and forearm acuity of the index finger of darkness (in each test, $p < .001$). Again, the aftereffects seemed to persist for a number of days. However, for the finger, only the differences observed on days 1 and 2 are significant (in each test, $p < .01$); for the forearm, the day-7 difference is still significant ($p < .05$). In the case of the forearm, however, the unusually long aftereffect may partly be due to a change in standard of judgment. Finally, Fig. 3 shows that not only did tactual acuity increase but also sensitivity to heat and pain (in each test, $p < .01$). Furthermore, this supersensitivity still persisted on day 2 for pain ($p < .05$) and on day 1 for heat ($p < .05$).

An examination of the individual performance of the 16 experimental subjects revealed that the effect of visual deprivation was uniform. The supersensitivity was shown by all subjects, on all skin areas, and on all cutaneous measures. On the other hand, the control subjects exhibited a chance distribution of increases and decreases in sensitivity. It is of interest that the subjects' spontaneous remarks seem to support some of the experimental results. Several individuals reported that during darkness the soles of their feet or their arms were very sensitive. One subject also stated that he was ticklish for the first time in his life. There were also indications of auditory hyperacuity. Several subjects reported, on their return home, that the radio was unusually loud. It is possible, therefore, that a general enhancement of sensory functioning may occur as a result of visual deprivation. This possibility is currently under investigation.

These results suggest that a severe reduction in sensory input from several modalities may not be essential for the appearance of cutaneous supersensitivity and of certain other deprivation phenomena. Some of these may be specific to a particular sense modality or, alternately, may be produced by interference with any one modality. In this regard, it is interesting to note that diminished proprioceptive stimulation alone can produce many of the classical deprivation effects (*7*). These results on cutaneous supersensitivity also suggest that one of the effects of the functional deafferentation produced by the visual deprivation technique may be to "sensitize" certain areas of the central nervous system. Some support for this hypothesis is offered by Grey Walter (*8*) who reported that in some congenitally blind children the nonspecific cortical responses evoked by tactile and auditory stimuli are unusually large in relation to those of sighted children of the same age. Krech *et al.* (*9*) have also demonstrated that rats, subjected to peripheral blinding at the time of weaning, subsequently show an increase in the weight and cholinesterase activity of the somesthetic cortex. Furthermore, Krech (*10*) recently observed similar somatosensory changes in sighted rats reared in darkness. Thus, it would appear that visual deprivation alone can produce cortical changes of a type which could result in cutaneous supersensitivity. Whether the cortical changes in man, however, are similar to those reported by Krech is open to speculation, particularly in the light of our short deprivation period.

Although some of the studies on blind organisms appear to support our findings, others do not. For example, if pronounced increases in cutaneous sensitivity can occur after only a week of darkness, similar or even greater increases might be expected in blind human subjects. This, however, does not appear to be the case. What literature is available is contradictory in nature, both increases and decreases in sensitivity being reported (*11*). Although the reasons for this discrepancy are not clear, our results, together with those of Krech, suggest that perhaps a "new look" at the centuries-old controversy over sensory compensation in the blind may be justified.

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3 April 1964

Prevention of a Mental Defect of Phenylketonuria with Serotonin Congeners such as Melatonin or Hydroxytryptophan

Abstract. *Mice made phenylketonuric from birth until maturity by continuous administration of phenylalanine plus tyrosine had a subnormal maze-learning ability which was largely prevented when serotonin congeners such as melatonin or 5-hydroxytryptophan were administered continuously from birth to maturity. These results were interpreted to mean that the mental failure of experimental phenylketonuria is attributable to the serotonin deficiency imposed by it in infancy.*

In previous papers (*1–3*) we have presented evidence to suggest that the mental defect of the inherited idiocy of phenylketonuria is the result of a serotonin deficiency imposed in infancy. In this paper we want to offer direct proof of this idea by showing that the mental defect can be prevented (at least in part) through correction of the serotonin deficiency by means of continuous administration of those serotonin congeners which can penetrate into the brain and act there. All of these experiments have been done in laboratory animals (mice) because the nature of the disease in human beings is such that it is impossible to make the trials with them. Because an effective preventative treatment is available for human beings (the phenylalanine-low diet) it would be morally unjustifiable not to use it in preference to some other treatment.

Phenylketonuria was produced in newborn mice by the method previously described (*1*). It consisted of continuous oral administration of DL-phenylalanine and L-tyrosine from birth to maturity. Whenever a serotonin derivative was to be tested, it was also administered continuously from birth to maturity. Care was taken that all animals (controls as well as test) were handled to the same extent so as not

to prejudice the performance in the learning test. It was demonstrated in the previous paper (*1*) that when mice were made phenylketonuric in this way from the time of birth, they exhibited a readily demonstrable and reproducible defect in maze-learning ability. By contrast, when the phenylketonuria was not established in them until time of weaning, they did not exhibit such a learning deficit.

