Wheat Gluten as a Pathogenic Factor in Schizophrenia

Abstract. *Schizophrenics maintained on a cereal grain–free and milk-free diet and receiving optimal treatment with neuroleptics showed an interruption or reversal of their therapeutic progress during a period of "blind" wheat gluten challenge. The exacerbation of the disease process was not due to variations in neuroleptic doses. After termination of the gluten challenge, the course of improvement was reinstated. The observed effects seemed to be due to a primary schizophrenia-promoting effect of wheat gluten.*

The causes of schizophrenia are largely unknown, beyond the knowledge that genetic factors are important but probably act in conjunction with certain environmental factors (*1*). Dohan and co-workers (*2, 3*) have suggested that this condition may be genetically linked with celiac disease and that cereal grain proteins may likewise be pathogenic in schizophrenics. We present here evidence that supports this hypothesis.

Fourteen schizophrenics (*4*) were studied on a locked research ward where strict dietary controls were maintained and only a cereal grain–free, milk-free diet (*5*) was given. Three of the patients were diagnosed as paranoid, four as catatonic, and seven as hebephrenic schizophrenics. Their mean age was 19.57 years at the onset of illness and 25.43 years at admission to the study. Three were male and 11 female; nine were black and five white. The mean number of years of illness from onset was 5.86; mean number of previous hospitalizations, 3.93; mean years of education, 11.68; and mean IQ (Wechsler adult intelligence scale, administered at end of study), 78.57.

The study involved a longitudinal research design in which each patient served as his own control, which obviated the problem of heterogeneity in schizophrenia. Patients were observed drug-free for the first 2 weeks of the study and then for 12 weeks on neuroleptic medication (primarily haloperidol) individually titrated to maximize therapeutic effects and minimize side effects (*6*). During the period on medication, a "special drink" was also given daily in divided doses. It contained Kool-Aid powder, acacia, dextrose, water, and soy flour (30 g a day, as a placebo) during the first and the last 4 weeks (weeks 3 to 6 and 11 to 14 of the study). During the middle 4 weeks (weeks 7 to 10 of the study), the test substance, wheat gluten (30 to 45 g a day), was substituted for soy flour (*7*). The study thus involved a period of wheat gluten challenge along the course of treatment (*8*). Both patients and raters were "blind" to the nature of the drinks. Patients entered the program on a staggered schedule in order to control behavioral contagion and coincidental elements as determinants of the results. It was hypothesized that if wheat gluten were pathogenic to schizophrenics, the therapeutic course would be interrupted or reversed during the period of gluten challenge.

Three types of observations were made. Every 2 weeks, each patient was interviewed for 90 minutes and independently rated by a specially trained psychiatrist and a psychologist on 33 dimensions of a psychopathology rating schedule (*9*). Five measures of social avoidance behavior (*10*) and a measure of social participation in planned recreational activities (*11*) were obtained twice daily, 5 days a week, by the day and evening ward staff. One of us (M.M.S.) maintained detailed clinical notes but did not perform any ratings. The three types of observation were carried out independently and thus served to validate each other.

The data from all three forms of observation showed that wheat gluten had the effect of exacerbating the schizophrenic process and diminishing response to treatment. Typical results are illustrated in Fig. 1, which depicts ten of the characteristic features of schizophrenia plus an average of 33 dimensions of psychopathology. The therapeutic progress stopped or appreciably reversed during the period of gluten challenge and resumed its course after gluten was withdrawn and patients returned to soy flour drinks. A statistical analysis of all the objective data, comparing measurements at the end of the gluten period (week 10) with an average of those at the end of the pregluten and postgluten periods (weeks 6 and 14), showed that 30 of 39 measures (26 of 33 psychopathology parameters and 4 of 6 social avoidance and social participation ratings) had changed in the hypothesized direction with gluten challenge ($\chi^2 = 11.30$, $P < .001$). A parametric analysis of each dimension, using correlated t-tests, showed that the nontherapeutic changes with gluten were sufficiently large and prevalent to reach statistical significance (all P values are one-tailed) in the following measures: preoccupied behavior ($P < .01$); hostile or fearful social avoidance ($P < .02$); poor rapport ($P < .02$); poor impulse control ($P < .10$); tension state ($P < .02$); anxiety ($P < .05$); depression ($P < .10$); elation ($P < .10$); poor judgment and insight ($P < .05$); difficulty in abstract thinking ($P < .02$); stereotyped thinking ($P < .10$); bizarre and unusual thought content ($P < .10$); and clouded consciousness ($P < .10$). Only one parameter significantly changed in the opposite direction, namely passive or apathetic withdrawal ($P < .10$). A correlated t-test comparing

