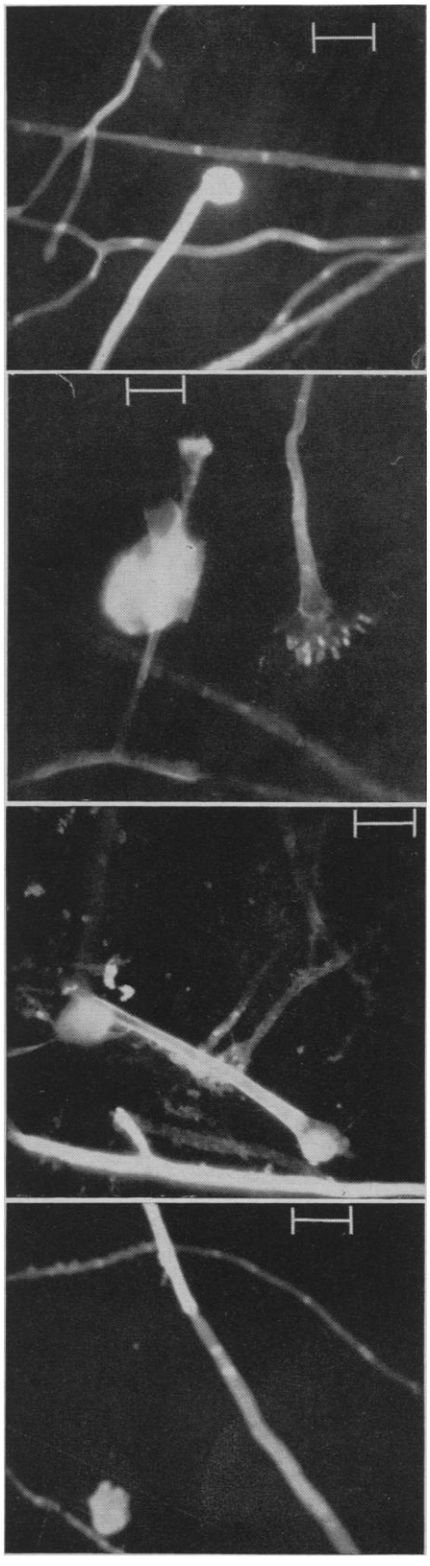

Fig. 1. Fields observed by fluorescence microscopy on slides that had been buried in soil inoculated with strains of *A. flavus*. All slides were stained with fluorescein labeled antiserum of *A. flavus* strain CS. Reference lines represent 50 μ. (Top and upper middle), *A. flavus*, strain CS structures; (lower middle), *A. flavus*, strain F9807; (bottom), *A. flavus*, strain F921.

observed with 10×, 20×, or 40× dry objectives.

Contact slides bearing the antigen but not stained with the antiserum gave no evidence of interfering fluorescence when examined with fluorescence microscopy. Fields were black to dark blue for the most part with nothing visible. Soil particles, when visible, fluoresced in bright blue or red most commonly, but occasionally minerals with yellow fluorescence were seen. Autofluorescence of *A. flavus* was barely apparent as faintly bluish white mycelium. Slides with or without the antigen gave little evidence of interference through nonspecific absorption of the fluorescein label to soil materials. Characteristic fluorescence was restricted to structures of the fungus antigen visible in the field. Figure 1*a* is a photomicrograph from a slide buried in soil, inoculated with the antigen strain of *A. flavus*, and treated with the immunofluorescent stain. The bright areas associated with the conidiophore and the enlarged apex of the conidiophore (vesicle) in the foreground, and the cross wall and hyphal segments in the background, reflect regions of most intense fluorescence. These light areas were brightly yellow green against the dark background when viewed through the microscope. The duller sections of hyphae visible in the photomicrograph reflect a lower intensity of fluorescence commonly associated with much of the hyphae. It is likely that the age of the mycelium has an effect on the intensity of the staining reaction. A conidiophore of *A. flavus* strain CS with some fluorescent conidiospores still in place is shown in Fig. 1*b*. The other conidiophore is partially obscured by a soil mineral which fluoresced as a bright blue.