In the work to be described in the present paper, the testing of learning ability of the adult animals (rendered phenylketonuric from time of birth) was done in two different ways in order to insure that the whole conclusion about any mental defect did not rest on a single way of assay. The first method of testing was that which measured the rate at which the mice learned to run a maze correctly in response to a reward of being able to hide (*4*). When conducted in the manner previously described with individual units of ten mice each, this method gave answers for which the standard deviation was ±0.2. A score of 10 meant that the mice had learned perfectly, and a score of 5 meant that they had learned nothing. Normal mice uniformly gave an average score of 7.5 in this test.

The other method of testing was similar to that described by Flexner *et al.* (*5*) in which the rate of learning to avoid a shock was measured. This test was first introduced for measurement of memory (that is, the retention of the learning to avoid a shock), but in our experiment a similar apparatus was used to determine how many errors resulting in punishment were required before the animal learned to avoid making the error. The scores represent the number of shocks received before the lesson was learned perfectly. The higher the score, the less the learning ability. Normal control animals made an average score of 3.7, that is, on the average they received 3.7 shocks before they learned to avoid being shocked.

The results of the tests for maze-learning ability of phenylketonuric mice, and of such mice treated continuously with serotonin derivatives, are summarized in the table. It can be seen that, although the phenylketonuric animals made low scores (indicative of subnormal learning ability) the ones given continuously either melatonin or 5-hydroxytryptophan gave scores not greatly different from those of normal mice.

Table 1. Prevention of the learning deficit in maze test of phenylketonuric mice with serotonin derivatives. All compounds were administered continuously from birth. Daily dose of serotonin derivatives (per gram of body weight) was melatonin, 10 γ; DL-5-hydroxytryptophan, 10 to 100 γ.

Treatment	No. of mice	Maze score
Controls (none)	105	7.5
DL-Phenylalanine + L-tyrosine (P + T)	91	6.3
P + T + melatonin	103	7.2
P + T + HTP	17	7.2

When 5-hydroxytryptophan was given most of the animals suffered from the severe diarrhea which resulted from the action of the excess serotonin on the intestines as previously described (*6*). Although a specific antiserotonin, such as 1-benzyl-2-methyl-5-methoxytryptamine (*6*) prevented the diarrhea, preliminary trials with it in infant mice led to rather high mortality at the dose tested. On the other hand, melatonin caused no detectable undesirable peripheral effects, and hence it was studied more intensively.

In the learning test involving shock avoidance, the differences between the various kinds of mice were less marked than in the maze test, but the observed differences were in the same direction. Thus, 41 normal controls gave an average score of 3.7. Fifty-eight phenylketonuric mice gave an average score of 4.3, and 64 phenylketonuric mice which had been treated with melatonin gave an average score of 3.6. The animals used in this test were some of those that had been used in the maze-learning test. All animals were not tested in the shock-avoidance because this technique had been introduced only in the last of the series of experiments.

Because the measurement of intelligence in laboratory animals is subject to much uncertainty both in method and interpretation, much care was taken to make sure that results were reproducible. The experiments cited in this paper were repeated three times (twice for the 5-hydroxytryptophan experiment) and the results were found to be reproducible. Also, the numbers of animals employed were large enough to reduce the possibility that the differences observed were due to chance alone.

It is important to note that the effective serotonin congeners were administered prophylactically from the time of birth continuously to adulthood. No attempt was made to cure the mental defect once it had been established. There is reason to believe (*1, 3*) that the serotonin deficiency must be prevented very early in life if the serious mental defect is to be avoided, and that it cannot be cured.

The results of these experiments indicated that the mental defect of phenylketonuria (insofar as it can be measured by the tests used) was largely the result of the deficiency of serotonin or its derivatives. This deficiency has been demonstrated to occur in the disease of both man and laboratory animals (*1, 3*). When it was corrected (as in the present experiments) the mental defect was prevented even though excesses of phenylalanine and of its derivatives such as phenylpyruvic acid still remained in the tissues (*1*). The results furthermore suggested that the deficiencies of catechol amines which also occur in the disease were not the cause of the mental failure. Which symptoms, if any, of phenylketonuria are to be attributed to the deficiency of catechol amines remains to be seen.

The results raise the question whether the effective agent in prevention of the mental change was serotonin itself or a derivative such as melatonin. 5-Hydroxytryptophan probably owed its effect to its conversion to serotonin (*7*) (even despite the partial inhibition of the decarboxylase), but whether the serotonin was then converted by the brain to melatonin before it was effective cannot be said. This latter possibility remains because, although preformed melatonin was quite effective, its conversion back to serotonin cannot be excluded. The results however, represent the first demonstration of an effect of melatonin on mental ability whether it be direct or indirect (*8*).

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20 February 1964