hyaluronidase on thromboplastin generation by defatted platelet material.

Although there is no indication that the apparent interactions between hyaluronidase and platelets play any role *in vivo,* further studies in regard to a possible relation of this phenomenon to vascular physiology and pathology may be warranted.

Summary. Bovine testicular hyaluronidase preparations inhibited formation of thromboplastin in absence of platelets or equivalent materials. This effect was not due to destruction of an essential component of the coagulation mechanism. Inhibition was prevented or reversed by platelets, thromboplastin-generating components extracted from platelets and tissues and by defatted platelet material.

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A New Group of Psychotomimetic Agents.* (23782)

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During the past few years, much interest has developed in psychotomimetic agents, particularly with regard to LSD 25 and mescaline. At the same time, considerable emphasis has been placed on the possible role of adrenalin and serotonin in psychoses, particularly because they are structurally related to the psychotomimetic agents and are pharmacologically antagonistic. The role of acetylcholine and acetylcholine-like substances, on the other hand, has received relatively little attention.

Knowledge of the hallucinogenic properties of cholinergic blocking agents, such as atropine and hyoscine, dates back to the time of the ancient Hindus. Recently, a group of piperidyl benzilates possessing anticholinergic properties were synthesized by Biel and associates(1) as possible antispasmodics in the treatment of duodenal ulcer(2). In the course of therapeutic trials, it was found that the tertiary amine hydrochlorides of the benzilate esters, although active anticholinergics, produced undesirable side effects, particularly hallucinations. The quaternary ammonium salts, on the other hand, were entirely devoid of such effects. We have recently obtained a series of such substances and examined their psychotomimetic effects on animals and human subjects(3).

Methods. The psychotogenic effects of the N-methyl-3-piperidyl benzilate and related congeners were tested on over 40 human volunteers who were either normal or patients complaining of minor disorders. Although some of the patients had limited knowledge of the psychotogenic action of the drugs, the majority of subjects were completely unaware of their nature. Ceruloplasmin determinations were made on many subjects, employing a method described previously(4). All of the agents were tested for their behavioral effects in animals, including some 30 Siamese fighting fish, 50 rodents, and 5 cats. The action of these agents on the Siamese fighting fish is comparable to those described for LSD by Abramson(5). In rodents there were marked behavioral changes, such as initial excitement and marked hyperactivity, spontaneous squealing, lack of responsiveness to stimuli, muscular weakness, and lethargy.

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The anticholinergic effect of the agents was determined on isolated smooth muscle preparations and the rectus abdominus according to the method of Chang and Gaddum(6).

Results. Experimental findings have indicated that the compounds are extremely powerful hallucinogens, in many respects more interesting than LSD and mescaline. When administered in 5-15 mg doses, orally, to human volunteers, distinct auditory and visual hallucinations occurred within one hour in every individual and recurred periodically for periods up to 10 hours after administration of the drug. Hallucinations were accompanied by gross distortions of visual images and severe alterations in feeling state. A number of subjects exhibited paranoid and megalomanic delusions, while the affective states ranged from a feeling of unpleasantness to extreme terror. Some of the subjects actually carried on conversations with imaginary individuals involving situations dating back 10-20 years. The following are almost exact quotations from different subjects: "People from India are standing outside a tent. They have turbans and those are camels." "I see six people sitting around a table playing cards . . . a monkey is over the table hanging by his tail." "I am walking down a narrow corridor and suddenly stop and cannot move . . . a band is playing . . . a drum is beating 3/4 rhythm."

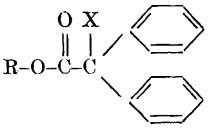
The subjects receiving 10 mg (orally) of N-methyl-3-piperidyl benzilate were in complete loss of contact with the environment for many hours while experiencing dramatic visual and auditory hallucinations. In many respects these anticholinergic agents come closer to simulating clinical psychoses than do mescaline and LSD.

