that PTZ, by its predominantly synchronizing and recruiting action, is not a perfect antagonist to barbiturates, which lengthen the period of recovery following preliminary excitation (in addition to having a depressant action on the amplitude of the response) (207). Amphetamine, in contrast to PTZ, shortens the recovery time; in the intact animal, however, this drug is not a good barbiturate antagonist (see V).

On the other hand, evidence for an antagonistic action of PTZ (and of picrotoxin and strychnine) against the depressant action of barbiturates on synaptic transmission has been obtained in studies with microelectrode recording on the unit activity of diencephalic and mesencephalic structures (584, 680). Whereas PTZ and barbiturates have opposite effects with respect to frequency and amplitude of spontaneous unit activity (probably by acting on the rate of recovery of the unit firing), convulsants and light barbiturate anesthesia cause similar changes by forming a pattern of rhythmic grouped discharges (584). The convulsive waves differ from the slow waves of spindle-bursts under barbiturates, although there is a possible relationship between them (680).

7. Fate and elimination. Approximate values for the rate of elimination of PTZ have been obtained from experiments in which the speed of injection was varied (49, 285, 326, 704). The rate of inactivation of PTZ depends on its concentration in the body (649, 704); its half-life was found to be 2.5 hours (178). High doses, on the other hand, are retained for a surprisingly long time (10 hours or more) (90). Older experiments stressed the importance of the liver for the elimination of PTZ (149, 326, 649), but the importance of the kidneys, which was unappreciated for a long time (150, 193, 326, 599), has now been established (178). The elimination through the kidneys is said to be dependent on the formation, in the liver, of an unknown inactive intermediate substance, which is retransformed to active PTZ in the urine (178). However, the elimination of unchanged PTZ through the kidneys has not been excluded (285).

II. PICROTOXIN

1. Chemistry. Picrotoxin (Pi), from *Anamirta cocculus*, can be separated by chemical means into two substances, both of which are dilactones: picrotoxinin $C_{15}H_{16}O_6$ and picrotin $C_{15}H_{18}O_7$ (294, 636). Picrotoxadiene, a degradation product of picrotoxinin, has been synthesized (120). Picrotoxinin, the active principle, has been used in barbiturate poisoning but does not appear to have any advantages over picrotoxin (381).

2. Convulsant action. a. General. An outstanding property of Pi is the latency

which precedes any response (34, 129, 269, 491, 638, 704). The latency, which decreases with increasing dose, complicates the therapeutic use of Pi, especially in analeptic therapy where overdosage is to be avoided. The latency period is shortened by injection into the cisterna magna (553), or into the vertebral or carotid arteries (354).

In the rabbit the difference between the convulsant and lethal doses is much smaller than that for pentylenetetrazol or nikethamide (280, 704), and Pi causes a more pronounced postconvulsive depression than does pentylenetetrazol (34, 148, 280). The bases of their differences should be studied in more detail, since Pi has been proposed for shock treatment (441).

b. Sites of the convulsant action. Experiments on frogs (592) suggest the midbrain as the primary site of action. The cortex, however, also takes part in the convulsant response, as demonstrated by the effect of topical application of Pi (638), by the EEG (187, 279, 298, 637), and by the lowering of the threshold for electrical irritability of the anesthetized cortex (139, 395). The glycogen content of the cortex is increased during Pi-induced convulsions (99), and the acid phosphatase activity in the largest cells of the motor cortex (as well as in cerebellar neurons) is decreased (88, 637). There are, however, some indications that the brain stem may be more involved in the convulsant response to Pi than in that to pentylenetetrazol [*e.g.*, increase in glycogen in the brain stem (99), pronounced response to injections into the vertebral artery (354)].

The spinal cord of the frog is less sensitive to Pi than are the higher levels of the CNS (592). Picrotoxin has been observed to produce a reflex strychnine-like and strychnine-synergistic action in the frog (592), and an increase in the sensitivity of rabbits to sensory stimuli (142, 533). The drug has a position intermediate between pentylenetetrazol and strychnine when tested against anticonvulsants (102). Optic or acoustic stimuli do not elicit generalized convulsions in cats treated with Pi (211). In contrast to strychnine and pentylenetetrazol, it causes a simultaneous increase in reflex irritability and a convulsant response in the spinal cord of dogs (377).

3. Autonomic actions. Older publications stressed the parasympathomimetic action of Pi (665). Signs of this action include salivation (299), vomiting (98, 300, 441), increased intestinal peristalsis, tetanic response of the turtle stomach (566), contraction of the bladder, bradycardia, and antagonism of the inhibition of vagal centers by barbiturates (248). The central origin of some of these actions has been demonstrated by experiments involving nerve section, anesthetics, and topical application of Pi. Mydriasis (404) and tachycardia are observed only during convulsions. On the other hand, even subconvulsant doses produce some signs of sympathetic activity: pronounced hyperglycemia (567, 570, 648), stimulation of the sweat centers of the spinal cord, rise in blood pressure, inhibition of diuresis (probably by constriction of the renal blood vessels) (384), mydriasis if the ciliary ganglion has been removed previously (612), and inhibition of intestinal movements (363). In contrast to what is seen in the dog and cat, the rectum and the bladder of the rabbit are inhibited and the nonpregnant uterus is stimulated by Pi (522). The central origin of these effects has been shown by appropriate

sectioning of the spinal cord or the splanchnic nerves. The hyperglycemia is abolished by anesthetics, especially by barbiturates (568). Picrotoxin, unlike pentylenetetrazol, does not bleach the frog skin (278). It is uncertain whether Pi, in contrast to pentylenetetrazol, acts predominantly on the parasympathetic or the sympathetic centers. The fact that Pi has a more marked hyperglycemic action than pentylenetetrazol (80) may reflect a stronger general action on the autonomic centers, and not necessarily a difference in the balance produced between sympathetic and parasympathetic tone.

The action of Pi on the peripheral autonomic nervous system and on its end-organs is so weak that its contribution to the response of the whole animal is negligible (665). Several effects on isolated organs, which have been described more recently (216, 404, 513), are probably "nonspecific", although a cholinergic mechanism has been postulated for the action of Pi on the guinea pig ileum (543).

In contrast to pentylenetetrazol, there are no indications of a stimulant action of Pi on the neuromuscular junction (334, 335, 337). Picrotoxin does not inhibit cholinesterase or sensitize the leech muscle to acetylcholine (312). Its action on the acetylcholine content of the brain depends on the anesthetic used (171).

4. Vasopressor action. In cats under chloralose anesthesia the rise of the blood pressure after subconvulsant doses of Pi is of the same magnitude as, but slower and more prolonged than that after identical fractions of the convulsant dose of pentylenetetrazol (269). Convulsant doses of Pi may cause a fall in blood pressure. An action on inhibitory centers has been revealed by injections into the vertebral artery (282). Picrotoxin very strongly antagonizes the failure of circulation due to barbiturates (279, 453) and improves the depressed carotid sinus reflex (98, 152), including the depressor responses (154).

5. Respiratory action. The respiratory action is due to stimulation of the respiratory center and not of the carotid chemoreceptors (313, 397, 459). The sensitivity of the inspiratory center to electrical stimulation is increased (697). There is no foundation for the hypothesis (459) that Pi should be effective only on respiration depressed by anesthesia, since the stimulation of respiration can also be observed in normal animals (665). Moderate depression of respiration by morphine is antagonized by Pi (678), but the convulsant actions of the two substances are additive (306).

More important is the respiratory stimulant action of Pi in barbiturate poisoning (33, 34, 98, 129, 451, 453, 655). Some authors (491, 638) have reported failure of Pi in severe respiratory depression, but this was probably due to insufficient adjustment of the dose of Pi to the depth of anesthesia (17, 129). Picrotoxin offers greater risk of convulsions than pentylenetetrazol (34, 129, 655), but has greater potency (129, 551, 655). When Pi is injected intracisternally the therapeutic index is greater than when it is injected intravenously (553).

Picrotoxin antagonizes also the respiratory depressant action of other anesthetics but not that of ethanol (459) or of the hemicholiniums (595).

6. Action on body temperature. The hypothermic action of Pi (665 for ref.) is more pronounced than that of pentylenetetrazol and bemegride (80, 271). It is mainly due to an increased loss of heat (271) but there is also a reduction of heat

production (567). The central site of action has been demonstrated by injection of Pi into the infundibular region (569). The hypothermic action of Pi is affected by anesthetics just as is that of pentylenetetrazol; barbiturates have the strongest inhibitory action (389, 568, 569). Ethyl ether and amylene hydrate potentiate the hypothermic action (665 for ref.). In spite of its cooling action in normal animals, Pi prevents or antagonizes the fall in body temperature normally caused by anesthetics, especially that caused by barbiturates or paraldehyde (395, 453, 569) and, to a lesser extent, that caused by ethanol (703).

An increase in the surrounding temperature increases the convulsant and lethal action of Pi in mice (109); lowering the body temperature of anesthetized cats decreases the convulsant and lethal actions (634).

7. Antianesthetic action. Although the mutual antagonism between Pi and various hypnotics was known in the last century (665), only the discovery of its very pronounced antagonism to the barbiturates (451) led to its widespread clinical use (54, 78, 383, 393). Animal experiments demonstrated the life-saving effect of Pi after pretreatment with lethal amounts of barbiturates (33, 34, 43, 68, 98, 286, 350, 371, 395, 413, 448, 451, 453, 704). The lethal doses of the barbiturates are increased by factors of 2 to 4, depending on the duration of action and the site of action of the barbiturates, and the experimental procedures. When the dose of barbital-sodium is increased progressively from 0.2 to 1.0 g/kg subcutaneously, the effective dose of Pi, given intravenously in one to thirteen injections, increases from 0.9 to 85.6 mg/kg; doses of barbital greater than about double the lethal dose cannot be overcome by any amount of Pi (350).

The general analeptic action of Pi is seen in decorticate rats (483); by microelectrodes, it can be recorded in the diffusely projecting nuclei of the thalamus (680). The participation of the cortex is seen by reactivation of the EEG (136, 279). The latter effect is slight if the doses of Pi are too small (94, 638).

Picrotoxin has no effect on the elimination or distribution of barbiturates in the body (361, 395). Analepsis is observed at a higher blood level of barbiturates than in animals waking up spontaneously (76, 395). Further studies on this problem are desirable, since the investigations reported were not based on a sufficient number of experiments.

When compared with several analeptics (33, 34, 98, 448, 704) as well as with electrical stimulation of the CNS (413), Pi has the greatest effectiveness in combatting the mortality of barbiturate poisoning. Its superiority to pentylenetetrazol against barbital and pentobarbital in mice is more obvious at the limit of the effectiveness of pentylenetetrazol (286, 287) than at less severe degrees of poisoning by the barbiturates (34, 68, 98, 371). Perhaps in less severe poisoning the convulsant activity of Pi limits its efficacy. Even in light barbiturate anesthesia, Pi was found to be more effective than pentylenetetrazol when the analeptics were administered in identical fractions of their normal LD50's (371). However, Pi raises the lethal dose of phenobarbital to a smaller degree than does pentylenetetrazol (280).

