appears less likely as an explanation for the present results, but further investigations are needed.

In view of the availability of 'fate maps' for the various components of the developing limbs[7], investigations were undertaken in order to determine if distinctively located populations of deoxyguanosine-sensitive cells could be detected. Fertile eggs which had been incubated 48, 72, 96 or 120 h were injected with 50, 50, 100 and 200 μg of deoxyguanosine, respectively, and embryos were collected at various times after treatment. Live embryos were then vitally stained with Nile blue sulphate according to the procedure of Saunders *et al.*[8], and the location of degenerate cells in the leg buds noted. With only rare exceptions, embryos killed 24 h after treatment showed a fairly even distribution of degenerate cells throughout their leg bud mesenchyme. The response pattern then did not appear to be related to the spatial distribution of sensitive cells. Presumably it was determined by subsequent internal rearrangements possibly directed by factors such as the competitive interactions among the long bone rudiments which have been reported in recent years[9].

The investigations described here confirm and extend the earlier observations of Karnofsky and Lacon[1] regarding the teratogenic capability of deoxyguanosine. Failure to record such a capability in our previous investigation[3] can presumably be traced to a combination of factors such as duration of experiments, small dosage of deoxyguanosine and sampling error. Previous experiments were terminated at the end of 8 days, a time at which it is difficult to detect either the relatively slight effect of 25 μg of deoxyguanosine on thoracic development or even the eventually more marked shortening of the neck. The reasons why deoxyguanosine is cell toxic and consequently teratogenic are not known. That embryos can be protected against the effects of deoxyguanosine by supplementary treatment with cytidine has been reported by several investigators[2,10]. It has been suggested that deoxyguanosine inhibits the enzyme deoxycytidylate deaminase[2], and thereby interferes with DNA synthesis, but direct evidence for this inhibition is lacking. Deoxycytidylate deaminase has been shown to be inhibited in an *in vitro* test system by deoxyguanylic acid, however, and it is possible that deoxyguanosine becomes teratogenic only after phosphorylation *in vivo*[2]. We have found that the latter is not so effective a teratogen in our *in ovo* test system as is deoxyguanosine, but the possibility that permeability to the phosphorylated compound is reduced has yet to be examined.

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PSILOCIN: EFFECTS ON BEHAVIOUR AND BRAIN SEROTONIN IN MICE

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PSILOCYBIN and psilocin have recently been included on the list of psycho-active agents. Psilocin, or dephosphorylated psilocybin, has been structurally identified as 4-hydroxy-*N* : *N*-dimethyltryptamine[1]. Clinical reports have indicated that the hallucinogenic effects of psilocin in man are quite similar to those of LSD-25, but of shorter duration[2], and that its distribution in the brain and other organs is more uniform[3]. Other findings have indicated that psilocin is an analogue of 5-hydroxytryptamine and possesses certain serotonin and antiserotonin properties[4].

Although a number of investigations have reported behavioural differences in laboratory animals to experimental serotonin alteration[5,6], and others have indicated brain amine variations following administration of psychotomimetic compounds[7], few multidisciplinary investigations have attempted to relate changes in brain serotonin and behaviour following psychotropic drug treatment in a single experimental design.

The present experiments were conducted to determine specific directional behavioural changes in mice to psilocin administration, to correlate these changes to possible directional variations in total-brain serotonin, and to separate the effects of psilocin on serotonin-levels from possible non-pharmacological effects.

Groups of 20 adult female mice from the highly inbred *C57BL/10J* strain were used as subjects. All experimental mice were maintained under rigid laboratory conditions with free access to Purina mouse chow and water until 90 days of age. At the beginning of experiments, subjects were matched for age and weight and then randomly assigned to experimental groups. Groups designated '*A*' and '*B*' received 10 mg/kg psilocin or an equal volume of placebo, respectively. Psilocin was dissolved in dilute hydrochloric acid and administered orally by means of a beaded-tip syringe. On each of five successive test days, groups received psilocin or placebo 1 h before testing. To evaluate possible carry-over effects as well as changes in performance following psilocin withdrawal, both groups received oral placebo during five additional days of testing. Naïve groups were used in each behavioural test.

Psilocin-induced changes in behaviour were evaluated in the following tests: (1) shock-elicited escape-avoidance conditioning; (2) open field exploration; (3) locomotor activity wheel running. Details concerning apparatus and procedure have previously been presented[8].

Serotonin content (5-hydroxytryptamine, 5-HT) in individual whole brains was determined by the spectrofluorometric technique of Bogdanski *et al.*[9]. To ensure that serotonin measurement would not be confounded with systematic differences in daily runs, 5-HT-levels were evaluated from randomized treatment group samples on an individual day. Concurrent daily standards were run, and all scores corrected for daily percentage recovery. Recovery ranged from 87 to 93 per cent. Psilocin was run under identical spectrofluorometric conditions but it could not be detected.