Isolates of *A. flavus* other than the one used as the antigen reacted well when stained with labeled antiserum of *A. flavus* strain CS. Two such strains are shown in Figs. 1*c* and 1*d*. Immunofluorescence of strain F9807 in Fig. 1*c* was intense on the conidiophores and hyphae in the foreground; soil particles in the background appeared dark green or dark blue. A field with strain F921 is shown in Fig. 1*d* and again shows areas of good to intense fluorescence on the hyphae, with a blue soil mineral in the lower center.

The specificity of the staining reaction extended to numerous other isolates of *A. flavus* as well. Relatively little evidence of cross reactions with other fungi has been encountered. Work dealing with the specificity of the strain CS fluorescein labeled antibody will be reported in more detail (*5*).

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19 December 1961

Serotonin-like and Antiserotonin Properties of Psilocybin and Psilocin

Abstract. These psychotomimetic analogs of serotonin act like this hormone in some tests and against it in others.

The evidence which originally led Woolley and Shaw to suggest in 1954 that serotonin was concerned in normal mental processes and in schizophrenia was that a variety of antimetabolites of this hormone induced schizophrenia-like symptoms in normal persons (*1*). This evidence was interpreted at first to mean that cerebral deficiency of serotonin could be the basis of the mental disorder. Subsequently new evidence indicated that many of these hallucinogenic analogs of serotonin exerted a serotonin-like action on some kinds of tissue in addition to their antiserotonin effects (*2*). This and independent evidence obtained in other ways has led to the idea that hallucinations and other kinds of agitation may be related to cerebral excess of serotonin (*3*), and that depressions may be the result of cerebral deficiency of this hormone. In any event it is clear that many drugs which are relatives of serotonin and which affect the mind can be shown to have either serotonin-like or antiserotonin actions, depending on the nature of the test system. Consequently, it is of interest to determine whether newly discovered psychotomimetic agents also

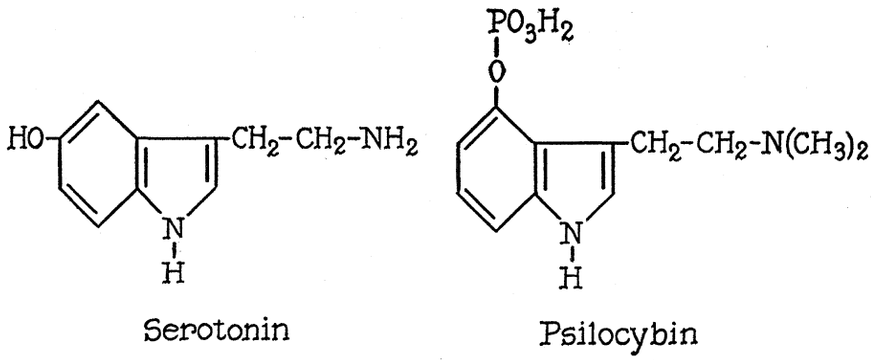

Fig. 1. Structure of serotonin and psilocybin and psilocin (psilocin is dephosphorylated psilocybin).

