

highly sensitive bioassay. This would be important in evaluating the role of $1,25\text{-(OH)}_2\text{D}_3$ in both normal and disordered states of Ca metabolism. Until circulating concentrations of $1,25\text{-(OH)}_2\text{D}_3$ can be measured, the proposal that it is the only biologically active D vitamin in vivo seems premature.

R. A. CORRADINO

Department of Physical Biology,
New York State Veterinary College,
Cornell University, Ithaca 14850

References and Notes

1. R. A. Corradino and R. H. Wasserman, *Science* **172**, 731 (1971).
2. ———, *Biophys. Soc. Annu. Meet. Abstr.* **11**, 276 (1971).
3. A. N. Taylor and R. H. Wasserman, *Fed. Proc.* **28**, 1834 (1969).
4. R. A. Corradino, in preparation.
5. H. F. DeLuca, *Fed. Proc.* **28**, 1678 (1969).
6. M. R. Haussler, *ibid.* **31**, 693 (1972).
7. D. E. M. Lawson, D. R. Fraser, E. Kodicek, H. R. Morris, D. H. Williams, *Nature* **230**, 228 (1971).
8. Materials were obtained as follows. McCoy's 5A medium Grand Island Biological Co., Grand Island, N.Y.; vitamin D_3 , Mann Research Laboratories, New York, N.Y.; OHD_3 , a gift of Upjohn Co., Kalamazoo, Mich.; $1,25\text{-(OH)}_2\text{D}_3$, a gift of A. W. Norman, University of California, Riverside; $[4\text{-}^{14}\text{C}]$ -vitamin D_3 , Amersham/Searle, Arlington Heights, Ill.; Nuclear-Chicago, solubilizer, Amersham/Searle.
9. D. Schachter, E. B. Dowdle, H. Schenker, *Amer. J. Physiol.* **198**, 275 (1960).
10. A. Bar and S. Hurwitz, *Poultry Sci.* **48**, 1105 (1969).
11. A. N. Taylor and R. H. Wasserman, *J. Histochem. Cytochem.* **18**, 107 (1970).
12. Y. Tanaka, H. F. DeLuca, J. Omdahl, M. F. Holick, *Proc. Nat. Acad. Sci. U.S.A.* **68**, 1286 (1971).
13. M. R. Haussler and A. W. Norman, *Arch. Biochem. Biophys.* **118**, 145 (1967); S. J. Stohs and H. F. DeLuca, *Biochemistry* **6**, 3338 (1967); M. R. Haussler, J. F. Myrtle, A. W. Norman, *J. Biol. Chem.* **243**, 4055 (1968); M. R. Haussler and A. W. Norman, *Proc. Nat. Acad. Sci. U.S.A.* **62**, 155 (1969); R. J. Cousins, H. F. DeLuca, T. Suda, T. Chen, Y. Tanaka, *Biochemistry* **9**, 1453 (1970).
14. R. B. Hallick and H. F. DeLuca, *Proc. Nat. Acad. Sci. U.S.A.* **63**, 528 (1969).
15. A. W. Norman, *Biochem. Biophys. Res. Commun.* **23**, 335 (1966); S. J. Stohs, J. E. Zull, H. F. DeLuca, *Biochemistry* **6**, 1304 (1967).
16. R. R. MacGregor, J. W. Hamilton, D. B. Cohn, *Clin. Orthopaed. Relat. Res.* **78**, 83 (1971).
17. E. G. Bligh and W. J. Dyer, *Can. J. Biochem. Physiol.* **37**, 911 (1959).
18. C. A. Frolik and H. F. DeLuca, *Arch. Biochem. Biophys.* **147**, 143 (1971).
19. M. R. Haussler and H. Rasmussen, *J. Biol. Chem.* **247**, 2328 (1972).
20. R. A. Corradino, unpublished results.
21. M. R. Haussler, J. F. Myrtle, A. W. Norman, *J. Biol. Chem.* **243**, 4055 (1968); M. R. Haussler and A. W. Norman, *Proc. Nat. Acad. Sci. U.S.A.* **62**, 155 (1969); E. B. Olson and H. F. DeLuca, *Science* **165**, 405 (1969); R. B. Hallick and H. F. DeLuca, *J. Biol. Chem.* **247**, 91 (1972); H. E. Harrison and H. C. Harrison, *J. Clin. Invest.* **51**, 1919 (1972).
22. I. T. Boyle, L. Miravet, R. W. Gray, M. F. Holick, H. F. DeLuca, *Endocrinology* **90**, 605 (1972).
23. Supported by NIH research grants AM-15355 and AM-04652 and AEC contract AT(30-1)-4039. I thank S. Travis for able technical assistance, R. H. Wasserman for continuing interest and encouragement and for critical review of the manuscript, and A. N. Taylor for critical review of the manuscript.