Serotonin content in individual whole brains was determined for six groups of mice. Groups 1 and 6 were identically matched non-handled controls; these mice were obtained directly from laboratory stock and immediately killed. Brains from Group 1 subjects were analysed concurrently with those of the treatment groups, while Group 6 was added at the completion of the analysis to

further verify serotonin-levels in non-handled mice. Group 2 received 50 mg/kg psilocin. Group 3 received an equal volume of HCl vehicle. Group 4, designated sham placebo, received experimental manipulation alone without oral administration of either drug or vehicle. Group 5 received 5 mg/kg reserpine. With the exception of non-handled mice, all treatment subjects were returned to individual cages for 1 h before being killed. A total of sixty whole brain serotonin determinations were made.

Analyses of variance were used to detect differences in behaviour, while an unweighted means analysis of variance was used to assess the serotonin data in which there were slightly unequal sub-class numbers[10]. In addition, an extension of the Newman–Keuls' multiple range test was used to perform all intergroup serotonin comparisons (carried out in pairs)[11]. Unless otherwise noted, degrees of freedom for F-ratios were 1/190.

Table 1. Summary of Mean Behavioural Performance for Group *A* (10 mg/kg Psilocin) and Group *B* (Placebo)*

	Open field exploration				Avoidance conditioning			
	Latency (sec)		Squares traversed		Latency (sec)		Avoidance number	
Group	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Day 1	3·06	2·44	46·0	52·1	4·88	4·55	0·7	0·6
2	2·42	2·25	46·7	63·6	3·70	3·37	5·7	6·3
3	2·83	2·34	47·4	61·7	3·11	2·60	9·2	11·3
4	2·62	2·26	38·9	59·2	2·53	2·27	12·9	13·7
5	2·39	2·21	59·3	79·5	2·22	1·90	14·7	15·3
Mean	2·66	2·30	47·7	63·2	3·29	2·94	8·6	9·4
Day 6	2·88	2·37	70·5	64·8	2·12	2·21	15·3	14·5
7	2·71	2·05	76·6	66·4	2·10	2·06	15·7	15·3
8	2·94	2·32	66·9	66·2	2·11	1·91	15·7	15·3
9	2·81	2·14	72·3	61·3	1·94	2·02	16·6	16·8
10	2·10	2·14	69·9	64·2	2·22	2·15	15·3	15·3
Mean	2·69	2·20	71·2	64·6	2·10	2·07	15·7	15·8

* Both groups received oral placebo during days 6–10.

Table 1 summarizes the mean performance scores for open field exploration and avoidance conditioning for psilocin and placebo groups. During the first 5 days, psilocin-treated mice explored less in an open field than placebo mice ($P < 0{\cdot}0001$; $F = 17{\cdot}4$). On days 6–10, during which all mice received oral placebo, the exploration mean of Group *A* was higher than Group *B*. This reversal suggested that cessation of psilocin facilitated exploration performance. However, the statistical analysis did not reject the null hypothesis that this shift was a chance event ($P \simeq 0{\cdot}08$; $F = 3{\cdot}15$). Psilocin mice exhibited longer latencies to move from the middle square during the first week ($P < 0{\cdot}025$; $F = 5{\cdot}83$), as well as during the second week ($P < 0{\cdot}005$; $F = 9{\cdot}01$). Thus, the effect of psilocin on open field latencies persisted beyond drug withdrawal.

Both groups learned to avoid shock to an asymptotic level by 5 days of testing. However, mice which received psilocin traversed the runway more slowly ($P < 0{\cdot}001$; $F = 12{\cdot}6$). This 0·35 sec mean decrement was relatively constant during the 5 days of psilocin administration. During days 6–10, Group *A* performance did not differ from that of Group *B* ($P > 0{\cdot}5$; $F = 0{\cdot}3$). To distinguish whether the increased latency of psilocin-treated mice during the first week reflected a learning deficit or decreased locomotor ability, the mean number of avoidances per session were analysed for both groups. During the first 5-day period, Group *A* averaged 8·64 avoidances and Group *B* 9·44 avoidances. The difference between these averages was not significant ($P > 0{\cdot}25$; $F = 1{\cdot}17$). During the final 5-day period, the averages for Groups *A* and *B* were 15·7 and 15·8 avoidances, respectively. Whereas the analyses indicate that psilocin resulted in a decreased ability to traverse the runway, they did not indicate a differential effect on avoidance acquisition.

