glucagon effect under these conditions.

As Sutherland has pointed out (*15*), when normal, fed animals are used, changes in phosphorylase activity in the liver slices are reflected by changes in glucose output. He and his coworkers have shown that dog-liver phosphorylase is inactivated *in vitro* by liver-phosphorylase inactivating enzyme, which is a phosphatase (*16*), and is reactivated by dephosphophosphorylase phosphokinase, which is referred to as phosphokinase (*17*). He has deduced that epinephrine and glucagon may act by stimulating some portion of the phosphokinase system. If this is the case, it is suggested that Orinase may be effective in the experiments reported here by inhibiting phosphokinase, so that it cannot be activated by epinephrine or glucagon. However, there are several alternative explanations for the observed effect, including the possibility of an action of Orinase on glucose-6-phosphatase or phosphoglucomutase in the intact liver slice. Studies are now in progress to evaluate some of these alternatives and to determine whether the Orinase effect reported here is the mechanism by which it causes hypoglycemia *in vivo*. In view of the failure to demonstrate inhibition of insulinase activity by Orinase in concentrations that might reasonably be expected to occur *in vivo*, it seems unlikely that its hypoglycemic action is due to an effect on this enzyme. In addition, inhibition of insulinase alone would not easily explain the observations mentioned here on liver glycogen levels in animals given Orinase.

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Intravenous Bufotenine Injection in the Human Being

Evarts *et al.* (*1*) found that *n*-dimethyl serotonin, or bufotenine, causes a delay in trans-synaptic transmission at the geniculate ganglion in the optic tract of the cat. When the compound is injected I. V. in the monkey, the hind legs splay out in pseudoparaplegic fashion, and the animal becomes indifferent to noxious stimuli (*2*). A somewhat similar clinical motor response is seen in the rat after intraperitoneal injection, plus a perseverative beating of the forepaws, as if a virtuoso were attacking a piano *fortissimo*. In the dog, I. V. administration of bufotenine in doses of 4 mg/kg causes the same pseudoparaplegic splaying out of the hind legs, salivation, pilomotor response, an unearthly howling, which may persist for the better part of 2 hours, indifference to noxious stimuli, and apparent inability or unwillingness to defend itself when it is attacked by other dogs.

Plant preparations containing bufotenine have been used by primitive man to produce temporary ecstatic states of depersonalization and hallucination. Cohoba, the narcotic snuff of the Indians of Hispaniola and South America, was found by Stromberg (*3*) to contain this substance. The *mouch-more* (*4*) of the Koryaks and other Siberian tribes of the Kamchatka peninsula and the *flugsvamp* (*5*) of the Vikings, which also produced temporary psychoses, were the *Amanita muscaria* mushroom, which contains bufotenine (*6*). This indole is a constituent of the skin of poisonous toads and seems to be present in normal human urine in minute amounts (*7*).

On 12 October 1955, experiments on the I. V. injection of bufotenine were conducted at the Ohio State Penitentiary (*8*). Four healthy, young male convicts were used as subjects. All were above the normal intelligence level, all had been college students, none were recidivist criminals, and all were considered to be relatively stable emotionally. They were denied breakfast on the morning of the experiment.

Bufotenine (*9*) was dissolved in sterile, distilled water and drawn into a syringe. After venepuncture, blood was drawn into the syringe and admixed with the aqueous solution to a volume of 10 ml. This was injected slowly and steadily over a 3-minute period. The first subject received 1 mg of bufotenine in this fashion. Within 1 minute, after one-third of the injection had been completed, he complained of a tight feeling in the chest and a prickling sensation in the face as if he had been jabbed by nettles. Before the injection was completed, he experienced a fleeting sensation of pain in both thighs and a mild nausea. The prickly sensation in the face persisted for 6 minutes. There was no significant change in blood pressure or pulse.