Picrotoxin is generally regarded as a drug with an especially narrow margin between the analeptic and convulsant doses; the danger of postconvulsive depres-

sion is thus assumed to be great (34, 129, 655, 704). Under nonlethal barbital anesthesia, analeptic doses of Pi cause hyperexcitation with secondary relapse (280). Identical amounts of barbiturates are less effective against Pi-induced than against pentylenetetrazol-induced convulsions (110, 395, 549, 704), and barbital raises the lethal dose of pentylenetetrazol more than that of Pi (280). Increasing amounts of barbiturates, however, antagonize increasing amounts of Pi (107, 538); careful dosage thus makes it possible not to surpass the convulsant threshold. The optimal mode of administration of Pi is therefore by repeated injections spaced over a long period of time (34, 350, 451). Total amounts of Pi as high as 14 g have been administered to patients (503). It must be realized that overdosage of Pi causes convulsions even in the presence of very large amounts of barbiturates (279, 350). The effectiveness of Pi is not limited by primary (*i.e.*, non-postconvulsive) depressant effects (704); with the exception of some experiments (148) which cannot be regarded as conclusive (450), there is no evidence of such.

There are reports of a mutual antagonism between Pi and the following anesthetics: chloral hydrate (33, 263, 371), paraldehyde (263, 666), ethanol (702), bromethol (33, 263, 450), ethylchlorvinyl ether (371), and urethane (217, 263, 538). In general there is no proven life-saving action of Pi against these anesthetics, in spite of some analeptic activity. Picrotoxin, pentylenetetrazol, and bemegride were not life-saving against ethynylcyclohexanol carbamate (Valamin) in mice (280).

Picrotoxin is used commonly as a test substance for anticonvulsant agents. With most drugs its effects are antagonized less completely than those of pentylenetetrazol; this problem will not be discussed here. Reserpine (668), chlorpromazine, and promethazine (474) are ineffective, and a facilitating effect of reserpine has been observed (577). Mephenesin antagonizes Pi less effectively than it antagonizes strychnine (43).

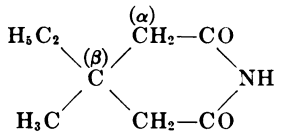
8. Mode of action. Pi fails to increase the respiration of normal or anesthetized brain tissue *in vitro* (223, 376, 397, 515). The increase in oxygen consumption of the brain *in vivo* (136, 203, 469, 585, 586) may thus be a consequence of stimulation rather than its cause; the electroencephalographic appearance of signs of convulsions precedes the fall in oxygen tension of the brain tissue (203). There is no evidence that the actions of Pi on enzyme systems *in vitro* contribute to the analysis of its specific mode of action.

Of interest is the recently discovered antagonistic action of Pi on the inhibitory neuron of the abductor muscle of the crayfish claw (674). γ-Aminobutyric acid mimics the effects of the inhibitory transmitter on the crayfish muscle; its action, too, is blocked by Pi (673). Picrotoxin blocks also the action of this substance on the crustacean heart (190).

9. Fate and elimination. By testing the rate of inactivation of Pi by biological methods, the following values were obtained: inactivation of a single convulsant dose per hour (147, 704), and a half-life of 46 minutes (129). About 10% of the biological activity of administered Pi is found in the urine (147). Two hours after intravenous injection, Pi is not detectable in blood, liver, or muscle (162).

III. GLUTARIMIDES

1. Structure-action relationship. β,β-Methylethylglutarimide (3,3-methylethylglutarimide; 4,4-methylethyl-2,6-dioxopiperidine; NP 13; Megimide; eukraton; malysol; *bemegride*) was prepared by Guareschi in 1901 (245 for ref., 654a), but its action as a so-called barbiturate antagonist was discovered only in 1954 (609). Its convulsant action was first described in 1950 (41). An analytical and chemical study has been presented by Singermann (623). The history of the discovery of its analeptic activity has been described by Dumont (163).



Bemegride

Up to 1950 only the hypnotic and sedative effects of the glutarimides had been of interest (245). These are increased by substitution in *alpha*-position (460).

For the analeptic action of bemegride the intact glutarimide ring and an unsubstituted imino group are required (614, 625). The weak analeptic activity of β,β-methylethylglutaramic acid (16) is an exception to this rule. β-Spiro-cyclopentane-, β,β-methyl-*n*-propyl- and β,β-diethyl-glutarimide are bemegride-like; the first of these is nearly as effective as bemegride. β,β-Methyl-*n*-butyl-glutarimide and its *n*-amyl and *n*-hexyl analogs are hypnotic substances and are antagonized by bemegride (625).

2. Functional versus competitive antagonism. Although the Danish school of anesthesiologists rejects the use of analeptics in favor of symptomatic treatment of poisoning with hypnotics, bemegride became a widely used substance soon after its introduction for this purpose; this was mainly due to the belief that its mode of action differs from that of other analeptics (605). Bemegride has been said to act by competing with barbiturates (281 for ref.). In this connection the term "specific" is often used in order to emphasize the particular mechanism of action of bemegride. However, the term "specific" should be used only for characterizing the range of action. Many clinicians have been convinced that bemegride lacks those actions which are undesirable in the usual analeptics. Without presenting comparable results obtained with the usual analeptics (*e.g.*, pentylenetetrazol, picrotoxin), most authors have emphasized the greater therapeutic index of bemegride and the lack of pronounced side-effects, although the danger of convulsions and of other side-effects (*e.g.*, vomiting) has been pointed out (60, 116, 295, 440, 605, 609, 617). Bemegride is supposed not to increase the O_2 consumption of the brain tissue (440), although such an action should in principle be associated with any convulsive activity. Its analeptic effect on the respiration in barbiturate poisoning (605, 625) has been described as unique. It is also said to differ in not causing hyperthermia (440), but it has already been pointed out in this review that this applies also to other analeptics (pentylenetetrazol, picrotoxin). It has been claimed not to cause a pressor response (440), although, in fact, it has been found clinically to raise the blood pressure (605).

Recently such a "specific" mode of action of bemegride has been challenged. *Clinical* reports show that bemegride antagonizes barbiturates as well as other structurally related and unrelated hypnotics (153, 163 for further ref., 295, 527, 591, 617, 688). Determinations of the blood levels of barbiturates in patients have not contributed substantially to our understanding of the mode of action of bemegride (440, 525). The elimination of barbiturates in patients has not been found to be accelerated by bemegride (332, 440). Patients treated with bemegride seem to awake earlier than those untreated (163 for ref., 617). This observation, however, has been questioned by some authors (440, 525). If the observation is correct, we have to expect that patients treated with bemegride awake at higher barbiturate blood levels than do untreated patients. This, of course, implies that bemegride is not able to accelerate the elimination of barbiturates. Awakening at higher blood levels of barbiturates has been found by one author (332) and denied by another (525). The question deserves further investigation. Perhaps the application of higher doses of bemegride may be useful in the further elucidation of this problem. In contrast to the situation after treatment with other analeptics psychotic-like signs and symptoms have been observed after treatment with bemegride, especially in barbiturate addicts (374). The significance of this observation is still a matter of debate (623). The use of bemegride as an activator of cortical potentials in the diagnosis of epilepsy and as a therapeutic agent in the shock treatment of psychoses (140) demonstrates its close relationship to pentylenetetrazol in related fields of therapy.

Neither *theoretical* considerations nor *experimental* results favor a competitive mode of action of bemegride (163, 197, 281, 371). The original concept of such was based on the structural resemblance between the barbiturates and the glutarimide ring. Since bemegride is a convulsant agent and a general stimulant of the CNS, it may very well act against hypnotics by means of a functional antagonism. This antagonism is, in fact, not restricted to the barbiturates (pentobarbital, thiopental, hexobarbital, barbital, phenobarbital); an antianesthetic action of bemegride has been observed against ethanol, chlorbutol, bromethol, methylpentynol and its carbamate, ethchlorovynol, paraldehyde, chloral hydrate, phenyldiethylacetamide, urethane, carbromal, bromvaletone, α-ethyl-α-phenylglutarimide and other glutarimides, 5-phenylthiazolidine-2,4-dione, 5,5-diethyl-2,4-diketothiazolidine, 3,3-diethyl-2,4-piperidinedione (Persedon, Dihyprylone), 3,3-diethyl-5-methyl-2,4-piperidinedione (Noludar, Methyprylone), 5-ethyl-6-phenyl-2,4-diketometathiazane (Dolitrone), 5-methyl-5-phenyl-succinimide and other succinimides, and sterols; it is ineffective against diethyl ether (35, 67, 103, 197, 245, 280, 286, 371, 550, 609, 614, 615, 616, 625, 631, 681, 718a). Bemegride antagonizes the respiratory and circulatory depression but not the hypnosis and analgesia induced by morphine and other analgesics in rabbits under urethane anesthesia (163 for further ref.). A "specific" barbiturate antagonism can be questioned even after the administration of lethal doses of barbiturates, since under these conditions a life-saving effect is seen also with pentylenetetrazol and picrotoxin. A study of the EEG of the rabbit showed that bemegride antagonized barbiturates, but not ether or chloralose (94); similar results, however,

were obtained with pentylenetetrazol (159). Söderberg stated that bemegride has about the same action against pentobarbital, chloralose, urethane, and glutethimide (624). This contradicts the experiments of Cass with bemegride (94), and of Driesen *et al.* (159) with pentylenetetrazol, which resembles bemegride in so many respects. Since Söderberg gave no details about the doses of anesthetics and bemegride he used, this comparison deserves further investigation. Bemegride is able to antagonize also lethal amounts of chloral hydrate (371) as well as of carbromal and hydroxydione (280, 698). These findings also weaken the postulated importance for mutual antagonism of a certain molecular structure (*e.g.*, —NH—CO—NH—; 614) found both in bemegride and in certain anesthetics. It has been said that only bemegride is able to restore to normal the barbiturate depression of the cortex of cats, dogs, and rabbits (94, 605). However, the negative results obtained with pentylenetetrazol (94) were unquestionably due to the use of inadequate doses (159, 279). The fact that rabbits can alternately be brought under narcosis with a barbiturate and awakened with bemegride (605, 614) is not strong evidence for a "displacement reaction," since similar effects can be produced by other analeptics. In contrast to the contradictory clinical observations, experiments on animals have revealed that bemegride, if given in large enough doses, shortens barbiturate anesthesia (67, 163 for further ref., 286, 608, 609). The effect can be demonstrated in different animal species (with the possible exception of the cat) and with different barbiturates (with the possible exception of butethal). Unfortunately, it has not been determined whether bemegride-treated animals awake at a higher barbiturate blood level than do untreated ones. However, such a finding alone would not support the assumption that earlier awakening is caused by acceleration of barbiturate elimination. The observation that bemegride in animal experiments decreases the concentration of thiopental in the brain and increases its excretion in the urine (3) does not allow any conclusions as to the mode of action of bemegride as long as the effects of bemegride on body temperature, metabolism, and circulation have not been taken into account. Control experiments with other analeptics should also be done.

Studies of the interaction of bemegride and barbiturates on isolated organs lend no support to the theory of competition (163). There are other observations as well which cannot be easily reconciled with this theory; for example, within the CNS the effect of bemegride is variable and depends on the structural elements involved (624). Doubt is thrown on the competitive mechanism also by an analysis of the dose-response relationship of pentobarbital in the presence and absence of bemegride in the intact animal (163); the conclusions, however, are not convincing.

