Specialized Analgesic Effects of β-Hydroxy-α : β-diphenylethylamine

CLINICAL trials by other workers not yet reported have confirmed our original observation[1] that β-hydroxy-α : β-diphenylethylamine will relieve pain due to pressure on nerve in patients with inoperable tumours. This was the only type of pain included in our trials, and it is now clear that the compound has no universal analgesic action and cannot be used generally as a substitute for morphine. Tests using the method of Sivadjian[2], which measures the tolerance of rats to electric shocks, have now been carried out with morphine and the diphenylethylamine compounds the morphine-like properties of which we have described[1]. The results, which will be reported in detail elsewhere, were entirely negative for the diphenylethylamine compounds; but analgesic activity was demonstrated in the hydrochlorides of morphine and pethidine, showing that the negative results were not due to the method used. The cause of the specific action of β-hydroxy-α : β-diphenylethylamine on nerve pressure pain awaits further pharmacological investigation.

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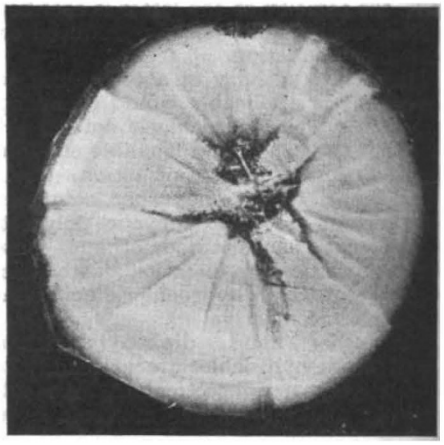
[1] Dodds, E. C., Lawson, W., and Williams, P. C., *Nature*, **151**, 614 (1943); *Proc. Roy. Soc.*, B, **132**, 119 (1944).
[2] Sivadjian, J., *Arch. Int. Pharmacodyn.*, **52**, 142 (1935).

Genetic Proof of Heterokaryosis in *Penicillium notatum*

IN a recent paper, Baker[1] has given an account of nuclear behaviour in *Penicillium notatum*. We had, independently, reached the same conclusions, summarized as follows: (*a*) the older 'cells' of the mycelium, the sterigmata and the conidia are usually uninucleate; (*b*) the 'cells' at the growing edge of the colony are usually multinucleate, containing up to a dozen nuclei each; (*c*) hyphal fusions occur between branches of the same hypha and also between hyphæ of different origin. From her cytological work, Baker infers that *P. notatum* is liable to be 'heterokaryotic', that is, may carry genetically unlike nuclei in a multinucleate cell, or in different cells of a hypha. This condition, widespread in fungi, well deserves careful investigation in view of its important implications for the theories of gene action and of the evolution of genetic systems. Some of these implications have been discussed by Hansen[2], Dodge[3], Lindegren[4] and, especially, by Beadle and Coonradt[5].

The above cytological inference, in the case of *P. notatum*, needs the support of a genetic counter-proof: this can now be supplied. Even though *P. notatum* has no known sexual stage involving alternation of karyogamy and meiosis, the fortunate circumstance that conidia are uninucleate makes a genetic analysis possible. The technique—an obvious simplification of those used[3,5] for species with a sexual stage and multinucleate conidia—is as follows: (1) production by X-rays of mutant strains; (2) mixed inoculation two by two of different mutant strains; (3) search for non-mutant ('wild type') patches, or



MIXED COLONY OF TWO WHITE STRAINS SHOWING GREEN HETEROKARYOTIC PATCHES AT THE CENTRE AND ALONG THE LINES OF CONTACT BETWEEN THE TWO STRAINS.

for patches differing from either strain, at the centre of the mixed colony and along the radii where the mycelia of the two strains are in contact. The following are the results of mixed inoculation two by two of five such X-ray induced mutants, all characterized by a reduced pigmentation of conidia or by complete failure to form conidia. The formation of patches with wild type (green) conidia, or with conidia differing from those of either parental strain, is represented by +, and failure to form such patches by −.

Designation of strain	Type of conidium	Results of mixed inoculation				
		y—1	*w*—16	*w*—2	*w*—3	2*C*4
y—1	yellow	—	+	+*	+	—
w—16	white		—	+*	+	—
w—2	white			—	+	—
w—3	white				—	—
2*C*4	no conidia					—

* Very pale green conidia.

All combinations of any two of the first four strains, and none of the combinations involving the non-conidial strain 2*C*4, produce patches of mycelium with green conidia, or with conidia differing from either of the strains used (see accompanying reproduction). When these conidia are plated out, the two component strains are recovered, thus confirming that fusions between hyphæ of the two strains had taken place, followed by migration of nuclei from one strain to the other, and the nuclei segregated later. Segregation of parental nuclei does not take place at the formation of the conidiophore but at some stage between this and the formation of conidia, probably at the formation of the sterigmata. In fact, even though each conidium gives rise to one or the other parental type, both types may be recovered from different conidia of the same (green) penicillus.

Points of interest are, first, that despite the fact that each conidium carries a single nucleus, all those of one penicillus are uniform in their pigmentation: hence this pigmentation is controlled not by the genetic constitution of the nucleus segregated into each conidium, but by the constitution of the hypha from which the penicillus arose. Secondly, if the familiar criteria of genetics are valid in the present case, four out of the five X-ray mutations tested, namely, *y*−1; *w*−16; *w*−2; *w*−3, behave as if they were recessive, involving four different loci. As for the fifth mutation—the non-conidial 2*C*4—failure to produce green conidia in mixed inoculi is probably due to dominance of the non-conidial effect, as inter-