The second subject received 2 mg of bufotenine over the same 3-minute period. During the first minute, he felt a tightness in his throat and a racing pulse, but objectively the pulse remained at the basic rate of 84 beats per minute. There followed a complaint of "tightness in the stomach," then a tingling in both pretibial areas. His face developed a purplish hue, and he had questionable nystagmus. Within 7 minutes after the end of the injection, all subjective complaints were gone, the facial color was normal, and no nystagmus was seen. No significant changes in blood pressure or pulse occurred.

The third subject received 4 mg of bufotenine in the afore-described fashion. Within a minute, he complained of a tingling and burning sensation in the face. In the second minute of injection, he complained of chest oppression, which quickly changed to "a load is pressing down from above and my body feels heavy." Before the injection was completed, he experienced a hollow feeling in the stomach, a numbness of the entire body, "a pleasant Martini feeling —my body is taking charge of my mind." At the time of completion of the injection, his pupils were dilated and he had bilateral nystagmus. Within a minute he reported, "I see red and black spots—a vivid orange-red—moving around." The spots changed in size and shape and persisted for 2 minutes. His face perspired and became purplish. Pupillary dilation and nystagmus were absent by the tenth minute of the experiment, but the facial color did not return to normal for 15 minutes. In retrospect, he stated that it was difficult to concentrate but that he had a feeling of great placidity during the experiment. No significant change in blood pressure or pulse occurred.

The fourth subject received 8 mg of bufotenine in the same fashion. He developed an almost immediate sensation of light-headedness as the injection began, then complained of a burning sensation in the face, which turned purple. Nausea and air hunger followed. He developed a transient hyperpnea for 30 seconds. The pupils were grossly dilated and there was moderate nystagmus. As the needle was withdrawn he blurted, "I see white straight lines with a black background. I can't trace a pattern. Now there are red, green, and yellow dots, very bright, like they were made out of fluorescent cloth, moving like blood cells through capillaries, weaving in and out of the white lines." This visual experience was present with eyes both open and closed, facial sweating and purpling was intense, nausea had abated, and the

subject felt calm. Within 2 minutes the hallucinations were gone, as was the nystagmus, and the pupils were normal in size. Eleven minutes later he said, "Even at the height of this, my mind felt better and more pleasant than usual." There was no significant change in blood pressure or pulse during the experiment.

The fifth observation was made on the second subject who had received 2 mg of bufotenine 90 minutes previously. On this occasion he received 16 mg of bufotenine I. V. Almost immediately he reported a burning sensation in the roof of his mouth. His face turned a livid purple, and he experienced generalized tingling of the body. During the second minute of injection his pupils were in wide dilation, and the ceiling of the room appeared "fuzzy" to him. During the third minute of injection he retched and vomited and stated, "My chest feels crushed." As the needle was withdrawn, marked mydriasis and nystagmus were noted. At that time, he saw red spots passing before his eyes and red-purple spots on the floor, and the floor seemed very close to his face. Within 2 minutes these visual phenomena were gone, but they were replaced by a yellow haze, as if he were looking through a yellow lens filter. Attempt to subtract serial 7's from 100 was abandoned because of many errors. His face remained deeply purple and sweating was profuse.

Nine minutes after the beginning of the experiment he stated, "Words can't come. I can't express the way I feel. My mind feels crowded." The pupils assumed normal size, but the nystagmus persisted for 30 minutes longer. At the 12th minute there was a fleeting return of the red spots before his eyes. At the 16th minute he said, "When I start on a thought, another one comes along and clashes with it, and I can't express myself clearly," and at the 25th minute, "I feel dopey but not sleepy. I feel physically tense and mentally clouded. I am here and not here." Time and space perception were grossly impaired, the yellow haze persisted, and his face remained purple. After 40 minutes he was able to report, "I feel better, but I still feel like I want to walk it off—like a hangover." His face assumed its normal color at the end of an hour. No significant change in pulse or blood pressure occurred throughout the experiment.