In summary, bemegride is a convulsant agent which probably stimulates all parts of the CNS. In this way it may antagonize drugs with a central depressant action—especially, but not exclusively, the barbiturates.

3. Action of bemegride. Only a detailed comparison of bemegride with other barbiturate antagonists (*e.g.*, pentylenetetrazol and picrotoxin) would permit determination of the group of analeptics to which it belongs. The available evidence

is scanty. Nevertheless, the following conclusions may be drawn (280). Bemegride injected intravenously into rabbits, rats, and mice is approximately two and one-half times as effective a convulsant agent as pentylenetetrazol. When it is tested as a barbiturate antagonist in man, it is nearly twice as potent as pentylenetetrazol (71). The lethal doses of bemegride and pentylenetetrazol are about four times the convulsant doses in rabbits, and about twice the convulsant doses in rats; the lethal and convulsant doses are similar in mice. Thus, in this respect the convulsant action of bemegride resembles that of pentylenetetrazol, but differs from that of picrotoxin in rabbits. The use of bemegride or pentylenetetrazol in psychiatry or neurology, therefore, would seem to entail the same risk, although clinical reports stress the greater margin of safety of bemegride and the absence of side-effects.

Bemegride and pentylenetetrazol seem to act on the same parts of the brain. As with pentylenetetrazol, the origin of bemegride convulsions is the cortex (163), and from there the convulsant action is propagated to lower parts of the CNS. The convulsant effect involves the spinal cord as well (652), but less intensively than the upper parts of the CNS (624). Bemegride does not decrease the inhibition of spinal motoneurons; in this respect it resembles pentylenetetrazol and picrotoxin, but differs from strychnine (127a).

The effect of bemegride on the EEG of unanesthetized animals or humans is basically analogous to that of pentylenetetrazol (161, 163, 502, 565, 608). In subconvulsant doses, bemegride, like pentylenetetrazol, exhibits a synchronizing effect, and increases the amplitude and radiation of induced potentials at the cortical level. This effect changes its character with increasing doses: there are spikes and waves, and finally an EEG pattern typical of convulsive seizures. The synchronizing effects counteract the desynchronizing action of reticular stimulation. Both bemegride and pentylenetetrazol may act, therefore, by general stimulation of the CNS rather than by stimulation of reticular structures (163). Nevertheless, an action on the reticular system has been postulated (712). The arousal reaction induced by bemegride differs from the normal one by its larger amplitude (624). Some authors have described certain differences between the actions of bemegride and pentylenetetrazol on the EEG of normal or anesthetized humans or animals (15, 279, 524). The extensor seizure response of mice to bemegride (like pentylenetetrazol, but unlike picrotoxin) is facilitated by reserpine (103).

Bemegride antagonizes completely severe respiratory depression induced by pentobarbital in rabbits (163) and by barbital in dogs (136). However, in rabbits it antagonizes only slightly the respiratory depression induced by urethane (163). The previously mentioned effect of bemegride on the action of morphine and related analgesics in rabbits under urethane (163) was very pronounced. This may be explained by assuming that urethane acts as an antagonist to bemegride-induced convulsions. In dogs under morphine, but not in dogs under urethane, the analeptic effect of bemegride on respiration was linked with convulsions. In dogs and mice there was a definite synergism of the convulsant effects of bemegride (like those of pentylenetetrazol) and of morphine (718a). However, in rab-

bits not treated with urethane there was antagonism of subconvulsant doses of bemegride to the depressant effect of morphine on respiration (280). Subconvulsant doses of bemegride had but a moderate effect on morphine-induced hypnosis in dogs (607) and did not influence the analgesic action of morphine in rabbits (163). The effect of bemegride on respiratory depression in rabbits lasted longer than that of equieffective amounts of pentylenetetrazol. In summary, it can be said that to produce equivalent effects, the doses of pentylenetetrazol must be about two to three times those of bemegride. This ratio was found also for the convulsant doses of both drugs (163, 280). The site of the respiratory stimulant action of bemegride is in the CNS, and not on the chemoreceptors of the carotid body (163).

Bemegride causes a pressor response in animals under barbiturate or chloralose anesthesia, after morphine, and in unanesthetized animals (with or without curare) (94a, 136, 163, 279, 286, 718a). The central origin of this effect has been indicated by injections into the vertebral arteries (286) and by destruction of the CNS (94a). No observations suggest peripheral sites of action (heart, blood vessels, ganglia) (94a, 163). The pressor action is quite similar to that of pentylenetetrazol when both analeptics are administered in equivalent fractions or multiples of the convulsant doses (136, 163, 279, 286). Like pentylenetetrazol, bemegride antagonizes severe barbiturate depression of the circulation (136, 163, 279) and impairs the circulation when given in supraoptimal doses (136, 279, 624).

Furthermore, bemegride resembles pentylenetetrazol in having the same hypothermic (see 109a, 286) and hyperglycemic action in rabbits when given in identical fractions of the convulsant dose. Picrotoxin, on the other hand, has greater effects on the blood sugar and body temperature (80, 194, 280).

Little information is available as to other autonomic effects of bemegride, and no peripheral effects are known.

In summary, bemegride causes general stimulation of the CNS. Its mode of action is very similar to that of pentylenetetrazol. The effects of both these drugs seem to be even quantitatively similar if the doses are compared on the basis of the ratio between the convulsant doses.

4. Antagonism of bemegride to barbiturates. Like pentylenetetrazol and picrotoxin, bemegride is used in barbiturate poisoning because of its effects on respiration and circulation, and its general arousal effects. The antagonism of bemegride to barbiturates is functional and reciprocal. Barbiturates increase the convulsant and lethal doses of bemegride. In this connection two problems are important. Is bemegride able to lower the death rate in patients with barbiturate poisoning? Is it superior in this respect to other analeptics such as pentylenetetrazol and picrotoxin? Curiously enough, hitherto these problems have not been studied extensively. The life-saving effect of bemegride has been demonstrated only in mice poisoned with pentobarbital, phenobarbital, cyclobarbital, and barbital (280, 286, 371, 698). A few other observations indicate that bemegride increases the lethal doses of thiopental in rabbits and of pentobarbital in rats (605, 609).

A comparison of bemegride with pentylenetetrazol has been made in mice against pentobarbital (163, 197, 371). Doses of the two analeptics were used against pentobarbital which were equally effective in arousing the animals, in shortening the duration of anesthesia, and in reducing mortality. These studies thus determined the relative potencies rather than the selective effectiveness; the latter can be determined only by finding the limits of effectiveness of the analeptic substances as the dose of pentobarbital is gradually increased. Kimura and Richards (371) reported that bemegride (on a mmol/kg basis) is about as potent as pentylenetetrazol against pentobarbital. A reinvestigation showed that in mice picrotoxin is more effective, and pentylenetetrazol less effective, than bemegride against increasing amounts of pentobarbital (280). Similar results have been obtained in cats with bemegride and picrotoxin (413).

The determination of the mortality-reducing effect against increasing doses of barbital in mice (286) showed that bemegride still saves up to 90 % and picrotoxin up to 60 % of the animals, when pentylenetetrazol reaches the limit of its effectiveness. The EEG of the cat showed that the action of bemegride and of picrotoxin reaches its limit at 1100 mg barbital/kg, whereas pentylenetetrazol becomes ineffective at 900 mg barbital/kg (279). The O_2 consumption and the cerebral blood flow in dogs under barbital are changed by bemegride-induced analepsis and convulsions in the same manner as by picrotoxin and pentylenetetrazol (136). The effective dose of all three substances increases with increasing severity of barbital poisoning. The ratios of the effective doses of the three analeptics reflect to a certain degree their relative potencies as convulsants in normal animals. This may be considered as a further evidence against the postulated "specific" mode of action of bemegride. It is therefore not justified to compare bemegride and other analeptics on a molar basis as has been done by some authors (163, 371) in order to measure the relative potency. Against increasing doses of phenobarbital, bemegride has been found to be more effective than pentylenetetrazol and picrotoxin (280).

The therapeutic tolerance range of bemegride in comparison to that of the other analeptics has not yet been determined accurately. Söderberg considered it to be broader than that of pentylenetetrazol (624), but did not report experiments with analeptics other than bemegride. Much depends upon the definition of the "therapeutic tolerance range" and on the conditions of the experiments. In cats and dogs treated with barbital, the ratio between the dose which reactivates the EEG and the threshold dose for convulsions is identical for bemegride and pentylenetetrazol, and greater than that for picrotoxin (136, 279). In rabbits a given dose of barbital increases the lethal dose of bemegride to the same extent as that of pentylenetetrazol and more than that of picrotoxin (280). The isobolometric method, on the other hand, showed that the lethal dose of bemegride is increased by phenobarbital more than that of pentylenetetrazol and still more than that of picrotoxin (280). Little is known about the action of other (nonbarbiturate) anesthetics on the toxic dose of bemegride in comparison to that of pentylenetetrazol.

A "therapeutic index" has been calculated from the ratio between the lethal dose in unanesthetized animals and the analeptic dose as observed in anesthetized

animals (371); this "therapeutic index" was greatest for picrotoxin. Such a procedure, however, disregards the influence of anesthesia on the lethal doses of analeptics; this may be less against picrotoxin than against other analeptics (280).

It has been proposed that it should be possible to avoid barbiturate intoxication by administering the barbiturate mixed in constant proportion with bemegride (215). It would be of interest to know whether or not the ratio "optimal dose of bemegride/amount of ingested barbiturate" is constant with increasing amounts of the barbiturate.

5. Mode of action. The mode of action is not known. The concept that bemegride facilitates both the repolarization of neuronal membranes and the influx of potassium is hypothetical (38); these hypotheses were based on observations which do not justify such far-reaching conclusions. Bemegride does not antagonize the depression by Amytal (amobarbital) of mitochondrial respiration (rather, in high doses it enhances the depression) (346), nor does it antagonize the depression of respiration of cerebral tissues caused by barbital (470). In contrast to pentylenetetrazol-induced convulsions (644), convulsions and death caused by bemegride are prevented by *l*-asparagine, *l*-glutamine, γ-aminobutyric acid, and 2-pyrrolidinone (305).

6. Fate of bemegride. The duration of the action of bemegride has not been compared with that of other analeptics. The urine of a patient who received bemegride was found to contain β,β-methyl-oxyethylglutarimide (466). Bemegride and this metabolite interfere with the determination of barbiturates in the UV-spectrum (127). Gentle hydrolysis of the glutarimide ring in alkali avoids this complication.

After the intravenous injection of bemegride into guinea pigs there is a phase of rapid removal from the blood stream, which is followed by a period of slow removal. The latter phase is apparently due to excretion (16); the former may be due to breakdown of bemegride or to distribution through the body. A widespread distribution of bemegride has been confirmed by administration of C^{14}-labeled bemegride (230).