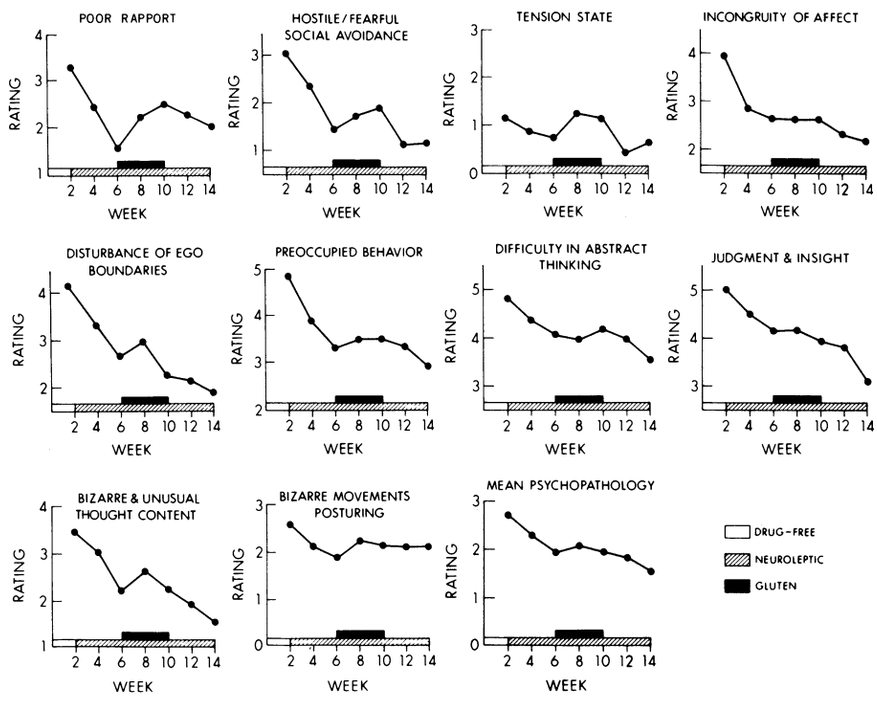

Fig. 1. Effect of wheat gluten on therapeutic course. Ten dimensions of psychopathology and means of all 33 dimensions of a psychopathology rating schedule are presented to show that a gluten challenge appreciably interrupted or reversed the treatment course. The data are averages for 14 subjects.

group changes across all 33 dimensions of the psychopathology rating schedule showed the hypothesized changes with gluten challenge to be significant at $P < .0001$ ($t = 4.51$; d.f. = 32). All these changes, it must be recognized, occurred against the expected course of improvement with neuroleptic treatment. Therefore, even the nontherapeutic changes during the gluten challenge which did not reach statistical significance were probably clinically significant.

The clinical notes suggested that schizophrenic exacerbation with gluten was particularly marked in the more seriously ill patients with a less favorable therapeutic outcome. Thus five patients, who at the end of the program were considered as therapeutic failures, were all judged to have regressed completely to their pretreatment levels of pathology during the gluten challenge. In contrast, of the five patients who recovered fully, one showed a moderate regression while others showed little or no regression with gluten challenge. The remaining four cases fell in between in terms of both therapeutic outcome and gluten effect. At the same time, the pharmacological side effects such as the extrapyramidal reactions were as marked and prevalent during the gluten period as before or after it, which suggests that clinical worsening in the gluten period was probably not due to impaired absorption or reduced pharmacological activity of the neuroleptic medication.