These observations indicate that slow (3-min) I. V. injection of bufotenine is feasible in healthy young males in quantities as high as 16 mg without jeopardizing life, that the drug is hallucinogenic, that there is a linear progression in symptoms as dose increases, and that its effects are reminiscent of LSD_{25} and mescaline but develop and disappear more quickly, indicating rapid central action and rapid degradation of the drug. The presence of nystagmus and mydriasis provokes the thought that at least a portion of its effect is localized in the brainstem tegmentum. There is surprisingly little cardiovascular effect; neither systolic nor diastolic blood-pressure changes exceeded 14 mm-Hg throughout these observations, and pulse rates never varied more than 12 beats per minute. If the color of an eggplant were diluted, it would approximate the unique purple hue of the faces of these subjects, which may be due to a serotoninlike bronchiolar constriction and consequent anoxemia. Serotonin does not produce transient model psychoses of this type, but the possible role of anoxemia in the production of the hallucinogenic effects of bufotenine requires clarification. These studies will be expanded.

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Stepwise Reaction via Intermediates on Separate Catalytic Centers

In heterogeneous catalysis an observed chemical reaction may take place via consecutive steps involving one or more real reaction intermediates. The term *real* shall distinguish them as existing as desorbed species in finite concentration; they may or may not be observable with given analytic methods. In porous, solid catalyst particles, the fate of such intermediates is determined by chemical kinetics as well as by the laws of diffusive transport (*1*). If individual reaction steps require different kinds of catalytic sites, the over-all reaction rate will be influenced by the diffusive transport velocity of the respective intermediates between such different sites. We will be interested in the ability of such a catalyst system to catalyze the over-all reaction, especially when the partial pressure of intermediates is very small.

It is possible to formulate quantitatively the requirements for geometric intimacy of the different catalyst materials to obtain an over-all reaction rate unimpeded by transport difficulties of the intermediates.

For an ordinary single step reaction, $A \rightarrow B$, following arbitrary reaction kinetics, a general condition can be derived for having the reaction rate uninhibited by diffusion effects. We shall consider a given catalyst particle (pellet, granule, or the like), with essentially all reaction sites located within the pore structure, and approximated by a sphere of radius R_0. The rate of reaction from the entire particle per (external geometric) particle surface, dN_s/dt, must equal the net diffusive flux across its boundary

$$\frac{dN_s}{dt} = D_{eff} |\text{grad } C|_{R=R_0} \qquad (1)$$

where C is the reactant concentration and D_{eff} is the effective internal diffusivity. For negligible inhibition of the reaction rate by diffusion, we require a negligible internal loss of reactant concentration; that is,

$$|\text{grad } C|_{R=R_0} \ll \frac{C_0}{R_0} \qquad (2)$$

where C_0 is the external reactant concentration. This condition, together with Eq. 1, results in the criterion

$$\frac{1}{3} \frac{dN_v}{dt} \frac{1}{C_0} \frac{R_0^2}{D_{eff}} \ll 1 \qquad (3)$$

in which we have introduced the observed reaction rate per unit particle *volume*, $dN_v/dt = 3\, dN_s/R\, dt$.

For a reaction of nth order—that is, $dN_v/dt = aC^n$—a given internal concentration decrease will result in a smaller effect on the rate, the smaller n is, since

$$d\left(\frac{dN_v}{dt}\right) \Big/ \frac{dN_v}{dt} = n \frac{dC}{C}$$

However, Wheeler (*2*) has pointed out how even for the zero-order reaction inhibition by diffusion effects will result: The reaction rate must begin to vanish at some finite or, at least, at zero concentration; inhibition becomes noticeable when the reactant concentration at the particle center reaches such minimum or zero value. Following Wheeler's rigorous solution of the zero-order case, we can show that this condition obtains when

$$|\text{grad } C|_{R=R_0} = 2 \frac{C_0}{R_0}$$

Thus, even for the extreme case of zero-order kinetics, the condition 2 and, therefore, the theorem 3 are not altered by more than a factor of 2. We may accept this condition as sufficiently independent of detailed reaction kinetics.