Summary: The experimental data now available hardly confirm all the special properties of bemegride which have been claimed by some clinical reports. It is firmly established, however, that bemegride is an analeptic agent which combines an activity evidently stronger than that of pentylenetetrazol with a therapeutic range equal to, or even larger than, that of pentylenetetrazol. Depending on the nature of the anesthetic, bemegride is either more or less effective than picrotoxin, the therapeutic range being always larger for bemegride. This property represents a real advantage in the therapy of poisoning with hypnotics, especially with barbiturates. In many other respects bemegride resembles pentylenetetrazol more than picrotoxin.

IV. ALKYLATED ACID AMIDES

A. Structure-action relationship

It was shown long ago by Nebelthau *et al.* (502a) that the analeptic activity of these substances is due to the alkylation of the nitrogen of the acid amide group;

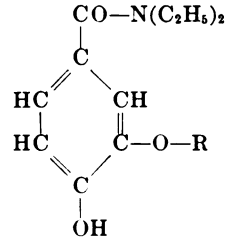
the unsubstituted acid amides are anesthetics (66 for ref., 221). A certain depressant action persists, especially in poikilothermic animals (267, 277, 325, 670). In homeothermic animals the depressant action manifests itself as a synergism with anesthesia.

Such substances are usually screened by the determination (on a weight unit basis) of their stimulant action on respiration which has been depressed by morphine or by hypnotics. The recent trend has been to search for substances which are effective in low doses and have a high therapeutic index. This type of screening gives information about neither their mortality-reducing activity nor their depressant effects; the latter are more easily observed in deep anesthesia and after high doses of the analeptic substances.

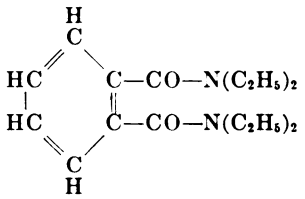
The study of the respiratory actions of these analeptics nevertheless has provided some interesting information about their structure-activity relationship. Among the derivatives of the aromatic and heterocyclic acid amides, complete substitution of the amide nitrogen with ethyl groups provides optimal activity (329, 670). A large number of derivatives of nikethamide (87, 250 for further ref., 444, 462, 670) or of Cycliton (329) with alkyl- or aryl-substituted amide nitrogen atoms has been investigated.

Furthermore a large variety of substances has been produced by variation of the acid component of the molecule:

a) Many derivatives of benzoic acid-diethylamide have been prepared (63, 66, 175, 221, 329, 398), and the following substances have been found to be the most potent (*i.e.*, to have the smallest effective doses) as to analeptic activity: 3-methoxy-4-oxy- (Vandid), 3-ethoxy-4-oxy- (Anacardiol), 3-methoxy-4-acetoxy-, and 3-ethoxy-4-acetoxy-benzoic acid-diethylamide. Equieffective doses of Anacardiol, Vandid, nikethamide, and benzoic acid-diethylamide have the ratios, 1:1.5 to 2:20 to 22:33 to 40 (66).



R = CH_3: Vandid
R = C_2H_5: Anacardiol



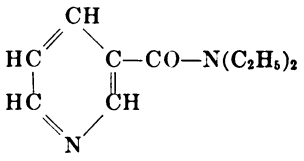
Neospiran
(Geastimol)

2-Methoxy-4-allylphenoxyacetic acid-N,N-diethylamide (G 29505) is remarkable insofar as it has an analeptic-like action on respiration, while otherwise having the properties of a short-acting anesthetic and of an anticonvulsant agent (656).

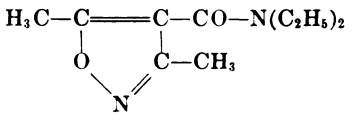
The presence of two carboxydiethylamide groups in the *ortho*-position results in pronounced effectiveness [tetraethylphthalamide, Neospiran, Geastimol (265, 266)].

b) Substitution of the ring of the acid component of the molecule led to vari-

ous substances of which pyridine-3-carboxylic acid-diethylamide (nikethamide) is the most important. It is the most effective of the three isomers having the carboxydiethylamide group in positions 2, 3, and 4; but it is the least potent of all therapeutically used substances, when equieffective doses are compared. Several derivatives, produced by hydration of the ring or by substitution of the pyridine nitrogen with halogen-alkyl groups (87, 114, 444, 670), 5,6-dichloro, 5-bromo, and 6-methyl derivatives (229), β-oxypyridine-O-acetic acid-diethylamide (329), pyridine-3-sulfo acid-diethylamide (444), pyridine-3-carboxyurethane (63), diethyl derivatives of pyridine-2,3-, -2,5-, and -3,5-dicarbonic acid, and of pyridine-*ortho*-dicarbonic acid (63, 229, 250, 364), have been described. Methyl-nikethamide is said to have a life-saving action against barbital in rats (217a).



Nikethamide



Cycliton

The close relationship of pyridine to thiazole and isoxazole led to the investigation of derivatives of isoxazole-3- (and -4-) carbonic acid-diethylamide, thiazole-5-carbonic acid-diethylamide (329), thiazole-4,5-dicarbonic acid-diethylamide (176) and some related compounds (62, 364). 3,5-Dimethylisoxazole-4-carbonic acid-diethylamide (Cycliton) was the most effective. Because of the relationship of pyridine to the nitrobenzene ring, *m*-nitrobenzoic acid-diethylamide is nikethamide-like (175). 3-Methylpyrazole-5-carbonic acid-diethylamide also has a stimulant action on respiration and blood pressure (496), and 1, 2, 3-trimethylpyrazole-5-carbonic acid-diethylamide is effective likewise (329). For the substituted amides, diamides and esteramides of several other carbonic and dicarbonic acids (phenylquinoline, α-pyrone, pyrazine, pyrroline, imidazole, indole, thionaphthene carbonic acid, tetrahydropyran, furan dicarbonic acid, *etc.*) see (63, 364, 696).

Diethylamides of several tetrazole carbonic acid derivatives (229, 242, 249) and products of the reaction of pyridine carbonic acid with aminopentamethylenetetrazole and dipentamethylenetetrazoleamine (364) are structurally related to both the pentylenetetrazol and the nikethamide groups of analeptics. They have no practical importance, however.

Monodiethylamide, the tri- and tetra-substituted diamides of camphoric acid (*d-cis*-form or *l-trans*-form), the diethylamide of camphorcarbonic acid, and the diethylamide of camphorsulfonic acid are substances with some analeptic properties (222, 364). The β-diethylcarbonic acid amide of camphorsulfonyl-N-methyl-pyridine (Camphramin) is the salt of N_1-methylnikethamide and camphorsulfonic acid (31).

Alkylated dicarbonic acid amides of Warnat's (692a) lobeline-like compounds have also been prepared.

d-Lysergic acid-diethylamide (*d*-LSD) as well as *d*-2-bromo-LSD belong chemically to this group of substances. Their action on the CNS is not fully explained by their antagonism to 5-hydroxytryptamine (204). It is unknown which of their actions are associated with the diethylamide structure. Both *d*-LSD and *d*-2-bromo-LSD inhibit the prolongation of barbiturate anesthesia by 5-hydroxytryptamine (97); but only *d*-LSD, and not *d*-2-bromo-LSD, antagonizes reserpine sedation and also inhibits the prolongation of barbiturate anesthesia by reserpine (83). *d*-LSD (not *d*-2-bromo-LSD), on the other hand, prolongs barbiturate anesthesia in the absence of reserpine (84).

c) Aliphatic compounds: Substituted amides of several aliphatic acids are convulsants and may have some respiratory stimulant action. Of the several dicarbonic acid derivatives tested succinic acid-*bis*-diethylamide was the most effective (95), but it enhances rather than antagonizes anesthesia (2). A number of tetraethyldiamides of several dicarbonic acids have been prepared but not studied pharmacologically (628).

N-substituted imino-di-fatty acids (*e.g.*, Micoren) and N-ethylimides of dibasic acids have also been studied.

d) Urea derivatives: Of the urea derivatives tetraethylurea is the most effective. Also very active are tetraallylurea, tetraethylsulfamide and the ethylated phosphamides. N-diethylethylurethane was the most effective urethane derivative (4).

Boon (63) prepared compounds of the chemical structure $X \cdot CO \cdot NR \cdot [CH_2]n \cdot NR' \cdot CO \cdot Y$ and discussed the structure-activity relationship. N,N′-dimethyltrimethylenediamine-N,N′-*bis*-carboxydiethylamide and N,N′-di-*n*-propylethylenediamine-N,N′-*bis*-carboxydiethylamide are twice as effective as nikethamide and have a larger therapeutic index. When X and Y = the water-soluble morpholine group, and R and R′ = the lipophilic propyl or *n*-butyl group, the effectiveness is up to 12 times, and the duration of action up to 10 times that of nikethamide.

Bargeton *et al.* (31) investigated numerous urea derivatives and alkylated acid-amides. Very small amounts of N,N′-di-*n*-butylethylenediamine-N,N′-*bis*-carboxymorpholid (1064 Th) (30, 32) are said to be effective against the depressed respiration and the fall of blood pressure due to barbiturate anesthesia without shortening the duration of anesthesia.

Compounds of the type $NH \cdot R \cdot (CH_2)n \cdot Y \cdot (CH_2)n \cdot NH \cdot R$ (R = alkyl or alkoxyl group; n = 1 or 2; Y = 0 or $CHOCH_3$ or $CHOC_2H_5$) are not more effective than the previously mentioned compounds (64).

1,3,7-Trimethylxanthine (caffeine), 1,3-dimethylxanthine (theophylline), and 3,7-dimethylxanthine (theobromine) also belong to the alkylated urea derivatives.

Conclusions. Several factors have been considered to cause the reversal from anesthetic to analeptic action after alkylation of the nitrogen atom: a reduction in acidity of the remaining molecule, an increase in lipoid solubility, and an increased tendency of the nitrogen moiety to form salts and complexes (4, 251, 265, 329). Reduction in acidity has thus been thought to cause reduced fixation

of the substance in the CNS; this then elicits excitation rather than anesthesia (251). It has also to be considered that the more neutral alkylated substances react with receptors different from those reacting with the relatively acid amides. An optimal ratio of water to lipoid solubility seems to be of some importance (63, 329), but the stimulant action probably depends on the chemical properties of the alkylated nitrogen. These properties are reflected in an increase in basic character, in a dependence of the solubility on the pH, in reaction with agents which precipitate alkaloids (265), and in the ability to react with phenol-like substances (407). Other factors which influence the stimulant action are the size as well as the compactness of the molecule (4), and the presence in the ring of basic groups (*e.g.*, pyridinecarbonic acid) which cause dipole formation (329).

B. Nikethamide

1. Site of action. Nikethamide (Nik) (pyridine-3-carboxylic acid-diethylamide) was originally introduced under the trade name "Coramin" (670). Its pharmacological properties were first described in 1922 by Lagier (409) and were reviewed in 1937 by Hildebrandt (325).

The typical response of poikilothermic animals to Nik consists of both stimulant and depressant components (81, 277, 278, 325, 409, 670), whereas *unanesthetized* homeothermic animals respond predominantly with excitation. In unanesthetized animals, depression is observed only as postconvulsive paralysis (325). Subconvulsant doses increase the motor activity of homeothermic animals (598); contradictory results (200) are probably due to differences in methods or species, or both. Several authors have studied the difference between the convulsant and the lethal doses of Nik in comparison with other analeptics (273, 311, 325, 326, 382, 704). The results differ, probably because of the different factors mentioned above. Nikethamide- but not pentylenetetrazol-induced convulsions of newborn rabbits are lethal (428).

