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Folic Acid, Pernicious Anemia and Pendulums

FOLIC acid, pteroyl glutamic acid (PGA), was heralded in 1946 as one of the "wonder drugs" of the year. A few mg. of the drug given orally was often found sufficient to cause a dramatic remission in typical cases of pernicious anemia. In such related conditions as sprue, pernicious anemia of pregnancy, "tropical" macrocytic anemia and the like, the drug seemed to have an even greater therapeutic effect than did liver extract. The two chief questions which followed in the wake of the initial successes were, (1) how did it work so effectively even when given by mouth, and (2) would it prevent the development of neurologic manifestations?

The physiologic mechanisms by which PGA is effective are still quite obscure, but there can be no doubt that the various studies which have followed its introduction have illuminated certain aspects of the pathogenetic mechanisms in pernicious anemia. Of greatest importance to the clinician however is whether or not PGA will in and of itself adequately protect the patient with pernicious anemia against the development of progressive involvement of the central nervous system, granted that other aspects of the deficiency state (bone-marrow, blood, gastrointestinal disturbances) are kept under control. During 1947 it became apparent that PGA often failed to prevent the development or progression of neurologic symptoms and that the signs of spinal cord involvement might develop explosively in patients taking the drug.

Towards the end of 1947 an editorial entitled, "A Warning Regarding The Use of Folic Acid," appeared in the New England Journal of Medicine which not only cast doubt on the ability of PGA to prevent neurologic involvement but even raised the possibility that the material might have a more or less directly harmful effect on central nervous system tissue. The editorial closed with the following statements: "... sufficient evidence has accumulated to justify a warning that synthetic pteroyl glutamic acid (folic acid) should not be used in the treatment of pernicious anemia. In view of the reports of folic acid induced neurologic lesions in sprue this restriction should probably also apply to other nutritional macrocytic anemias... Consequently the use of folic acid as a therapeutic agent appears to offer no new benefit but only risk to the patient." (Italics ours.) So striking has been the impact of this editorial that many physicians have discontinued completely the use of PGA in their practice.

The above editorial stemmed in part from the work of Ross and his collaborators, based on the treatment of 22 cases of pernicious anemia with folic acid. In 7 cases, neurologic relapses developed, and in 4 there was progression of combined system degeneration. Neurologic relapse occurred with considerable suddenness and progressed rapidly in several patients, especially in those receiving large (10 to 25 mg.) doses. This suggested the ingenious possibility that PGA, particularly when given in large doses, might contribute to dysfunction of the central nervous system by interfering with its metabolism of l(+) glutamic acid.
Some observations had already been made indicating that both the naturally occurring l(+) and d(-) glutamic acid are involved in nerve tissue metabolism (quoted by Ross). Glutamic acid is one of the constituents of the folic acid molecule, and Ross points out that its position in the molecule suggests that it may enter into competition with the naturally occurring l(+) glutamic acid and thus interfere with normal nerve metabolism. Ross implies that this interference might explain the greater frequency of neurologic relapse in patients receiving large doses of folic acid and the progression of neurologic disease in others.

From the available evidence, it appears probable that PGA cannot be relied upon as the sole agent in the treatment of pernicious anemia since its use may not only prevent injury to the central nervous system but may actually be attended with harmful effects to nerve tissue. Liver extract must therefore remain, at least for the present, the sheet anchor in the treatment of Addisonian pernicious anemia. This does not exclude the possibility that PGA may also be useful (1) as an adjuvant to liver extract therapy and (2) as a more specific substance than liver extract in certain conditions related to Addisonian pernicious anemia but not identical with it.

As regards the first possibility, Meyer, for example, holds to the opinion that small doses of PGA, combined with liver extract injections, induce better remissions, both hematologic and neurologic, than either substance alone. Ross et al. also state: 'These observations suggest that a combination of orally administered folic acid and parenterally injected liver extract may maintain a better hematologic status than either substance alone.' In my own experience, small doses of folic acid, e.g., 5 mg. per day, have proved useful in the maintenance therapy of pernicious anemia, in conjunction with injections of liver extract at two to four week intervals. This combination has seemed desirable on physiologic grounds since (1) an active therapeutic agent is given daily to supply a chronic deficiency state and (2) the patient receives at stated periods a deposit of a known and time-tested material, i.e., liver extract. Under this regimen, all the patients treated have stated that their feeling of vitality is considerably improved; in addition, their red cell counts have tended to be higher than on liver extract alone. No evidence of neurologic relapse has occurred. As an adjuvant to liver extract therapy, PGA gives one the impression as being of distinct value.

