Maternal Schizophrenia And Sex of Offspring

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Introduction

Three years ago Shearer, Davidson and Finch[1] made the startling discovery that women who became schizophrenic within one month of conception gave birth to female infants only. This alteration of secondary sex ratio was statistically significant at the .001 level.

In a later study, Taylor[2] supported Shearer's findings; his data, too, were significant at the .001 level. In addition to confirming Shearer's results, Taylor reported findings which seemed to indicate that post-partum schizophrenia occurred more often after the birth of a male than a female infant. Taylor's suggestion that this was the result of a hormonal "release phenomenon" was refuted by Melges[3] who found no predominance of male infants born to women who d e v e l o p e d post-partum schizophrenia. While no one has yet challenged Taylor's hypothesis linking hormonal levels with the birth of exclusively female infants to women who conceived within one month of becoming schizophrenic, an alternative rationale based on immunological mechanisms can be proposed.

Negatively Charged Cells Protect Fetus

The question of why fetal tissue is not rejected by the mother's body has not yet been definitively answered. One possible reason, according to Currie and Bagshawe[4] is that placental fibrinoid "can effectively mask major histocompatibility differences between foetal and maternal tissues." Fibrinoid tissue has a high net negative charge, and Currie and Bagshawe hypothesized that "pericellular sialomucins (fibrinoid) present an important electrochemical barrier to immunologically competent cells . . . in normal mammalian pregnancy ..." They pointed out that "human lymphocytes have a high negative surface charge" and are thought to play a decisive role in the detection and rejection of antigenic cells. Electrostatic negative charges cause cells to repel each other and during the rejection process some contact between cells must take place.

Trophoblast cells come into contact with the maternal tissue, and therefore would seem to be the cells most vulnerable to attack by lymphocytes in an immune response. But each trophoblast cell has a coating of fibrinoid which, because of its negative charge, masks the trophoblast from maternal antigens. Glemser[5] has

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called attention to the fact that when this fibrinoid layer was removed (by treatment with neuraminidase), maternal lymphocytes destroyed the trophoblasts. Currie and Bag-shawe noted that the ionized carboxyl groups on the N-acetyl neuraminic acid (a sialic acid), was decisively related to the net negative surface charge of cells.

Immune Reactions and Schizophrenia

Bogoch[6] found that "clinical improvement in psychotic patients is accompanied by an increase in the protein-bound neuraminic acid in cerebrospinal fluid." Hexosamines (pre-cursors of neuraminic acid) were found to increase in concentration in cerebrospinal fluid glycoproteins when clinical improvement occurred. Bogoch postulated that in schizophrenia, "a disturbance in these substances would be reflected in a disturbance of membrane transmission, barrier and defense function in the nervous system." Burch[7] also believes that changes in membrane permeability could result from immune reactions.

A number of authors (Kamp,[7] Fessel and Hirata-Hibi,[8] and Erban[9]) have found structural abnormalities and quantitative increases in lymphocytes and reticulum cells in schizophrenics. These findings would seem to strengthen the hypothesis that the immune system is involved in schizophrenia. Heath and Krupp[10] believe it is possible that acute schizophrenics, who are actively combating the disease, have greater quantities of circulating antibodies than do chronic schizophrenics. It may be that in women who are developing antibodies in response to the schizophrenic process, the increase in the number of circulating antibodies results in a change in the normal immunological relationship between mother and fetus or embryo. Burch[1] who found the latency period for schizophrenia to be longer in females, interpreted this "to mean that the . . . antibody defense mechanism in females may be superior to that in males."

Histocompatibility and Sex of Fetus

If the above principles are extended to apply to the changes in secondary sex ratio of infants conceived by women in whom a schizophrenic disease process is developing, it is possible that the heightened immune reactions, which may be characteristic of early acute schizophrenia, might lead to differential reactivity in male and female embryos. Studies in Finland by Renkonen[12] have shown that there may be an incompatibility between the male fetus and the maternal host. The female concep-tus, being histologically more similar to the mother, might be capable of adequately defending itself against the increase of circulating antibody.

The male fetus, on the other hand, being histologically less similar to the mother, might be more liable to attack by the maternal antigenic forces mobilized by the schizophrenia. This could account for the spontaneous abortion of male fetuses in the very early stages of pregnancy when the schizophrenia, and presumably the immune responses, are at their height. Such a process might also explain Taylor's finding of a high incidence of deformity in live male infants born of mothers in whom schizophrenia developed after the first month of pregnancy.