Nikethamide has a greater convulsant effect on the lower parts of the CNS, including the spinal cord, than pentylenetetrazol, although the Nik-induced convulsions are of supraspinal but not of cortical origin (158, 270, 325, 354, 409, 651).

Combinations of Nik and pentylenetetrazol elicit a subadditive effect (6, 272). Strychnine convulsions and the effect of strychnine on the spinal cord are not more strongly enhanced by Nik than by pentylenetetrazol (272, 386). Nikethamide, pentylenetetrazol, and strychnine have a similar action on the homolateral spinal reflex (377).

In rabbits under barbiturate anesthesia, Nik causes nystagmus and rhythmic head movements (271). It enhances the flight reaction caused by stimulation of the hypothalamus of the rabbit (501).

Various effects of Nik indicate that it stimulates the parasympathetic nervous system (81, 82, 85, 121, 270, 273, 278, 409, 463, 497, 557, 579, 670). This effect is more conspicuous than that on the sympathetic system, especially in poikilothermic animals (81, 82, 278). In homeothermic animals Nik surpasses pentyl-

enetetrazol in its effect on the parasympathetic system, whereas it may be equally or less effective on the sympathetic system (270, 273, 557).

Salivation is so pronounced after Nik that it may cause asphyxia by aspiration, especially after chloralose anesthesia (273). This finding explains the incompatibility of chloralose and Nik (321). The aspiration of saliva has repeatedly been described as lung edema (33, 271, 273 for ref., 449), but the incidence of the latter is similar after Nik and pentylenetetrazol (271, 557). The responses of the salivary secretion and of the blood sugar to Nik are antagonized by barbiturates (273); this indicates a central site of action of Nik on the autonomic nervous system.

A nicotine-like action on peripheral parasympathetic ganglia has been described, especially in poikilothermic animals (81, 82). In homeothermic animals the effect of Nik on the autonomic nervous system is said to be governed by a stimulant and (after higher doses) a depressant action on sympathetic ganglia (717), but this is in contradiction to the above-mentioned observations. The darkening of the frog skin by Nik (a typical nicotine-like action of Nik) does not depend on its pyridine group (278) as was postulated earlier (670). Nikethamide has no nicotine-like effect on frog muscle (670).

The effect of high doses of Nik on the neuromuscular junction has been described as curare-like (81, 186, 335), decurarizing, and synergistic with physostigmine and acetylcholine (174, 333, 335, 359). Nikethamide seems also to have a depressant action on the muscle itself (186). It has not been settled whether the atropine-sensitive effects on the isolated intestine (121, 543, 670) and on the isolated heart (497) are due to a direct action on the end-organs or to an action on peripheral parasympathetic ganglia. Nikethamide inhibits both true and pseudo-cholinesterase (290), but this does not justify the conclusion that the action of Nik in the intact animal is due to an interaction with a cholinergic mechanism.

Since relatively large doses of Nik are required for analepsis, those effects of Nik which have been found outside the CNS (see also 288, 325) may be of some importance for its action in the whole animal.

2. Action on blood pressure. Nikethamide is mainly pressor in rabbits (40, 219, 220, 288, 325, 604, 670), whereas dogs (463, 545, 633, 683), cats (128, 269, 325, 720), and monkeys (586) tend to respond with depressor effects. In cats this tendency depends very much on the choice of anesthetic: urethane favors a pressor response to Nik (219, 497, 604), and chloralose favors depressor responses (219, 269). In rabbits the pressor effect is not reversed by chloralose (288). In dogs it is abolished by barbiturates and by magnesium sulfate (405). In rabbits the pressor response to Nik is stronger than that to pentylenetetrazol (288), when comparable fractions of the convulsant dose are given.

Unanesthetized decerebrate cats respond to Nik with a pressor effect (675), but this effect is reversed under chloralose anesthesia (219). Spinal cats, however, show pressor responses to high doses of Nik, whether they are anesthetized with chloralose or unanesthetized (270). Conflicting reports (98, 325, 497, 670) are

probably due to differences in the quality of preparations. A vasoconstrictor effect of Nik can even be demonstrated by perfusion experiments in rabbits (670), cats (497), and frogs (227), but the effects of injections into the vertebral artery suggest that actions on the higher centers are mainly responsible for the pressor response in the intact cat (219).

The pressor effect of Nik in cats and rabbits is reduced and sometimes abolished by azamethonium bromide (Pendiomid) (220). This antagonism is reciprocal. Negative reports with ganglion-blocking agents (40, 604) are probably attributable to low dosage. Adrenergic blocking agents inhibit the pressor effect of Nik (40, 201). Nikethamide, on the other hand, antagonizes some of the effects of epinephrine (288, 497). The pressor response of cats to Nik is abolished by adrenalectomy and restored by cysteine (40). This is not easy to interpret unless it is a "nonspecific" effect of adrenalectomy on the very labile pressor response of the cat to Nik.

The depressor response of the cat to Nik is also mainly of central origin (219, 282, 284), but is not dependent on an intact vagus. Azamethonium, in contrast to hexamethonium (604), reduced the depressor response (220). A transient initial fall of the blood pressure can be observed which is independent of this response (219); this may be the result either of a direct effect on the blood vessels (497) or of a negative inotropic action upon the heart muscle (400, 497). Some observations, which indicate a positive inotropic effect of Nik on the heart of the cat, have been challenged (325).

For the depressor response of the dog, stimulation of the vagal centers has to be considered as well as a direct action of Nik on the heart and blood vessels (463). It has not yet been established whether there is, in the dog, a central depressor mechanism which is independent of the vagus. Nikethamide may have a negative inotropic cardiac effect in the dog (325, 463); it reduces myocardial efficiency and does not improve the force of contraction of the failing heart (231, 325). An increase in coronary flow has often been reported (325), but the mechanism is uncertain.

A central depressor effect of Nik has not been well established in rabbits (282). An initial depressor effect may be seen after central (354) as well as systemic injections. Both stimulant and depressant effects on the heart have been described (478, 497). The increase in cardiac output seen during the rise of the blood pressure (478) may be due partially to an increased venous return caused by general vasoconstriction.

The pressor response to occlusion of the carotid arteries is said to be increased by Nik in cats and rabbits (98, 493), and to be reduced in dogs (683). A direct stimulant action on the carotid sinus of the dog has also been postulated (713).

3. Respiratory action. The respiratory stimulation caused by Nik may be the result of either an action on the chemoreceptors of the carotid body or a central action.

The former effect has been found in the dog (724) but not in the cat (8) or rabbit (313); in contradiction to these findings, it has been reported (8) that Nik has in rabbits, besides its action on the respiratory center, an action on the

carotid body which has been shown by injection of small amounts of Nik into the ligated vessel. Intracisternal injection, on the other hand, failed to prove the existence of a central action of Nik on respiration (206, 551).

Nikethamide increases the sensitivity of the respiratory centers to CO_2 (262, 476). Nevertheless, Nik and CO_2 do not elicit similar responses: CO_2 increases primarily the tidal volume rather than the rate of breathing, whereas Nik has the opposite effect (477).

A high therapeutic index (*i.e.*, ratio of convulsant to respiratory stimulant dose) is generally considered to be a special advantage of Nik. In rabbits under morphine this index has been reported to be 1 to 5 (325 for further ref., 421, 594, 678, 724). Comparison with pentylenetetrazol has given varying results (66, 311, 325, 326, 594, 724). This may be explained partly by the fact that the difference between the minimal and the maximal effective doses of Nik is greater than that between the corresponding doses of pentylenetetrazol (421). Differences in the therapeutic indices of the two substances, therefore, change with the level at which the comparison is made. A depressant action of Nik in morphine-treated rabbits has also been found (121).

The respiratory stimulant action of Nik in morphine poisoning has been demonstrated in human subjects (292, 629, 630). Like other analeptics, however, Nik had no life-saving action in mice after poisoning with morphine (587). In cats under aprobarbital anesthesia, on the other hand, Nik increased the lethal dose of morphine (708). Morphine has been found to either increase (311, 421) or decrease (306) the convulsant threshold dose of Nik.

A respiratory stimulant action of Nik has been observed under the influence of various anesthetics (26, 33, 34, 98, 129, 168, 311, 325, 421, 449, 452, 459, 476, 477, 545, 724); this action is not dependent on a general antianesthetic action and may even coincide with a general depressant effect (226, 271). This effect has not been established against lethal amounts of anesthetics. The depressant effects of Nik (demonstrated with hexobarbital, bromethol, or chloroform anesthesia: 129, 168, 325, 459) probably antagonize its life-saving effect.

When tested under bromethol anesthesia Nik increased the tone of the respiratory muscles as well as the pulmonary surface and facilitated gas exchange (370). Other studies showed Nik to cause either a shift of the balance to the expiratory side (168) or an inspiratory dyspnea with occasional inspiratory arrest (262).

Nikethamide, like other analeptics, has an analeptic action only in the presence of O_2 (319). In mice, the resistance to lack of O_2 is increased by Nik only during the secondary phase of lowered body temperature (189); otherwise it is decreased (173). Likewise Nik, like other analeptics, has no analeptic activity in severe carbon monoxide poisoning and may even be dangerous (486), but it enhances the elimination of carbon monoxide when the poisoning subsides (494, 654).

Nikethamide causes but a slight analeptic response after poisoning with local anesthetics (325 for ref.). It has only a transient effect on the curare paralysis in the rabbit (359).

4. Action of nikethamide and body temperature. Subconvulsant doses of Nik

raise the body temperature of rabbits (271) and of mice (189). The hyperthermic effect of Nik is not strong enough to counteract the hypothermic effect of barbiturate anesthesia; instead, the administration of Nik is followed by prolongation of the anesthesia and by accentuation and prolongation of the fall in body temperature. A secondary depressant effect on body temperature has also been observed in unanesthetized mice. Nik, however, is effective against the hypothermic effect of ethanol (702, 703).

Cooling, administration of chlorpromazine, or both abolish the pressor response, but not the respiratory response to Nik (391). In the cooled organism, Nik (like lobeline) increases the already-present bradycardia and arrhythmia (247). This is due to the pronounced action of these substances on the parasympathetic system. The cooled organism is also very sensitive to acetylcholine. In hibernating ground squirrels (*Citellus tridecemlineatus*) Nik has twice its normal toxicity and causes a reduction of the threshold of convulsion which lasts for several days (529).

The hyperthermic action of Nik is accompanied by increased motor activity (271).

5. Antianesthetic action. a. Barbiturates. The antagonistic action of Nik has been studied in several species (26, 33, 34, 68, 98, 129, 159, 226, 235, 236, 271, 286, 325, 382, 421, 432, 449, 451, 491, 509, 704, 723). Most authors agree that Nik is only a weak antagonist to barbiturates (325). Even under light anesthesia Nik may lead eventually to convulsions without full arousal. Because of the depressant effects of Nik the initial excitation is followed by a relapse into prolonged anesthesia. Corresponding changes are observed in the EEG (159). For the same reason Nik increases the mortality after barbiturates; this is true even for doses of Nik which are sublethal in the unanesthetized animal. Small doses of Nik reduce the mortality only slightly if at all. Only a very narrow range of doses of Nik increases the LD50 of phenobarbital in mice (432). Various doses of Nik fail to reduce the mortality after barbital in the same species (286).