Has the drug a specific action in some cases which is not shared by liver extract? In 2 of our cases of neurologic pernicious anemia, the administration of PGA was followed by a distinct neurologic remission, after prolonged liver extract therapy had proved ineffective. In one of these cases, a reticulocytosis of 8.2 per cent developed at a red cell level of approximately 4.0 million per cu. mm., whereas previously, liver extract therapy had resulted in only a 2.4 per cent response at a level of 3.8 million. These findings seem to indicate that at least for these particular patients, folic acid was more nearly the required specific substance than was liver extract.

In non-Addisonian pernicious anemia (that is, in conditions such as sprue, the macrocytic or pernicious anemia of pregnancy, the so-called tropical macrocytic anemia, and the megaloblastic macrocytic anemia of infancy) the efficacy of liver
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extract, particularly of the refined type, leaves much to be desired. Lucy Wills,4 for example, writes that "the liver principle is actively curative in pernicious anemia but does not seem to be the missing factor in nutritional macrocytic anemia..." This "missing factor" was alluded to by Watson and Castle as the "Wills' factor" in an article dealing with the therapeutic inefficiency of parenteral liver extract in certain cases of atypical pernicious anemia. It is possible that the missing factor is PGA, especially since various workers have demonstrated that this material often results in a more marked therapeutic effect than does liver extract in cases of atypical pernicious anemia. Results in these cases suggest that the chemical acts specifically on certain enzyme systems that are not appreciably affected by liver extract. They also indicate that there may be different types of pernicious anemia brought about by varying mechanisms and even by different deficiencies.

The exact place of PGA in the armamentarium of therapy still remains to be clearly defined. That it is harmful to central nervous system tissue has not been conclusively demonstrated. Certainly the evidence at hand hardly justifies the categorical statements in the above mentioned editorial that the drug "should not be used in the treatment of pernicious anemia" and other nutritional macrocytic anemias and that its use appears to offer "only risk to the patient." These gloomy forebodings are hardly borne out by the results of many workers, particularly in the field of atypical pernicious anemia. Suarez,4 for example, states that in the treatment of over 100 cases of sprue, not only has he seen no evidence of harm neurologically but the patients do better than with liver extract. Spies and co-workers9 have recently shown that patients with nutritional macrocytic anemia can be maintained for as long as two years with folic acid as the sole medication without the development of subacute combined degeneration of the spinal cord.

Pendulums have a way of swinging too far in one or the other direction before they finally settle down. The "PGA" pendulum, it would seem, has now swung far over on the reactionary side, as opposed to the enthusiastic left swing of 1946. This is perhaps only natural, in view of the disappointing results attending its use as the sole medication in typical pernicious anemia. However, when the exact nature of the liver extract factor has been defined, and when we know more about the specific enzyme systems concerned in the development of pernicious anemia, the pendulum should settle down; and PGA will then find its rightful place in the treatment of certain aspects of the pernicious anemia "family" of deficiency diseases.

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REFERENCES

3. Personal observations.
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ERRATA

An error was made in Dr. F. H. L. Taylor’s review of Dr. Owren’s book, “The Coagulation of the Blood,” in the February issue of Blood (3: 229, 1948). The formulae as printed were incomplete and should have read:

1. Factor V + Prothrombin (?) \( \overset{\text{Cytokinase Ca}^{++}}{\longrightarrow} \text{Prothrombinase} \)
2. Prothrombin + Prothrombinase \( \overset{\text{Ca}^{++}}{\longrightarrow} \text{Thrombin} \)
3. Fibrinogen + Thrombin \( \longrightarrow \) Fibrin

The editorial footnote in “Pernicious Anemia from Addison to Folic Acid,” by Dr. Russell L. Haden, in the January Blood (3: 24, 1948) should have read: “Wilkinson and Israels, Waldenström and others report that free hydrochloric acid occurs in approximately 1 case of 100.” The term “achlorhydria” was used in error.
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