An analysis of the dosage data indicated that gluten period changes were not due to neuroleptic dosage variations. Average daily doses of haloperidol (*12*) in the weeks before, during, and after the gluten challenge were, respectively, 19.41, 23.18, and 23.99 mg. The average doses in weeks 6, 10, and 14 of the study, which had figured in the above analyses, were, respectively, 24.84, 24.19, and 23.71 mg. A correlated *t*-test showed that week 10 doses did not differ significantly from a combined average of doses in weeks 6 and 14.

We conclude that the study hypothesis was confirmed and that wheat gluten is pathogenic in schizophrenia. Insofar as this condition may be linked with celiac disease, it may be noted that glutamine- and proline-containing fractions of wheat gluten are considered as particularly toxic to celiacs (*13*) and that soy flour, which we used as placebo, although considerably less rich in these constituents than wheat gluten, has appreciable amounts of them (*14*). If another protein material with less glutamine and proline were used as a placebo, the gluten effects might be even more apparent than was the case in this study.

Our data do not unequivocally exclude the possibility that the gluten effect was due to inhibition of neuroleptic absorption or changes in neuroleptic metabolism or pharmacological action. Such information as we did have seemed to discount this possibility. The likelihood that wheat gluten is a true pathogenic factor is further suggested by reports on the psychiatric characteristics of celiac patients who are known to be intolerant to wheat gluten and its analogs (*15*). These patients have been characterized as being turned inward, difficult in temperament, negativistic, schizoid, paranoid, rigid and stereotyped, and repetitious in behavior. More importantly, it has been noted that these personality features tend to differentiate the celiacs from patients with other disorders associated with malabsorption and malnutrition, such as cystic fibrosis and ulcerative colitis. A recent ethological study has shown that celiacs resemble psychotic patients in showing increased "flight" and decreased "play" behavior (*16*); these behaviors diminished when gluten was eliminated from their diet. In susceptible individuals, therefore, wheat gluten per se seems able to produce schizoid changes in personality. This susceptibility may vary, however, as is well known from variations in the onset and severity of celiac disease and is probably reflected in differences among schizophrenics in terms of both gluten effects and prognosis. In the patients with poor prognosis, the pathological process may be more malignant or may begin earlier, causing more profound and persistent damage to the personality. How wheat gluten may contribute to the schizophrenic process is a matter of speculation at this stage, but it does seem to be an important exogenous factor which, when combined with genetic predisposition to schizophrenia, promotes the development of this condition.

