When a phenomenon can be partly explained by several hypotheses, it is rare for any one of the hypotheses to be exclusively correct. The problems are usually resolved by a synthesis which reveals that each hypothesis is correct but is describing only a part of the truth. The investigators, to use a classic analogy, have been blind men describing the various parts of an elephant.

I believe that we are close to the resolution of the problem of the schizophrenic elephant. For approximately 20 years the mainstream concept of schizophrenia has been that it is related to an excess of dopamine formation or activity in critical areas of the brain. The key piece of evidence is that almost all effective antischizophrenic drugs are dopamine receptor blockers (Carlsson 1978). Other supportive evidence has been hard to obtain, but it now seems that cerebral dopamine receptors may be supersensitive in schizophrenics.

The endorphins and enkephalins, a group of substances produced by the brain and other tissues which have morphine-like actions, aroused great interest when they were found to produce catatonia-like states in animals (Guillemin 1977). Naloxone, a drug that can antagonize some of the effects of opiate drugs, endorphins, and related compounds, was reported to control hallucinations in schizophrenics. Although this finding has been disputed (Volavka et al. 1977), interest in the possibility that an abnormal endorphin or an excess amount of a normal one may cause schizophrenia remains high.

My own interest relates to the observation that the antischizophrenic drugs, which are dopamine blockers, also all enhance prolactin secretion. We have found that a second messenger of prolactin action is probably prostaglandin (PG) E1. There are two natural series of PGs, one with a single double bond in the side chains and derived from dihomo-γ-linolenic acid (DGLA) and the other with two double bonds and derived from arachidonic acid (AA). AA and DGLA are both found almost entirely as esters, and the rate-limiting step in PG synthesis seems to be mobilization of free AA and DGLA. We have found that prolactin seems to have a highly selective effect in mobilizing DGLA and therefore stimulates the formation of 1 series but not 2 series PGs (Horrobin et al. 1978). There is direct evidence of a PGE1 deficiency in platelets from schizophrenics (Abdulla and Hamadah 1975), and there are many indirect pieces of evidence that point to a PG deficiency in the disease (Horrobin 1977; Horrobin et al. 1978). It is therefore possible that the prolactin-secreting drugs tend to enhance PGE1 synthesis and overcome an endogenous block.

All three concepts—dopamine, endorphin and prostaglandin—are attractive but apparently bear little relation to one another. Where does the elephant come in? We have recently found in muscle that β-endorphin has an effect diametrically opposite to that of prolactin. At concentrations close to those found in vivo it blocks the mobilization of DGLA and formation of PGE1 while having little effect on AA and 2 series PGs (Manku et al. 1978). Thus an abnormal endorphin or an excess of an endorphin could account for the PGE1 deficiency and the possible therapeutic effect of prolactin. It could also explain the dopamine supersensitivity since such supersensitivity is a consequence of chronic opiate treatment (Lal 1975).

Therapy should therefore be directed either to removing the endorphin (which is perhaps how
dialysis works) or to overcoming its action, which is presumably how the classic neuroleptics with their dopamine-blocking and prolactin-stimulating actions operate. We have recently been searching for agents that could have the desired prolactin-like effect in stimulating synthesis of 1 series PGs and to our surprise found that penicillin had the required properties. A clinical trial in chronic schizophrenics indicated that penicillin had a therapeutic effect suggesting that this regulation of PGE1 synthesis may indeed be the key (Chouinard, Annable, and Horrobin 1978).

Apart from proposing a unifying concept of the disease, the endorphin effect on PG synthesis suggests new ways of screening for antischizophrenic drug activity. It also promises to lead to exciting advances in the field of lithium therapy. Lithium and β-endorphin have apparently identical effects on PG biosynthesis, raising the possibility that mania might be related to an endorphin lack (Horrobin 1978; Manku et al. 1978).

**Summary**

The author presents a hypothesis relating prostaglandin E1 (PGE1) deficiency to schizophrenia. The hypothesis is consistent with the importance of prolactin-stimulating properties in currently used antipsychotic drugs, the effect of prolactin on PGE1 synthesis, and the deficiency of PGE1 regulation in schizophrenic platelets. The author relates the PGE1 deficiency hypothesis to theories implicating dopamine and endorphins in the etiology of schizophrenia. A clinical trial in chronic schizophrenics has suggested the possible therapeutic efficacy of penicillin, a drug without dopamine-blocking actions which can stimulate PGE1 synthesis directly.

**References**


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