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Positive Surface Charge Provokes Antigenic Reactions

Currie[13] has shown that "there is no intrinsic deficit of histocompatibility antigens" on trophoblast cells, since "their antigenicity may be unmasked by treatment with neuraminidase." Weiss[14] found that treatment with neuraminidase reduced the net negativity of cells and made them more easily deformable. Drzeniek[21] points out the polyanions are potent inhibitors of neuraminidase at extremely low concentrations because of their anionic character. Wilkins and Bliznakov[22] found that by changing the normal negative surface charge of sheep red blood cells to positive, they induced up to a four-fold increase of antibody titers in mice injected with the altered blood cells.

If the fibrinoid electrochemical defense system of the male fetal trophoblast tissue is rendered relatively ineffective in combating the maternal antigenic forces, the antibodies of the two may interact, causing deformity in the fetus, but provoking an increase in, and thereby a strengthening of, the immunological defenses of the mother against the schizophrenic process.

Severity of Symptoms Related to Fetal Sex

In a separate study, Taylor and Levine[15] were reported to have "correctly guessed the sex of all 17 children" in a study in which criteria were based on worsening schizophrenic symptoms in women pregnant with female infants and improving symptoms in women who were to bear males. Taylor and Levine attributed this difference in symptomatology to the suppression of maternal schizophrenic symptoms by the male fetal supply of androgens. The actual mechanism may be more complex.

Ceruloplasmin Levels Elevated in Schizophrenia

Wolf, Enlander, Dalziel and Swanson[16] found that the blood plasma of women who had been taking birth control pills has a greenish cast. This is attributed to the elevated level of copper-containing Ceruloplasmin.

As Martens, Vallbo and Melander[17] have pointed out, a rise in Ceruloplasmin levels has been demonstrated in both pregnancy and acute schizophrenia. Ceruloplasmin levels are normal in chronic schizophrenics, but over 60% of acute schizophrenics have been found to show an elevation of Ceruloplasmin, with levels rising to 200% above normal.

The coincidence of conception of exclusively female fetuses when maternal Ceruloplasmin levels are elevated is striking. Hoffer[18] has pointed out that "pregnancy sometimes cures schizophrenia and that puer-pural psychosis usually occurs within four weeks after parturition, a period after which Ceruloplasmin levels quickly become normal."

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Differential Sex Ratio May Be Related to Ceruloplasmin Level and Antibody Production

It may be possible to weave these threads of evidence into the hypothesis that the altered sex ratios may result not from differential hormonal levels but from the levels of Ceruloplasmin which are affected both by the onset of the schizophrenic process and by the sex of the fetus. In this case, the androgen protection provided to the mother by the male fetus, with resulting lessening of schizophrenic symptoms, would be the initiating, but not the sole, factor. The more immediate agent would be the elevated Ceruloplasmin levels produced by the more antigenic male fetal tissue. The early abortion of the male con-ceptus may be the result of activation of immunological mechanisms, while the female fetus, being more similar histologically, is preserved.

Heath,[19] among others, considers schizophrenia to be "an immunologic disorder, in which the elevation of serum globulin levels with onset of symptoms in some patients . . . suggests activation of immuno-logic defense mechanisms." Taraxein, Heath's[20] schizophrenogenic substance, was discovered "almost accidentally"[20] during the fractionation of Ceruloplasmin from the serum of schizophrenic patients, and Heath speculated "that taraxein may even represent a faulty Ceruloplasmin molecule."

Unlike taraxein, Ceruloplasmin is thought not to be a toxic, symptom-producing element, but rather an attempt on the part of the immunological defense system to combat the schizophrenic process. With this in mind, Martens, Vallbo and Me-lander[17] administered Ceruloplasmin to acute schizophrenics and obtained "favorable changes" in 19 of 22 cases, including nine complete remissions. This evidence lends further support to the hypothesis that Ceruloplasmin may be the common agent intertwining the fates of mother and fetus, reciprocally influencing the severity of the schizophrenic symptoms and the alteration of the secondary sex ratio.

Summary

Placental fibrinoid (which acts as a barrier between maternal tissue and fetal tro-phoblast cells) has cell-surface sialomuco-proteins which possess a high negative surface charge and act as an electrochemical repellant to the approach of negatively charged maternal lymphoid cells, thus inhibiting antigen detection. It is postulated that this relationship is disturbed via the change in circulating antibody levels during early acute schizophrenia, and that the alteration of secondary sex ratios of infants conceived during this period may be due to differential histocompatibility of fetal tissues. Ceruloplasmin levels may be in-volved in this immunologic reaction.

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