The depressant effects of Nik affect also the antagonism of barbiturates toward the toxicity of Nik. Small amounts of barbiturates increase the lethal dose of Nik (432, 475), but this effect is not seen when the dose of the barbiturate is increased. This explains why some authors have found only a slight decrease or even a slight increase in the toxicity of Nik after barbiturates (311, 382, 723).

Some authors have described a comparatively slight inhibition by barbiturates of Nik-induced convulsions (in comparison with pentylenetetrazol-induced convulsions) (271, 272, 311, 382). It may be pertinent to this that Nik acts more strongly on the lower parts of the CNS (271). However, the inhibition of Nik-induced convulsions is complex because Nik itself has depressant effects which probably facilitate the anticonvulsant action of the barbiturate. The depressant effect of Nik is seen mainly during the tonic phase and during the generalized clonic seizure (432). It is more pronounced in deep anesthesia; after pretreatment with lethal amounts of barbital (LD70) there are no convulsions even after lethal amounts of Nik (286). Death then occurs as the result of the depressant effect of Nik. Few authors have used Nik-induced convulsions to test anticonvulsant drugs (167, 202).

The depressant effects of Nik severely limit the usefulness of this substance in the treatment of barbiturate poisoning. Some clinical reports of unfavorable effects of Nik in barbiturate poisoning agree with these experimental findings (28).

b. Bromethol. The antianesthetic action of Nik is weak (33, 325, 382, 421, 450, 459) and is complicated by its depressant actions (168, 325). Some reports of an effective antagonistic action of Nik have been criticized (325). Since bromethol is an anesthetic with a very short duration of action, experiments with continuous infusions of bromethol have been carried out (325). They also showed only a slight antagonism of Nik whether given in single doses or by continuous infusion.

The toxicity of Nik has been found to be reduced (262, 263) or scarcely influenced (382) by bromethol, or even greatly increased by large doses of bromethol because of the synergism of the depressant effects of the two drugs (325). Bromethol usually scarcely affects the convulsant threshold of Nik (325), but convulsions have been found to be fully prevented by bromethol, even after lethal amounts of Nik (382). Delayed convulsions have been observed until 24 to 48 hours after bromethol anesthesia (421).

Nikethamide does not affect (325) or increase (262) the blood level of bromethol.

c. Other anesthetics. Urethane anesthesia is only slightly reduced by Nik (26, 235, 277, 325); large doses of Nik cause paralysis. There is, on the other hand, some antagonism of Nik by urethane (263, 475). A weak mutual antagonism exists between Nik and chloral hydrate or paraldehyde. Depressant effects have been seen in deep anesthesia after large amounts of Nik (33, 236, 263, 723). An awakening and respiratory stimulant effect of Nik after ethanol administration has been described (620).

6. Fate and elimination. In equivalent convulsant doses, Nik is eliminated 3.5 to 5 times more slowly than pentylenetetrazol (325, 704).

The renal elimination of N^1-methyl-nicotinamide chloride (nicotinamide-methochloride) is increased after the administration of Nik. The methylation occurs after the formation of nicotinamide (125, 170).

It has been postulated that a metabolite of Nik is responsible for the depressant effects of this substance (129). It is interesting, therefore, that large doses of Nik, or nicotinamide, and of the methylated derivatives depress the respiratory center (75).

C. Other alkylated acid amides

1. Neospiran. Neospiran (N,N,N′,N′-tetraethyl-phthalamide, Geastimol) is Nik-like in that decapitation does not reduce its convulsant action in cats (270), that it raises the body temperature of the rabbit (271), that it raises the blood pressure of the rabbit (14, 267, 500), that it lowers (after an initial rise) the blood pressure of the cat under chloralose (269), that it has a depressant action on fishes (277), and that it darkens the frog skin (278). It causes a long-lasting stimulation of respiration after previous administration of various depressants (14, 267, 271, 678). Decapitate cats (even under chloralose) respond to Neospiran with a rise in blood pressure (270). Neospiran constricts the vessels of the rabbit

ear at a concentration of 0.001%, and dilates them at 0.1 to 1%. Small doses increase, while higher doses decrease the contractility of the rabbit heart (500). Its antianesthetic action (267) is weaker than that of pentylenetetrazol (14, 271). It has no life-saving action against barbital in mice. Its synergism with anesthetics, however, is less pronounced than that of Nik (271, 286).

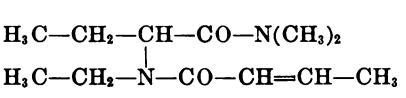
2. Cycliton. Cycliton (N,N-diethyl-3,5-dimethyl-4-isoxazolecarboxamide) seems to be similar to Nik. It stimulates the respiration (329, 678), lowers the blood pressure of the cat under chloralose anesthesia (269), and raises the body temperature of the rabbit (271). Because of its depressant effects, there is a synergism between Cycliton and the barbiturates (9, 271). A certain mutual antagonism between Cycliton and barbital has been observed, but only for a narrow range of doses below the LD50.

3. Vandid. Vandid (3-methoxy-4-oxybenzoic acid-diethylamide) has a respiratory stimulant action (66, 221), not only centrally but *via* the carotid body as well. It lowers (with a secondary rise) the blood pressure of cats and dogs under chloralose or barbiturate anesthesia and raises the blood pressure of decapitate cats (221). Its direct action on blood vessels results in dilatation. Its action on the blood pressure is said to be due not only to central stimulation, but also to an action on the carotid sinus and on ganglion cells. Antianesthetic effects other than a certain antagonistic action toward urethane have not been described. Postconvulsant paralysis is said to be lacking.

4. Anacardiol. In rabbits, Anacardiol (3-ethoxy-4-oxybenzoic acid-diethylamide) has, on a weight basis, a slightly stronger action than Vandid; it is also said to have a greater therapeutic index. An action of this substance against carbon monoxide poisoning has been described (66).

5. Micoren. Micoren is a mixture of two alkylamino fatty acids: 1) N-crotonyl-α-ethylamino- and 2) N-crotonyl-α-propylamino-butyric acid di*methyl*amide. It causes predominantly tonic-clonic convulsions of the cerebral type and some-

1)



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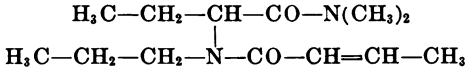
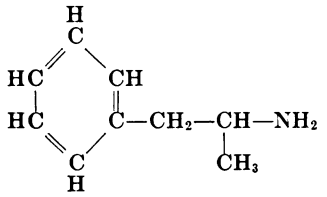


Micoren

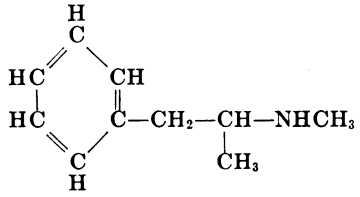
times tetanic convulsions, probably of spinal origin (420). Its respiratory stimulant action, which has a relatively high therapeutic index (420, 544), seems to be of therapeutic importance. This substance has no pressor action in dogs (420). As a result of its respiratory stimulant action it has proved to be life-saving in rabbits against short-acting barbiturates (thiopental or pentobarbital) (420). Little is known about its antianesthetic properties. No life-saving action has been found in mice under barbital (287).

V. AMPHETAMINE AND METHAMPHETAMINE

1. Chemistry. Amphetamine (Benzedrine) is racemic 1-phenyl-2-aminopropane or β-phenylisopropylamine. The dextrorotatory form (Dexedrine) is commonly used as the sulfate or phosphate.



Amphetamine



Methamphetamine

Methamphetamine (Desoxyephedrine, Methylbenzedrine), usually used in the form of the chloride, is the N-methyl derivative of amphetamine: 1-phenyl-2-methylaminopropane or N-methyl-β-phenylisopropylamine. These names are used for the two optical isomers as well as for the racemate; the *d*-form is most commonly used (Pervitin, Methedrin). The racemate is also known as Oxydrine, Vonedrine.

2. Central actions. a. General. The two amines differ from convulsant analeptics in having psychomotor stimulant and peripheral sympathomimetic actions. They do not cause typical convulsions (303, 304, 344, 507, 598). Increased motor activity is observed over a wide range of doses and has been measured by various methods which will not be discussed here. The reported values of the lethal dose vary considerably (69).

d-Amphetamine and *d*-methamphetamine have stronger central actions than the corresponding levorotatory compounds (11, 304, 507, 572, 597). The ratio of the lethal to the minimal stimulant dose is smaller for the *l*-form than for the *d*-form (572, 597).

The lethal dose of racemic amphetamine is smaller than that of racemic methamphetamine, and the stimulant action of racemic amphetamine is greater than that of racemic methamphetamine both in unanesthetized animals and in man (345, 693). In anesthetized animals, however, methamphetamine is more potent than amphetamine (344, 666). The lethal dose of racemic amphetamine in rats is about equal to, or slightly greater than, that of *d*-methamphetamine (304, 322). The therapeutic index of *d*-methamphetamine is 50, that of the racemate 20, and that of racemic amphetamine 25 (302).

b. Site and mode of action. Experiments with amphetamine and *d*-methamphetamine on decorticate, decerebrate and spinal animals show that the action of these drugs involves the major subdivisions of the CNS (58, 73, 442, 445, 447, 473, 504). Activation in the EEG has been observed in different animals with both cortical and subcortical recording, especially in the conscious state (73, 660). The frequently postulated action of these amines on the sympathetic centers is not yet established, although some evidence has recently been found (340, 352).

Several observations indicate a direct facilitatory action of the sympathomi-

metic amines on synaptic transmission (399, 442). Depressant actions, on the other hand, on ganglionic structures and several parts of the CNS (72, 456) as well as a reversal of the stimulant action have frequently been observed on increasing the doses (163, 473, 580). This may be related to a nicotine-like action of the amines (547). There are many reports on the effects of the amines on electrically or chemically induced convulsions as well as on the activity of some anticonvulsants; these will not be discussed here. They provide further evidence for the view that there is a stimulant as well as a depressant action of the amines. Amphetamine may also inhibit convulsions by stimulating structures in the brainstem (621). Amphetamine possesses both synchronizing and desynchronizing actions (437); the anticonvulsant action may be correlated with the latter.

It is possible that amphetamine and methamphetamine act on adrenergic systems in the CNS. Such an action could be either direct, or through interference with the metabolism of endogenous catecholamines, or through liberation of the latter from local sites of storage (308, 347). The possible role of epinephrine and norepinephrine as central transmitter substances is still under investigation. It has been suggested that both epinephrine and amphetamine act on the reticular activating system (73, 74, 141), but the action of amphetamine seems to be restricted to a part of the activating system (437). *d*-Amphetamine, in contrast to pentylenetetrazol and picrotoxin, does not regularly activate mesencephalic reticular unit activity (584).

