commentary on sleep and schizophrenia

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Some years ago, it was suggested that the putative biochemical causes of schizophrenia could be tested by the extent to which they met Koch's criteria for the microbial etiology of disease. These criteria may also serve as standards for the degree to which abnormalities of the physiological pattern of nocturnal sleep are causally implicated in the schizophrenic syndrome. Applied to this condition (with appropriate modifications), Koch's postulates would require that all schizophrenics—and no nonschizophrenics—manifest a given sleep abnormality and that experimental production of this abnormality elicit the schizophrenic syndrome.

It is immediately obvious that none of the known disturbances in sleep pattern come close to meeting these stringent criteria. But because the human misery and the economic loss caused by schizophrenia are so great, and the clues to its etiology so few, we can hardly neglect any reasonable possibilities; we should therefore be quite grateful to discover a *necessary* cause of schizophrenia, even if it did not prove to be a sufficient cause as well. Furthermore, Koch's requirements do not seem entirely appropriate to the investigation of a syndrome which may not result from a unitary disease entity or even to the investigation of a unitary entity whose etiology is, to a far greater extent than is true in bacterial disease, multifactorial.

In sifting the accumulating (and sometimes contradictory) data on sleep patterns in schizophrenia, my emphases would be somewhat different from those of Wyatt, Termini, and Davis. Given the uncertain state of the field, such differences should occasion neither surprise nor concern. I should, for example, place greater weight on the abnormalities of stage 4 sleep (the deepest stage of sleep, characterized by high voltage slow waves in the EEG and occurring predominantly in the first 2–3 sleep cycles of the night). Added to the fact that low values for stage 4 are more consistently present than disturbances of REM sleep—occurring in about 50 percent of the schizophrenic patients in two recent samples (Caldwell and Domino, 1967, and Feinberg et al., 1969a)—recent findings (Feinberg et al., 1969b) indicate that chlorpromazine may have the capacity to stimulate stage 4 sleep without suppressing REM sleep. If confirmed by studies now in progress, this observation could provide a clue to the mechanism of action of the major tranquilizers. Of course, as Wyatt, Termini, and Davis rightly indicate, low values for stage 4 sleep are not unique to schizophrenia and occur in a variety of other conditions. Similar embarrassment exists with respect to data for REM sleep, however, since the few REM abnormalities observed in schizophrenia have also been found in other conditions. In view of the biological truism that a variety of mechanisms may lead to the same end-organ response, the fact that neither REM- nor stage-4-sleep abnormalities are specific to schizophrenia need not unduly discourage us at this point.

An interesting observation is that the low values for REM sleep found during periods of exacerbation in some schizophrenic patients are not followed by compensatory increases when the intensity of symptoms wanes. Such increases ("rebounds") are, however, said to occur in depressed patients upon recovery. A possible explanation for this difference is that we are dealing with "recovery" in the case of depression, but only with a "waning" of symptoms in schizophrenia; the persistence of subacute pathology in the latter condition may prevent the occurrence of elevated levels of REM sleep. An alternative explanation is based on the age differences in the two populations studied. While it may seem improbable that the (presumably) older group—the depressives—would show a greater tendency for REM compensation, some ongoing studies in our laboratory at least raise this possibility. One must also bear in mind that REM and nonREM sleep exist in dynamic interaction (Feinberg, 1967); thus, when total sleep time is varied, an increase in REM might come about through decreased intensity of nonREM processes, rather than through increased "pressure" for REM.

The relationship between REM sleep and

schizophrenia remains ambiguous, but what of the possible relationship between aberrant REM mechanisms and this disorder's behavioral symptoms, such as hallucinations? Here, again, no definite conclusions can be drawn. Far from being unitary phenomena, hallucinations vary greatly from patient to patient and presumably have different underlying mechanisms in different clinical conditions (Feinberg, 1970). As we emphasized elsewhere (Feinberg and Evarts, 1969), the evidence for an intrusion of REM processes into the waking state (with consequent hallucinatory experiences) is greatest for narcolepsy, sedative-hypnotic withdrawal states, and some cases of nocturnal delirium in chronic brain syndrome. The available data do not implicate abnormal REM mechanisms in the hallucinations of schizophrenia. I am also quite reluctant to accept the hypothesis that the behavioral disturbances induced by PCPA administration in the cat provide an animal model for schizophrenia. Since Wyatt, Termini, and Davis completed their review, Dement and his colleagues (Zitrin et al., 1970) have reported that the occurrence of hypersexuality, one of the most striking features of the PCPA syndrome as initially described, was not substantiated by controlled observation. This failure of replication led Zitrin et al. to reemphasize the need for methodological care in the study of animal behavior. Accordingly, we must await more rigorous data on such behavioral effects of PCPA administration as rage, hyperphagia, and "activity reminiscent of humans undergoing hallucinations" before attempting to determine the extent to which the PCPA syndrome resembles schizophrenia.

I am not competent to discuss the biochemical significance of serotonin abnormalities in schizophrenia. As Wyatt, and Termini, and Davis indicate, the hypothesis that serotonin abnormalities in the brain cause schizophrenia antedates the more recent hypothesis that serotonin "plays a fundamental role in REM (sleep) production." This latter hypothesis is not yet supported by compelling evidence. The demonstration that interference with the biosynthesis of a normally occurring brain constituent (serotonin) impairs REM sleep, with reversion to normal when biosynthesis is permitted, hardly constitutes proof that this constituent normally controls REM activity. Other arguments for a "priming" role of serotonin in REM sleep (Jouvet, 1969) also merit, at this point, a Scotch verdict.

In summary, it has not been established that abnormalities of the EEG sleep pattern are either necessary or sufficient for the occurrence of the schizophrenic syndrome or its major behavioral components. Nevertheless, studies of sleep in schizophrenia have produced a number of observations which merit further investigation.

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