5 June 1972; revised 5 October 1972

Phenothiazine Dosage Levels and Auditory Signal Detection in Schizophrenia

Rappaport, Silverman, Hopkins, and Hall (1) suggest that in an auditory signal-detection situation nonparanoid schizophrenics are hypersensitive (presumably in comparison with normals) at low and moderate stimulus intensities, but have an attenuated response at high stimulus intensities. They hypothesize that paranoid schizophrenics have a primary difficulty of an attentional nature such that they scan the environment rather than focus on relevant stimuli, and that phenothiazines have differential effects on the auditory signal-detection performance of paranoid and nonparanoid schizophrenics. The design of their experiment and the results presented warrant questioning of their conclusions.

Determinations of drug dosages in clinical populations often conflict with the requirements of experimental design. Since the assignment of drug dosage in the study by Rappaport *et al.* was not random, but was "determined by the ward physician, and was based on clinical impressions of the patient's condition" (1, p. 724), the patients who received different dosages also differed on whatever clinical variables the ward physician used to determine dosages. Such a confounding of clinical state with dosage makes it impossible to attribute any observed performance differences to dosage alone. That Rappaport *et al.* state "there were no significant relations between severity of mental pathology in either group of schizophrenics and d' " (1, p. 725), is not an assurance that the groups were clinically equivalent in other respects.

Rappaport *et al.* do not present evidence that phenothiazines have a statistically significant effect on signal-detection performance within either the paranoid or nonparanoid schizophrenic groups. They state (1, p. 725), "As was predicted, nonparanoid schizophrenics showed a decrease in d' with each increase of phenothiazine medication. In contrast, paranoid schizophrenics showed an increase in d' with each increase in phenothiazine medication." However, our calculations based on the data in their table 1 suggest that there were no statistically significant effects within either group related to phenothiazine dosage. In the absence of significant differences, the data would conventionally be taken as support for the lack of a drug effect on perform-

ance on their experimental task, rather than for the presence of such an effect. Rappaport *et al.* do state (1, p. 725) that "among normal subjects no consistent overall drug effect was observed." The mean drug effects exhibited by normals (table 1) appear to be of the same order of magnitude as those presented for the schizophrenics. None of the mean differences between drug conditions in any of the subject groups appears to be very large. Our calculations indicate that the largest of all of these differences is approximately equivalent to the change in mean performance, which would be expected as a result of a 1-db change in signal (2). Such a small effect is presumably of little practical significance.

There are data provided by Rappaport *et al.* that may be interpreted as indicating a significant drug effect. In the difficult signal-detection condition the nonmedicated normals differed significantly from the nonparanoids receiving the highest drug dosage, but not from the other nonparanoids. Since nonparanoids receiving the high drug dosage may have differed clinically from the nonparanoids receiving lesser amounts of phenothiazines, it would seem unwarranted to conclude that a drug effect is indicated.

It should be pointed out that, from the results presented by Rappaport *et al.*, it does not seem possible to tell whether any given significant difference in performance was due to a difference in sensitivity, or to a difference in the ability to focus attention, or to both. Thus, even if significant drug-related changes in performance on the auditory task had been demonstrated, additional evidence would be required to establish that such changes were due to attentional factors in paranoid subjects, but were due to variations in sensitivity in nonparanoid subjects. In their experiment the subject had only a single response button. A press on this button was taken to be a "yes" response, and a failure to press the button was taken to be a "no" response. If the subject in such a situation fails to respond as a result of a lapse of attention, this failure to respond will be treated as a "no" response. If the subject had been given both a "yes" button and a "no" button, then failures to respond could have been distinguished from intentional "no" responses. This proce-

dures could have given additional information about the ability of the subject to focus his attention. The way in which failures to respond are treated will generally have a considerable effect on computed values of the d' statistic.

Finally, Rappaport *et al.* indicate that "support was found . . . for the hypothesis that nonmedicated nonparanoid schizophrenic patients perform as efficiently as normal subjects under the difficult S/N [signal-to-noise] condition . . ." and, presumably on the basis of this finding, state in their abstract that "the primary deficit in information processing in nonparanoid schizophrenics may be related primarily to their hypersensitivity to sensory stimuli. . . ." Such a conclusion is consistent with the theory of one of the authors, Silverman (3), but does not seem to be borne out by their data. The fact that in the difficult signal-detection condition nonmedicated nonparanoid schizophrenics were found to be slightly (though not significantly) *hyposensitive* does not seem to provide very strong support for the interpretation that they are *hypersensitive* under such conditions.