To evaluate the effect of psilocin and reserpine on spontaneous activity, four groups of mice were pretrained in activity wheels until a stable performance of 4,000 rev per 2 h period was attained. On each of five successive test days, treatment groups received oral administration of 50 mg/kg psilocin, 10 mg/kg psilocin, 5 mg/kg reserpine, or placebo 1 h before testing. Fig. 1 illustrates the group mean locomotor performance during five test days.

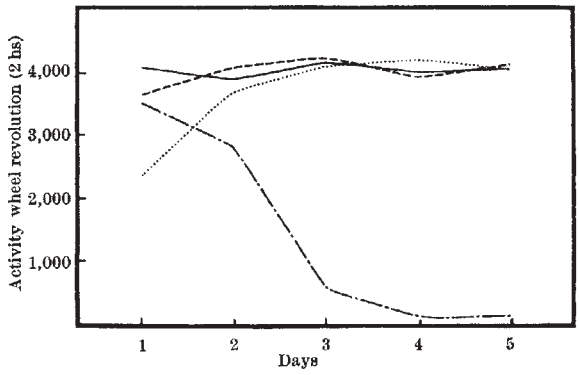

Fig. 1. Daily performance averages of spontaneous locomotor activity for four groups of mice administered psilocin, reserpine, or placebo. ———, placebo; – – –, psilocin, 10 mg/kg; ·····, psilocin, 50 mg/kg; –·–·–·–, reserpine, 5 mg/kg

Data analyses by simple-effects analyses of variance and multiple range tests indicated that the day 1 locomotor performance of both psilocin groups was significantly lower than placebo scores ($P < 0{\cdot}0001$; $F = 35{\cdot}3$, d.f. = 2/285). By the second day, groups which received psilocin regained asymptotic levels and did not differ from the control group ($0{\cdot}25 < P < 0{\cdot}5$; $F = 1{\cdot}02$, d.f. = 2/285). By contrast, the reserpine-treated group did not differ from controls on the first day of testing, but differed from the control group as well as psilocin-treated mice, beginning on the second day ($P < 0{\cdot}001$; $F = 11{\cdot}8$, d.f. = 3/380). These data indicate that psilocin administration produced decrements in locomotor performance on the initial treatment day, that the degree of decrement was a function of the dosage, and that psilocin had no effect on wheel running from the second day onward.

The results of the sixty serotonin determinations are summarized in Table 2. An unweighted means analysis of variance demonstrated highly significant differences in whole brain serotonin levels among the six groups ($P < 0{\cdot}0001$; $F = 46{\cdot}2$, d.f. = 5/54). Application of the Kramer–Newman–Keuls' multiple range test demonstrated that the mean serotonin-levels fell into three non-overlapping major groupings ($P < 0{\cdot}01$). Groups 4, 3, and 2 did not differ among themselves, but differed from all remaining groups. Both groups of non-handled controls did not differ between themselves, but differed from all other groups. In addition, the group which received reserpine differed from all other groups. The mean serotonin-level of the psilocin group did not differ from either the HCl or sham-placebo groups. By contrast, the serotonin content in both groups of non-handled controls was 11 per cent lower than sham-placebo, HCl, and psilocin scores. The analyses suggest that experimental handling alone may have been responsible for the significant elevation of 5-HT for Groups 4, 3, and 2, since one treatment condition common to these groups was experimental manipulation. The highly significant depletion of serotonin in Group 5 which received reserpine is consistent with many previous findings[12].

Some recent evidence has suggested that central nervous system amines are responsive not only to pharmacological alteration, but also to environmental stressors requiring extensive adaptation. Whereas Barchas and Freedman[13] reported an average 13 per cent increase in whole brain serotonin in rats exposed to prolonged forced activity or a 15 min cold swim, the present findings demonstrate that

Table 2. Mean Whole Brain Serotonin-levels (μg 5-HT/g Wet Tissue)

Treatment	Sham placebo	HCl vehicle	Psilocin (50 mg/kg)	Non-handled controls		Reserpine (5 mg/kg)
Group number	4	3	2	1	6	5
No. of subjects	10	10	9	11	11	9
5-Hydroxytryptamine	1·27	1·21	1·21	1·12	1·05	0·90

Group means underscored by a common line do not differ statistically among themselves, but differ significantly from remaining groups ($P < 0{\cdot}01$). Average standard error for treatment means equals 0·022 μg 5-HT/g wet tissue.

a comparable elevation in brain serotonin may result from relatively mild handling stress in mice. Since these results indicate that total brain serotonin content may be confounded with levels of adaptation or arousal, future pharmacological investigations which utilize neurohumour levels as dependent variables should incorporate adequate control procedures to separate possible treatment differences from placebo effects.