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References and Notes

1. D. Rosenthal, in *American Handbook of Psychiatry*, S. Arieti, Ed. (Basic Books, New York, 1974), vol. 3, p. 588; S. S. Kety, *Am. J. Psychiatry* **131**, 957 (1974); S. Arieti, *Interpretation of Schizophrenia* (Basic Books, New York, 1974), pp. 441–451.
2. F. C. Dohan, *Acta Psychiatr. Scand.* **42**, 125 (1966); *Ment. Hyg.* **53**, 525 (1969); ———, J. C. Grasberger, F. M. Lowell, H. T. Johnston, Jr., A. W. Arbegast, *Br. J. Psychiatry* **115**, 595 (1969).
3. F. C. Dohan and J. C. Grasberger, *Am. J. Psychiatry* **130**, 685 (1973).
4. Diagnostic criteria are described in E. Slater and M. Roth, *Mayer-Gross Clinical Psychiatry* (Williams & Wilkins, Baltimore, 1969). An unequivocal diagnosis of schizophrenia agreed upon by the referring psychiatrists and M.M.S. was needed for inclusion in the study.
5. Wheat, rye, oats, barley, rice, corn, and other cereal grains in any form were excluded. Soy, buckwheat, potato, sweet potato, arrowroot, tapioca, and peanuts were used as substitutes. Milk was eliminated because some celiacs do not improve unless milk as well as cereals is omitted from the diet. Soy milk was used instead. A multivitamin capsule (Vigran, Squibb) was also given daily.
6. All but one patient received antipsychotic medication. One patient began to remit within the first 2 weeks and was maintained throughout without any neuroleptics. In five cases, chlorpromazine or thioridazine was given in addition to haloperidol in an effort to reduce extrapyramidal reactions while supplementing the antipsychotic effects. The medications were prescribed by M.M.S., who was nonblind and did not perform any ratings. Clinical contingencies permitting, he attempted to hold the dosage factor constant in studying the effects of the gluten challenge.
7. Wheat gluten (Pro-Vim) was obtained from General Mills Chemicals, Inc., Food Ingredients, Woodbridge, N.J., and soy flour (Old Stone Mill Brand) from Balanced Foods Inc., North Bergen, N.J. Soy flour was used as a placebo as the soybean is not a cereal grain; it provided a drink comparable in texture to the gluten drink, and the use of soy products as dietary substitutes in the management of celiac disease has not been found to be harmful.
8. The daily amounts of wheat gluten we used in the challenge period were larger than the 19 g a day given by Dohan and Grasberger (*3*). This was done to maximize any possible gluten effects in schizophrenics. Healthy volunteers have been shown to tolerate much larger amounts than these (100 to 150 g a day) taken orally for prolonged periods (8 weeks) [R. A. Levine, G. W. Briggs, R. S. Harding, L. B. Nolte, *N. Engl. J. Med.* **274**, 1109 (1966)].
9. This rating schedule has been discussed in M. M. Singh and S. R. Kay, *Psychopharmacologia* **43**, 103 (1975). It provides a wide-ranging assessment of schizophrenic dysfunctions in the following areas: cognitive-integrative processes and thought content; social and verbal interaction; affective responsiveness and mood; perceptual functions; psychomotor functions; sensorium and attention; ego boundaries and reality-testing; and willful control of behavior. Each of the 33 dimensions was rated on an interval scale ranging from 0 for absence to 6 for extreme pathology. The agreement between raters within one scale point averaged at 73 percent (standard deviation = 14.46 percent) for the various scales.
10. The five social avoidance behavior scales were as follows: (i) withdrawal scale (0 to 4), reflecting reduction in general participation and verbal interaction; (ii) nonverbal communication scale (0 to 5), measuring the degree of communication through nonverbal gestures, eye contact, body attitude, and communicational distance; (iii) overactive–social avoidance scale (0 to 4), measuring diminution in ward participation and social interaction due to overactivity and excitement; (iv) affective response scale (0 to 5), reflecting the degree and range of emotional responsiveness to life situations and interactions with others; and (v) active hostile or fearful avoidance scale (0 to 4), measuring reduced participation and social interaction due to hostility, suspiciousness, or fear. The mean agreement between raters, within one scale point, for the five scales was 80 percent (standard deviation = 3.61 percent).
11. The social participation rating scale measures physical and emotional involvement in planned recreational activities on a seven-point scale, from 0 for no participation to 6 for innovative participation. For further details, see M. M. Singh and S. R. Kay [*J. Nerv. Ment. Dis.* **160**, 258 (1975)].
12. For this analysis, 50 parts chlorpromazine or thioridazine was taken as equivalent to 1 part haloperidol.
13. O. D. Kowlessar, R. E. Warren, H. D. Bronstein, in *Progress in Gastroenterology*, G. B. J. Glass, Ed. (Grune & Stratton, New York, 1970), vol. 2, p. 409.
14. Soy protein differs from wheat gluten in having relatively smaller percentages of proline and glutamic acid and larger percentages of lysine, alanine, arginine, and aspartic acid [P. L. Altman and D. S. Dittmer, *Metabolism* (Federation of American Societies for Experimental Biology, Bethesda, Md., 1968), pp. 55 and 59].
15. D. G. Prugh, *Psychosom. Med.* **13**, 220 (1951); H. Käser, *Ann. Paediatr.* **197**, 320 (1961); H. Asperger, *ibid.*, p. 346; R. R. W. Townley and C. W. Anderson, *Ergeb. Inn. Med. Kinderheilkd.* **26**, 1 (1967); J. W. Paulley, *Am. J. Dig. Dis.* **4**, 352 (1959).
16. E. C. Grant, in *Non-Verbal Communication*, R. A. Hinde, Ed. (Cambridge Univ. Press, Cambridge, England, 1972), p. 349; J. M. Mackintosh, personal communication.
17. We thank A. Tesori and O. Brown for providing the special diets and drinks, F. C. Dohan for making available his research files, L. Barrera for performing ratings, B. Mason for preparing the manuscript, and the staff of the Clinical Psychopharmacology Unit for their usual good work.

18 September 1975; revised 25 November 1975