DAVID S. EMMERICH
FREDRIC M. LEVINE

Department of Psychology,
State University of New York
at Stony Brook, Stony Brook 11790

References and Notes

1. M. Rappaport, J. Silverman, H. K. Hopkins, K. Hall, *Science* **174**, 723 (1971).
2. As is discussed by D. M. Green and J. A. Swets [Signal Detection Theory and Psychophysics (Wiley, New York, 1966)], estimates of the percentage of correct responses made can be obtained from d' values. A useful rule of thumb is that (except for percentages very close to chance or to 100) a 1-db change in signal level will lead to a 5 percent change in correct responses.
3. J. Silverman, *Psychosom. Med.* **29**, 225 (1967).

8 June 1972; revised 21 August 1972

Emmerich and Levine state that "the patients who received different dosages [of medication] also differed on whatever clinical variables the ward physician used to determine dosages." We would dispute this point, since each patient was interviewed and rated on the day of testing. Consequently, our assessment of clinical condition was considerably more current than the one on which the ward physician based his medication order. Furthermore, the rating scales that were used incorporated a wide range of clinical variables. The modified Brief Psychiatric Rating Scale (1) used contains 21 separate clinical items. From these a composite measure of overall mental disturbance was obtained. We found that at zero dosage and moderate drug dosages there were

no significant differences in this measure between paranoid and nonparanoid schizophrenics. At the heaviest dosage paranoid schizophrenics showed a greater overall mental disturbance score than did nonparanoids, yet their d' scores were closest together—quite the opposite of what might have been expected if severity of mental disturbance were the major factor affecting their signal detection performance.

They also comment that there were no direct statistically significant effects within either group related to phenothiazine dosage. It is true that we based part of our interpretations on indirect evidence of a differential effect of chlorpromazine on paranoid and nonparanoid schizophrenics—the fact that with increasing dosage nonparanoids showed a decrease in signal detection performance while paranoids showed an improvement in performance. This led to the finding that significant differences between the two groups of schizophrenics disappeared with increased medication, and this result could not be accounted for by differences in the clinical pathology displayed by each group. In fact, with the paranoids showing greater pathology than nonparanoids at the highest dosage level one would expect them to perform significantly worse. The fact that they did not makes it reasonable to suspect that medication enhances their ability to attend to and to detect auditory signals. Further, we have other evidence that, under four other signal-to-noise (S/N) conditions interspersed between the easy and difficult S/N conditions reported, the same results occurred consistently.

Emmerich and Levine's retrospective suggestion that both a "yes" and a "no" response button could have helped distinguish a true lapse of attention

from an intentional "no" response has merit. It would not have been compatible with our methodological design, however. We would not have been able to calculate other desired signal detection measures had we employed a two-button method. For example, we were interested in calculating each individual's normally occurring response propensity in order to determine whether schizophrenics underrespond or overrespond compared to normals. These results have been reported (2).

Finally we do not indicate in our report that the data directly reflect hypersensitivity of nonparanoid schizophrenics to auditory stimuli. In fact our hypothesis was quite conservative inasmuch as we stated (3) that we expected "nonparanoid schizophrenics would perform at least as well as normal subjects" where signals were difficult to detect. The hypersensitivity hypothesis has been put forward by Silverman (4) and was based upon averaged evoked potential data, which need not necessarily correlate highly with psychomotor response data such as we reported where in the latter situation attentional, cognitive, and motivational considerations can influence subject output. The hypersensitivity hypothesis was used primarily to predict a differential response to phenothiazine medication by nonparanoid and paranoid schizophrenics and this it appeared to do.

M. RAPPAPORT

Agnews State Hospital,
San Jose, California 95114

References and Notes

1. J. E. Overall and D. R. Gorham, *Psychol. Rep. Amer. Psychol. Ass.* **10**, 799 (1962).
2. M. Rappaport, H. K. Hopkins, K. Hall, *Arch. Gen. Psychiat.*, in press.
3. M. Rappaport, J. Silverman, H. K. Hopkins, K. Hall, *Science* **174**, 723 (1971).
4. J. Silverman, *Psychopharmacologia* **24**, 42 (1972).

1 December 1972

Fibrogenic Effect of Alcohol in Rat Liver: Role of Diet

Feinman and Lieber (1), in asserting a direct fibrogenic effect of alcohol on the livers of rats and baboons, make no reference to reports that show how diet can influence these results. Lillie *et al.* (2) reported that the cirrhosis induced in rats fed diets low in protein and choline was facilitated when the drinking water was substituted by a 20 percent ethanol solution. This type of alcohol-associated dietary cirrhosis was not only successfully prevented (3), but was also effectively reverted (4) by the inclusion of choline, methionine,

and casein, singly or in combination. Best *et al.* (5) showed that, under carefully controlled dietary conditions, rats consuming a 15 percent aqueous solution of alcohol in place of water developed histological evidence of hepatofibrosis. This occurred when the alcohol calories were superimposed on a diet that contained lipotropic factors only sufficient to prevent liver damage when the diet alone was fed. With the addition of alcohol calories (27 percent of total caloric intake), fatty and fibrotic livers developed.