The behavioural findings observed in this investigation indicate that psilocin produced consistent decrements in open field exploration parameters and avoidance conditioning running, but did not appreciably influence avoidance acquisition. The data suggest that open field exploration was enhanced following psilocin withdrawal, and that latency decrements persisted. In addition, psilocin treatment was associated with a dose-dependent decrement in spontaneous locomotor activity on the initial day of treatment, with rapid tolerance development by day 2.

The comparison of the biochemical and behavioural findings is noteworthy in several respects. For example, the significant decrease in day 1 activity wheel performance of both psilocin-treated groups was not associated with a corresponding variation in endogenous whole brain serotonin. Thus, psilocin significantly altered behavioural performance without altering serotonin-levels. Conversely, the locomotor performance of mice administered reserpine did not differ from placebo mice on the first day of testing, although brain serotonin-levels were depleted 29 per cent. Thus, a dramatic change in brain serotonin-level was not associated with a concurrent alteration in behaviour. These results indicate a lack of correlated response between brain serotonin content and certain behavioural criteria.

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EVOKED POTENTIALS CORRELATED WITH A VISUAL ANOMALY

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An incoherent succession of randomly patterned optical images ('dynamic visual noise') offers a useful stimulus to probe the visual system and reveal any bias present in perceptual mechanisms[1–3]. The present investigation concerns the physiological correlates of a curious visual anomaly discovered some years ago when using a stimulus of this kind[4]. If each frame of such a visual noise sequence is followed by a short bright flash of light in the same eye, illuminating the same area of the visual field, then with a certain critical time interval between frame and flash, and at frame repetition rates of the order of 5–20 per sec, the random 'Brownian movement' normally perceived in the visual noise field is disrupted. In its place (or in addition), the screen appears to be filled with elongated objects resembling maggots, which seem to wriggle to and fro at random and link up to form long chains or chain-mesh patterns. The critical lag between the onset of each noise frame and the blank flash varies with frame duration, repetition frequency and intensity[5], but is typically of the order of 18–25 msec.

This is not the only visual anomaly that may be observed with such interlaced sequences of stimuli. With a somewhat longer time interval between frame and flash, Dr. J. P. Wilson[6] has reported that spurious impressions of contour motion are produced with stationary stimulus figures. A stationary black disk on a stroboscopically-illuminated white ground, for example, may appear to be continually expanding or contracting according to the time interval between the illuminating flashes and the blank flashes[6]. (Explanations in terms of eye movements are ruled out, for with a more complex field such as a black annulus one may see simultaneously a contraction of the inner edge and expansion of the outer.)

On both scores it seemed worth while to ask whether the occipital evoked potentials, as recorded from scalp electrodes, showed any corresponding anomalies at the inter-stimulus intervals giving rise to these phenomena. The preliminary investigation to be reported here indicates that they do, and appears to give evidence of a specific sensitivity, at the critical phase, to the presence of spatial patterning in the visual stimulus.

In place of the cine projector used in the earlier investigations[4,5] a high-powered electronic stroboscope was used to illuminate an area of 'static visual noise'—an enlarged photograph of sand paper, mounted on a turntable, and viewed through a circular (non-concentric) aperture. The turntable could be rotated asynchronously, so as to present a substantially unrelated sequence of visual noise samples when required[2]. A second stroboscope illuminated a plain white disk of the same size as the exposed area of visual noise, the two being optically superimposed by means of a half-silvered mirror. These fields subtended an angle of about 10° at the observer's eye. The repetition period and relative timing of the two stroboscopes were adjustable in steps of one msec.

Scalp electrodes were positioned as shown in Fig. 1, with the reference electrode 2 cm above the inion and inter-electrode distances of 5 cm, so that longitudinal (A) and transverse (B) components of the electric field could be simultaneously recorded and compared. Conventional electronic computing equipment (a Mnemotron '*CAT*'), triggered synchronously with the visual noise exposure, enabled the two evoked components A and B to be averaged on separate channels; a typical run lasted for 1 min and represented the sum of 500–1,000 responses.

To summarize the results (to be presented more fully elsewhere), the critical phase of our double-flash stimulation was indeed found to be accompanied by anomalies in the evoked potential. A sample run with a repetition period of 63 msec is shown in Fig. 1, where the number on the left of each pair of tracings represents the lag in msec between noise and blank flashes, and that on the right shows the order in which runs were made (subject A. F.). Since the perceptual anomalies in question are visible only at repetition rates above 5 or 6 per sec, their corresponding evoked potentials have a large continuous and oscillatory component, and the waveforms shown represent one complete cycle of a repetitive train. Slow changes in