If an effect of amphetamine or methamphetamine is compared with the effect of epinephrine it should be borne in mind that epinephrine and norepinephrine seem to have a predominantly inhibitory action on synapses (456), but in small doses they facilitate synaptic transmission (79). Amphetamine and methamphetamine, like epinephrine, prolong the duration of electroshock (574) as well as cortical after-discharges (485). There are differences, however. Intracisternal or intraventricular injection of epinephrine causes states resembling anesthesia (184, 417), whereas intracisternal injections of amphetamine cause excitation (418). Systemic injections of epinephrine prolong the action of various anesthetics (390, 410, 534, 548), under conditions in which amphetamine and methamphetamine shorten it (484). Subcutaneously injected epinephrine antagonizes the increase in motor activity caused by *d*-methamphetamine (667). It is questionable, however, whether epinephrine exerted a direct action on the CNS in these experiments (582).

It has been emphasized repeatedly that the central actions of various sympathomimetic amines probably are not related to their peripheral sympathomimetic effects (344, 345, 412, 597). The antagonistic action of adrenergic blocking agents toward the central effect of methamphetamine is said to be "nonspecific" (667).

Amphetamine has a stimulant action on the respiration of isolated brain tissue only when the respiration is depressed by metabolites of tyramine (51, 541); this is due to inhibition of monoamine oxidase which prevents accumulation of the latter (51). Within a series of arylalkylamines there is a certain correlation between the central stimulant action and inhibition of aminoxidase; however,

concentrations required for the latter effect are high, and even then there are exceptions (52, 185).

Recently another site of action of amphetamine and methamphetamine has been suggested: the "tryptamine receptors" (52). When injected peripherally, the amines antagonize reserpine-induced central depression (83, 352), but methamphetamine is not effective against all effects of reserpine when injected centrally (352). After peripheral injection, amphetamine antagonizes the sedative effect of intraventricularly injected 5-HT. However, it potentiates the sedative effect when injected centrally (682). A peripheral mechanism seems to be involved, therefore, in the interaction between 5-HT, or reserpine, and amphetamine. Lysergic acid diethylamide (LSD) increases the excitement caused by amphetamine (573), but amphetamine, unlike LSD, does not abolish the effect of 5-HT on the rat uterus (682 for ref.). The findings are thus not explained satisfactorily by the assumed interaction at "tryptamine receptor" sites.

3. Cardiovascular action. The cardiovascular actions of *d*-amphetamine and *d*-methamphetamine are comparatively weak, as are all their other sympathomimetic actions (for ref. see 69). Nevertheless, the peripheral actions may represent an undesirable complication if the central actions of high doses are desired. Smaller doses, on the other hand, may increase CNS excitability by raising a depressed blood pressure and improving the circulation of the CNS.

A quantitative comparison of the optical isomers is complicated by the phenomenon of tachyphylaxis. The findings are therefore contradictory (11, 304, 411, 537, 572, 640). The difference in potency between the isomers is less pronounced on the blood pressure than on the CNS. The dextrorotatory compounds are preferred when only the central actions are desired.

The pressor action is not mediated through the CNS. The possibility of a CNS action has been considered (411, 640), but a central vasopressor action of *d*-methamphetamine has not been found by perfusing the head of the dog using the method of Heymans (199). Injections of *d*-methamphetamine into the vertebral artery of the cat cause only depressor effects (135). Experiments with perfused preparations (130, 490, 572) demonstrate the peripheral action of *d*-methamphetamine.

The pressor action is probably more prominent in animals than in human subjects, where the central actions prevail (303).

4. Respiratory actions. Amphetamine and methamphetamine have a respiratory stimulant action (10, 454), which is due to an action on the respiratory center and not on the chemoreceptors (246). It is not abolished by decerebration (58, 98). The pressor response to the amines may cause an initial reflex depression of respiration (113). The respiratory stimulant doses are usually higher than those required to produce a rise of blood pressure (44). Stimulation of respiration is usually accompanied by, and partly a component of, a general stimulation (146). In normal human subjects therapeutic doses of the amines do not regularly increase respiration (13, 45). The respiratory stimulant action has not been observed in anesthetized animals with any regularity, even in pressor doses (72). Many authors, on the other hand, have described some respiratory action of the

amines in anesthetized or morphinized animals (113, 117, 291, 457). The therapeutic index has been found in some of these experiments to be somewhat greater than that of other analeptics (98, 678). Clinical trials on human subjects have suggested that amphetamine is a more effective antagonist to morphine poisoning than other analeptics (292).

The effectiveness of the amines as respiratory stimulants has not been established against lethal doses of anesthetics. Recently, Dumont (163) reported that amphetamine was not able fully to restore the respiration of rabbits after it had been depressed to 15 to 25% of its normal value; full restoration was achieved readily with pentylenetetrazol or bemegride. High doses cause periodic breathing in animals (678) as well as in man (131, 246). The observations that repeated injections of amphetamine may cause depression of respiration (146) and that in mice under barbital anesthesia small doses of *d*-methamphetamine are more effective than larger doses (287) suggest the existence of a depressant component in its respiratory action. In normal rats and guinea pigs the action of *d*-methamphetamine resembles that of morphine to a certain degree (58).

Hyperventilation is reported as another risk associated with the use of these amines (5). Small doses should be preferred, since they are said to relax the bronchial muscles and slow and deepen the respiration (131). The bronchodilator action, however, is weak.

d-Methamphetamine causes a fall in the CO_2 tension and a rise in the O_2 tension of the tissues (454). In monkeys poisoned with carbon monoxide it caused an acceleration of its elimination (706). However, since control experiments were not performed with sympathomimetic amines lacking effects on the CNS, the possibility has not been excluded that these effects were due to the circulatory actions of methamphetamine.

These observations fail to provide a firm basis for recommendation of the use of the two sympathomimetic amines for the treatment of severe respiratory depression.

5. Pyrogenic action. The pyrogenic action (343, 369, 703) is probably caused by an increase in motor activity in combination with vasoconstriction (343), and not to a change in central heat regulation. The increase in the heat production of the brain (182, 183) is due to central stimulation and is not specific for these amines, since analeptics which cause a fall in body temperature have the same effect. The pyrogenic action of amphetamine is potentiated by thyroxine and abolished by procaine, dihydroergotamine, antipyretics and 883 F (diethylamino-methyl benzodioxan, Prosympal) (473, 622).

The increase in motor activity and in body temperature produces an increase in the metabolic rate. This is reflected in a decreased resistance to any lack of O_2 (172, 189, 535).

In contrast to pentylenetetrazol or picrotoxin (two cooling agents in normal animals), amphetamine does not antagonize the fall in body temperature observed after phenobarbital (622). The fall in body temperature after ethanol, on the other hand, is more effectively antagonized by amphetamine and nikethamide than by pentylenetetrazol or picrotoxin (703). Amphetamine antagonizes the fall of body temperature due to hypoxia (646).

In hibernating ground squirrels (*Citellus tridecemlineatus*), amphetamine and other sympathomimetic amines were found to be more effective and less toxic than the convulsant analeptic substances (529). However, the mortality of artificially cooled mice was increased by amphetamine (426).

6. Antianesthetic action. Many experiments allow the conclusion that the two amines have an antagonistic effect against nonlethal amounts of nearly all anesthetics without any clear-cut specificity, *e.g.*, against barbiturates (10, 11, 19, 20, 68, 69 for further ref., 98, 163, 198, 266, 303, 321, 328, 344, 443, 546, 572, 645, 666). The effectiveness of the amines, however, declines rapidly with increasing depth of anesthesia (98, 266, 302, 443, 546). It cannot be restored by increasing the dose, for synergism with the anesthetic will then be observed (98, 163, 198, 286, 443, 645). The optimal dose is only a small fraction of the normal lethal dose. This is quite contrary to observations with pentylenetetrazol, picrotoxin, or bemegride, the optimal activities of which are often reached with a multiple of the normal lethal dose. Amounts of *d*-methamphetamine greater than the LD50 increase the lethal action of barbital in mice (286). The lethal dose (or a fraction of it) of amphetamine increases the mortality in deep pentobarbital anesthesia (98). Amounts of *d*-amphetamine up to $\frac{1}{17}$ the normal lethal dose slightly increase the LD50 of barbital in mice (286); this is probably not due to a true central antagonism, but rather to the peripheral (cardiovascular) actions of the amine. The antagonistic effect of higher doses of the amines against the anesthetics may be limited either by depressant actions or by the peripheral sympathomimetic (especially the cardiovascular) actions of the amines. It is more probable that the central-depressant effects of the amines limit their effectiveness in deep barbiturate anesthesia since amphetamine has a weaker pressor action than bemegride or pentylenetetrazol (163). The lack of a pronounced mutual antagonism between the amines and the anesthetics is observed also when the action of the anesthetics on the lethal doses of the amines is studied (328, 668).

A certain functional antagonism between *d*-amphetamine and thiopental can also be demonstrated in the EEG, provided respiratory depressant doses have not been given (358). In contrast to pentylenetetrazol, single or repeated doses of *d*-methamphetamine fail to reactivate cortical potentials in cats after pretreatment with high doses of barbital or phenobarbital; they may even cause additional depression (509).

There is thus little basis for recommending the use of amphetamine or *d*-methamphetamine in cases of poisoning with barbiturates, especially as more effective substances are available. Some clinicians deny the existence of a life-saving effect of amphetamine and recommend the use of a combination of amphetamine with picrotoxin (50, 498, 503). Hypertension and excitation have been observed clinically after high doses of amphetamine. Anesthetized rats show marked exophthalmus when treated with methamphetamine (287).

Both amines have been used also in cases of ethanol poisoning. However, the antagonism of amphetamine toward ethanol (20, 266, 321, 546, 702, 703) is weak and does not extend to lethal amounts of ethanol. The action of amphetamine and *d*-methamphetamine against nonlethal amounts of ethanol, however, very

much resembles that of pentylenetetrazol, picrotoxin, or nikethamide (20, 321, 702). The ethanol level in human blood after oral ethanol administration is reduced by amphetamine, presumably by delaying both the emptying of the stomach and the absorption from the intestine (558).

7. *Fate and elimination.* Part of the amphetamine and methamphetamine appears unchanged in the urine of various species (51 for further ref., 119, 368, 671). These compounds are known not to be broken down by monoamine oxidase and are weak inhibitors of this enzyme. Some of the amphetamine undergoes deamination by another enzyme system, and in some species, some is hydroxylated in the *para*-position. Up to 45% of *d*-methamphetamine is demethylated in dogs (25).

VI. OTHER CNS STIMULANTS

A. Strychnine

The study of the mutual antagonism between barbiturates and strychnine is of twofold interest: barbiturates have been used as antidotes against strychnine poisoning and strychnine has been used as an analeptic agent against barbiturate poisoning. Many investigations have shown that barbiturates and other anesthetics antagonize or inhibit strychnine convulsions and may even raise the lethal dose of strychnine. This antagonism is complicated by some synergistic effects (433). It has also been shown recently that pentylenetetrazol enhances the life-saving action of barbital in strychnine poisoning (143). The antagonistic action of strychnine against barbiturates has been studied by various authors (33, 34, 68, 98, 286, 328, 387, 451, 723), though with contradictory results. However, it can be stated that strychnine is much less effective than pentylenetetrazol or picrotoxin; it has not been demonstrated to be life-saving in barbiturate intoxication (286). Strychnine not only differs from the above-mentioned analeptics by a more pronounced action on the lower part of the CNS, but it also operates through fundamentally different mechanisms (540). Although strychnine has been widely used as a circulatory stimulant, the experimental literature shows that it has no pronounced action in subconvulsant doses (269). In rabbits the action of strychnine on the respiratory center, depressed by morphine, has also been found to be feeble (678).