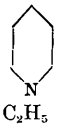
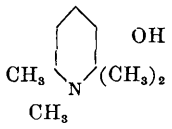
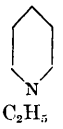
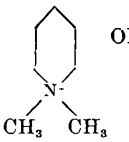
Thus far, a number of congeners have been tested for both hallucinogenic properties and anticholinergic effect on the isolated colon (Table I). Of all the compounds tested for hallucinogenic properties, N-methyl-3-piperidyl benzilate is the most potent, with the N-ethyl derivative being somewhat less effective. The tetramethyl derivative is considerably less effective than the N-ethyl derivative. The quaternary derivative is devoid of psychotogenic effects. As for the antispasmodic potency, although the 3 substances possessing psychotogenic properties are perhaps the most potent, the remaining compounds are still quite effective.

Ceruloplasmin determinations were made on all subjects, since this enzyme was shown to be increased in the serum of acute schizophrenics(4,7). The method used has been described previously(4). Preliminary observations have indicated that as much as a 50-75% elevation in the blood ceruloplasmin accompanies the hallucinatory episode produced by these agents. The enzyme increased only when marked psychogenic disturbances were apparent, returning to normal shortly after the psychogenic effects disappeared and while peripheral autonomic effects, such as mydriasis, muscular weakness, and dryness of the mouth, still persisted. A rise in ceruloplasmin has been shown to accompany changes in affective or feeling states, regardless of the mechanism by which the effects are produced(3).

Discussion. A discussion of the relative antispasmodic properties of this group of compounds appears elsewhere(1). It is apparent from the present study that in this series of compounds there is no direct relationship between the anticholinergic effect on smooth muscle and psychotogenic potency. The presence of the hydroxyl group in the acid moiety to yield the diphenylacetate ester is undoubtedly essential for hallucinogenic effect, while only slightly enhancing the anticholinergic effect. Since both the diphenylacetate and the benzilate derivatives penetrate the blood brain barrier, it would appear that the hydroxyl group is an absolute requirement. The presence of a quaternary nitrogen in the piperidine ring only slightly influences the anticholinergic effect, but apparently prevents the compound from penetrating the blood-brain barrier. As a rule, quaternary ammonium compounds are not able to enter the central nervous system through the blood stream. Preliminary observations have shown that intrathecal injections of the quaternary compound into rats produce much the same kind of neurological and behavioral disturb-

TABLE I. Structure-Activity Relationships of Some Piperidyl Benzilate Congeners. Anticholinergic effect was determined on isolated rat colon with concentrations of about 10^{-6} M.



Name	R	X	Relative hallucinogenic potency	Relative anticholinergic potency
N-methyl-3-piperidyl-benzilate		OH	++++	++++
N-ethyl-3-piperidyl-benzilate		OH	+++	+++
1,2,2,6 tetramethyl-4-piperidyl benzilate		OH	— +	+++
N-ethyl-3-piperidyl-diphenylacetate		H	0	+++
N-dimethyl-3-piperidyl benzilate		OH	0	+++

ances observed with the tertiary benzilates. At present, numerous other congeners are being examined for their hallucinogenic properties. Future synthetic work is contemplated in an effort to explore other structure-activity relationships from the point of view of hallucinogenic effect. In view of the work of others on anticholinergic substances, it may be predicted that the distance between the hydroxyl group and the piperidyl nitrogen is critical(8,9). Introduction of alkyl groups into the molecule would, therefore, presumably diminish the anticholinergic potency, and it will be of interest to determine the relationship of such a change to hallucinogenic effectiveness.

Summary. A series of synthetic anticholinergic agents have been shown to possess potent psychotomimetic properties. Chemically, the agents are esters of piperidine and benzilic acid. Among the effects produced are megalomanic and paranoid delusions, visual and auditory hallucinations, and a partial loss of contact with the environment. A number of congeners of the compounds have been examined with regard to structure-activity relationships.

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