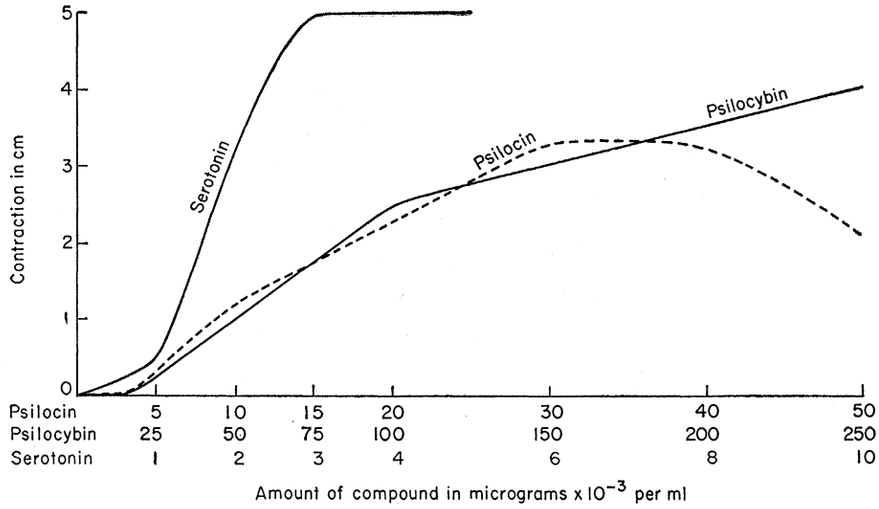

Fig. 2. Serotonin-like action of psilocybin and psilocin on isolated rat uterus.

have these two kinds of relationship to serotonin.

Two new drugs which affect the mind have recently been isolated from the Mexican fungus *Psilocybe mexicana*. These are psilocybin and psilocin which have, as Hofmann *et al.* have shown (*4*), the structures given in Fig. 1. The fungus is used by medicine men to induce greater insight and to cause hallucinations and other mental aberrations (*5*). Psilocybin and psilocin appear to be the active principles responsible for such changes in normal persons. The surprisingly close structural similarity of these drugs to serotonin especially has prompted us to study them. Because we have seen no reports of their functional relationship to this hormone, we wish now to show that they do have serotonin-like actions in some tests and antiserotonin effects in others. Experience of the past 8 years has proved that for many psychotomimetic analogs of serotonin this is the case. It has now been found true for psilocybin and psilocin also.

Psilocybin and psilocin (*6*) were assayed quantitatively for serotonin-like action on the isolated rat uterus (*7, 8*) and on the isolated strip of the rat stomach (*9*). In the rat uterus assay psilocin had 1/10 to 1/20 the activity of serotonin, and psilocybin had 1/50 to 1/100. The shape of the dose-response curves was somewhat different from that of serotonin (see Fig. 2), and consequently a precise comparison was not possible. Part of this difference in shape was due to the fact that the analogs began to exhibit antiserotonin activity as the dose was increased. This was especially marked with psilocin for which the size of the contractions actually began to decline as the dose was increased much beyond that which gave maximal contractions. In the rat stomach assay psilocin showed no serotonin-like action, but psilocybin did have some. This varied from specimen to specimen of stomach. Two specimens showed no serotonin-like action of psilocybin, but others gave values ranging from 1/1000 to 1/3.

The antiserotonin activity of both analogs was measured on the rat stomach and rat uterus according to the procedure described earlier (*8*). This gave indication of how much analog was required to reduce by 50 percent the contraction caused by an amount of serotonin just sufficient to give a large contraction in the absence of the analog. Both analogs showed antiserotonin activity in both tests. Psilocin was more potent. Thus, in the rat uterus half maximal inhibition of the effects of 0.01 μg of serotonin per milliliter was found with 0.03 μg of psilocin, whereas with psilocybin the values ranged from 1 to 0.03 μg. In the rat stomach psilocin produced half maximal inhibition at 0.5 μg, whereas with psilocybin 6 μg were required. The action of either compound on either tissue was characterized by an irreversible change in sensitivity to serotonin, that is, repeated washing did not restore to normal. This was more marked with psilocybin than with psilocin. After treatment with psilocybin, washing of the tissue frequently initiated contractions. Individual specimens of tissue varied greatly with respect to the amount of psilocybin required to show antiserotonin activity. Despite these atypical responses it was plain that psilocin was a quite potent antagonist to serotonin. In fact it was almost as active as the most potent known antiserotonin (*8*).

These findings show that psilocybin and psilocin, like other hallucinogenic drugs analogous to serotonin, have serotonin-like and antiserotonin activities. Possibly their effects on the mind may be related to these actions (*10*).

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