B. Camphor and hexeton

The usefulness of camphor as an analeptic agent is greatly limited by its depressant properties. Among a variety of terpenones, camphor showed minimal analeptic effect against hexobarbital poisoning (699). The use of camphor is obsolete. The few papers published in recent years are not relevant to this review and are not discussed.

Hexeton (3-methyl-5-*iso*propyl-2-cyclohexen-1-one) undoubtedly has more CNS-stimulating effect than camphor, but here again stimulation is associated with marked depressant effects (311, 382, 723). Hexeton antagonizes the respiratory paralysis caused by morphine, barbiturates, magnesium, cocaine, and carbon monoxide (311, 554, 594, 654, 678). Its vasopressor effect is more marked than

that of camphor, but it is also combined with a depressant effect (269, 545, 675). It has been postulated that sodium salicylate, which was used as solubilizing agent, causes the rise of the blood pressure; yet hexeton alone also elicits a rise of blood pressure without sodium salicylate (269).

C. Xanthines

In addition to its stimulating action, caffeine has demonstrable depressant properties. This accounts for the weakness of the antagonism between caffeine and anesthetics and for the occasional change into synergism (33, 34, 328, 449). The same is true for theophylline (512). Many derivatives of theophylline and theobromine have been described, but none of them has been established as an antagonist to anesthetics (137). The literature on the respiratory action of the xanthines has been summarized by Dallemagne and Heymans (127b). There is a synergistic activity on the respiration within the combination of theophylline with ethylenediamine (aminophylline). Theophylline-diethanolamine is much less effective in this respect. The pressor effect of caffeine is 5 times greater than that of theophylline (269) and is of central origin, as demonstrated by injections into the vertebral arteries (282). An additional depressor effect must be considered as peripheral (461).

D. Barbiturates with convulsant ability

Barbiturates and thiobarbiturates with convulsant ability and their structure-action relationship have often been described. Some of them have been studied in more detail with respect to their analeptic properties, especially 5-(1,3-dimethyl-butyl)-5-ethyl-barbituric acid. Extensive studies showed that this barbiturate has both stimulant and depressant effects (151). While other barbiturates antagonize the convulsant action of this barbiturate, there is no or only a questionable antagonism of this barbiturate against hypnotic barbiturates; its action is largely synergistic (151, 424). It stimulates the respiratory and the vasomotor centers to some degree.

A stronger stimulating action on respiration, circulation, and other autonomic functions has been described for 5-(3,3-dimethyl-allyl)-5-ethyl-barbituric acid. The substance 5-(3,3-pentamethylene-allyl)-5-ethyl-barbituric acid is said to possess an even stronger effect on respiration (677, 679 for further ref.). Barbital, phenobarbital and methylhexobarbital are not antagonized by their N-allyl derivatives (362).

Depressant and convulsant barbiturates have similar actions on various enzyme systems and on the cell division of sea urchin eggs (151 for ref.).

E. Miscellaneous CNS stimulants

4-Cyclohexyl-3-ethyl-1,2,4-triazole (Azoman, Triazol 156) has convulsant, blood pressure-raising, respiratory stimulant and antianesthetic properties (235, 655). It has been used in the treatment of schizophrenia. In mice given lethal doses of barbital it has a stronger life-saving action than pentylenetetrazol (286).

2,4-Diamino-5-phenylthiazole (Amiphenazole, Daptazole) has been recom-

mended as a morphine antagonist in the treatment of opiate overdosage; its combination with large doses of morphine was suggested for the relief of intractable pain. This drug has the property of arousing dogs from deep narcosis caused by morphine, or by morphine plus hyoscine, and of antagonizing, to a lesser extent, the respiratory depression; it is said not to affect the analgesia produced by morphine (607 for further ref.). However, it is not a specific morphine antagonist, but rather a convulsant agent like other analeptics; like these, and in contrast to N-allylnormophine, it has no established life-saving action in morphine poisoning (402). It lowers the blood pressure, and large doses produce respiratory depression (406, 618). Clinical studies have not been able to confirm that the effect of single doses or of chronic administration of morphine is influenced by Amiphenazole (195).

Because of its nonspecific stimulant action on the respiration it has been used in combination with bemegride for the treatment of barbiturate poisoning (609), but there is no experimental evidence for a superiority of this method of treatment over treatment with bemegride alone. Amiphenazole does not antagonize barbiturate anesthesia.

Many derivatives of acridine, quinoline, pyridine and thiazole including 5-amino-acridine, tetrahydro-5-amino-acridine, 2,3- and 4-amino-acridine have been investigated for analeptic activity against morphine and for other qualities (607 for further ref.). Some of these compounds are powerful anticholinesterase agents. This is of interest because there is some evidence for a respiratory stimulant and morphine-antagonistic action of cholinesterase inhibitors. However, there is no relationship between the anticholinesterase activity and the morphine antagonism of the above-mentioned compounds (606).

VII. CONCLUDING REMARKS

The only field of therapeutic use of analeptics where a life-saving action of these substances has been firmly established is that of depression of the CNS by anesthetics. The particular effect of analeptics on anesthetics is probably linked to the existence of a mutual antagonism between these two groups of agents. In severe depressions only such a reciprocal antagonism allows the administration of the required high doses of analeptics without entailing the risk of toxic side-effects, especially convulsions. A pronounced mutual antagonism is due to a certain congruence of the sites of action of both the analeptic and the depressant agent and to the absence of primary (*i.e.*, not postconvulsive) depressant and strong peripheral side-effects of the analeptics; on the other hand, the depressant agent should not have any excitatory side-effects. These conditions are only rarely met. It is therefore easy to understand that only a small group of analeptics shows a life-saving effect against only a small group of anesthetics.

The most important example is the antagonism between pentylenetetrazol, picrotoxin, and bemegride, on the one hand, and barbiturates, on the other. The antagonism of these analeptics also extends to other hypnotics and anesthetics, but the antagonism is often much weaker than the antagonism against barbiturates. For some nonbarbiturate hypnotics, however, a life-saving action of one or the

other of the analeptics has been described. There are few studies with quantitative evaluations of the relative potency of analeptics against different hypnotics and anesthetics. The barbiturates, too, are differently influenced by various analeptics; further research is required in this direction. Since systematic experiments are lacking, no definite judgment can be formed on the differences in effectiveness of the three analeptics. Pentylenetetrazol seems to be less effective than bemegride, whereas the position of picrotoxin apparently depends very much on the type of the anesthetic.

The effectiveness of an analeptic has to be determined by the evaluation of the limit of its effectiveness against increasing doses of the anesthetic. Other methods cannot supply this information. The optimal dose of the analeptic increases with increasing doses of the anesthetic. So far only a few studies of this problem have been made.

Because of mutual antagonism, anesthetics increase the threshold for convulsions and the lethal dose of analeptics, modify the type of convulsions, and alter the difference between convulsant and lethal doses. Little is known about the dependence of these effects on the type and depth of anesthesia or on the character of the analeptic. A knowledge of these interactions, however, is most important, since the therapeutic range of analeptics is determined by them.

At present it can be stated only that picrotoxin possesses the smallest therapeutic range. Anesthetics increase the convulsant as well as the lethal dose of picrotoxin to a lesser degree than those of the two other analeptics under consideration. Further peculiarities of picrotoxin are its considerable tendency to cause secondary depression, and the small difference between the convulsant and lethal doses. There is as yet no explanation for these phenomena. There are few studies of the question whether bemegride possesses a greater therapeutic range than pentylenetetrazol, although this has often been taken for granted.

The fact that these three analeptics exert a life-saving action against barbiturates strongly contradicts the opinion that these substances have harmful rather than beneficial effects in barbiturate poisoning. The danger of O_2 deficiency caused by therapeutic doses of analeptics has never been demonstrated in adequately devised awakening experiments in severe barbiturate poisoning. The danger of insufficient dosage seems to be greater than that of overdosage, since the antagonism of anesthetic toward analeptic is greater than the inverse antagonism. Repeated intravenous injections must be used clinically in order to find that dose of the analeptic which is optimal for any given depth of anesthesia.

The outstanding value of the analeptics is revealed in the treatment of poisoning with long-acting barbiturates; besides the arousing effects on medullary centers there is in addition shortening of anesthesia as a life-saving factor. With short-acting barbiturates artificial respiration may be superior; the simultaneous administration of analeptics is not necessarily contraindicated, however.

The similar type of antagonistic action of the analeptics pentylenetetrazol, bemegride, and picrotoxin toward barbiturates supports the hypothesis of a similar mechanism of action and of similar sites of action of the three analeptics. Pentylenetetrazol and bemegride are more closely related to each other than to

picrotoxin. The three analeptics are similar in their affinity for higher cortical, subcortical, autonomic, and medullary centers, as well as in their relative lack of peripheral actions and the absence of demonstrable primary depressant effects. Their action on the blood pressure is determined by their relative affinities for, and potencies on, the pressor and depressor centers, and depends also on the type and depth of anesthesia. The cooling action of the three analeptics is remarkable; it has certain relations to their sympathomimetic actions (*e.g.*, hyperglycemia) and is inhibited specifically by such anesthetics (especially barbiturates) against which there exists a strong antianesthetic action. During anesthesia, concomitantly with the awakening effect there is a temperature-raising action which restores body temperature to normal. The importance of the arousal system for the awakening from anesthesia probably is overestimated.

The elementary mechanism of action of the three analeptics is still unknown, especially whether they act primarily on the cell membrane or on cell metabolism. It is also not clear to what extent the excitatory actions of the three analeptics are identical. In barbiturate poisoning, pentylenetetrazol seems to facilitate mainly polysynaptic transmission.

The effect of the analeptics against morphine and other narcotics, as well as against local anesthetics, seems to be problematic. This is mainly because of the convulsant component of these CNS depressants. The same is true for the action in hypothermia, which likewise increases the convulsant action. In anoxia the convulsant effect of analeptics (*e.g.*, pentylenetetrazol) is suppressed, and the danger of an unexpected appearance of convulsions must be considered when O_2 is supplied. The effect of subconvulsant doses in the state of anoxia is complex and depends on several factors not yet sufficiently investigated. Hypoxia induced by barbiturate poisoning is antagonized by suitable analeptics. Subconvulsant doses of pentylenetetrazol show a life-saving action against O_2 deficiency in mice; this is due to the lowering of the body temperature. In carbon monoxide poisoning analeptics can accelerate the excretion of carbon monoxide only by restoring respiration. The effect of analeptics in asphyxia of the newborn is still not clear.

The antianesthetic effect of the other analeptics in general is weak. There is reason to believe that they either have unsuitable sites of action (nikethamide, strychnine) or have depressant components of action (nikethamide and other alkylated acid amides, amphetamine and methamphetamine, caffeine, camphor, and derivatives). For amphetamine and methamphetamine the peripheral sympathomimetic action is the limiting factor, since it prevents an increase in dosage as required by the depth of anesthesia.

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