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Point of View

Can Autoimmune Mechanisms Account for the Genetic Predisposition to Schizophrenia?

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Applications of molecular genetic techniques to schizophrenia have shown great initial promise but have then proved disappointing. In order to maximise chances of elucidating the genetic mechanism underlying schizophrenia, diverse strategies and diverse perspectives must be adopted. Most studies begin with the premise that, although schizophrenia may be a heterogeneous collection of diseases, some subtypes will be primarily single-gene disorders. We are concerned that this single-gene hypothesis may be incorrect. Schizophrenia research may benefit from application of knowledge from other disciplines and from other diseases which, in terms of epidemiology and apparent genetic mechanisms, bear some resemblance to schizophrenia.

During the last two decades psychodynamic theories have given way to a biological perspective on schizophrenia. The psychoanalytic view was not confined to diseases which are now regarded as mental illnesses. Lidz & Whitehorn (1949) described a group of patients in the following terms:

> "As a group . . . they had in childhood felt less wanted than a sibling, but eventually had become the successful rival for parental affection by becoming the good child who gains affection and attention by constant giving and doing for others and had persisted in this devoted, yet dependent, pattern after the rival siblings had become emancipated. . . . To have their offerings rebuffed, or to become unneeded, appears to reawaken the childhood insecurities, and they become resentful and depressed."

The patients referred to had Graves' disease, which is characterised by overactivity of the thyroid gland. In Graves' disease (autoimmune thyrotoxicosis), lymphocytes produce highly specific autoantibodies which bind to thyrotrophin receptors on thyroid cells and stimulate them to overactivity (Adams *et al*, 1987) – the first known example of antibodies mimicking the action of a hormone. Some patients develop clones of lymphocytes which have slightly different specificities, reacting with tissue in the eye to produce exophthalmos or in the shins to produce pre-tibial myxoedema. Here is a disease now known to be autoimmune, but once considered by some to be caused by personal interactions within the family, or by excessive amounts of a chemical transmitter (TSH) or its receptor, or by an altered form of the transmitter or the receptor. The following features are characteristic of Graves' disease: symptoms vary in different patients; patients are not born with Graves' disease (except for the transient neonatal form caused by transplacental transfer of the pathogenic autoantibodies) but show a variable age of onset; the concordance rate in monozygotic (MZ) twins is approximately 50% compared with 10% in dizygotic (DZ) twins (Bartels, 1941); there is some evidence for a role of infectious triggers.

A similar set of features is seen in insulin-dependent diabetes mellitus (IDDM), myasthenis gravis, pernicious anaemia, multiple sclerosis (MS), and many other diseases which are known or suspected to be autoimmune. Autoimmune diseases are known to affect virtually every organ in the body, establishing autoimmunity as a common mechanism of disease causation which must be seriously considered for any disease of unknown aetiology.

The possibility of immune processes underlying some forms of schizophrenia has been considered for a long time, but efforts to test this idea directly have proved disappointing (Knight *et al*, 1987). The field has been clouded by some controversial and non-confirmable work (Heath *et al*, 1989; Knight *et al*, 1990). Nevertheless, there are still many diverse observations hinting at an autoimmune basis, including: intrathecal synthesis of immunoglobulins in some patients with schizophrenia (Kirch *et al*, 1985), and reports of elevated levels of soluble interleukin-2 receptors in a proportion of schizophrenic patients (Rapaport *et al*, 1989; Ganguli & Rabin, 1989), a phenomenon observed in diverse presumed autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus (SLE), and MS.

Features of schizophrenia compatible with an autoimmune basis

In assessing the likelihood of autoimmune processes being involved in some forms of the illnesses encompassed by the term 'schizophrenia', we need

to consider the various known facts about schizophrenia and see whether they are compatible with an autoimmune mechanism.

Incomplete penetrance

Does the approximately 50% discordance of schizophrenia in MZ twins indicate that one-half of cases are genetic and half are sporadic phenocopies? Perhaps the most convincing evidence against this comes from the study initiated by Fischer in Denmark in 1971 and concluded by Gottesman & Bertelsen (1989). The strategy was to examine the offspring of twin pairs either concordant or discordant for schizophrenia, and to determine the morbid risk transferred by each class of parent to the offspring. The results are clear. The age-corrected morbid risk was the same whether the parent was an affected or non-affected member of an MZ pair in which one or both had schizophrenia. However, in the DZ pairs the high risk was transferred only by the affected twins and not by the unaffected co-twins. This indicates that the 50% discordance in MZ twins is due to incomplete penetrance of the disorder, with transmission of unexpressed genes to offspring in whom they may or may not be expressed.

An approximately 40–60% discordance in MZ twins has also been observed in diverse autoimmune diseases including: Graves' disease (Bartels, 1941), IDDM (Barnett *et al*, 1981), and SLE (Block *et al*, 1975). In a study of MZ twins with 'early-onset' diabetes (presumably IDDM), Pyke & Nelson (1976) found that 6 of 33 disease-concordant pairs had other diabetic first-degree relatives, and 4 of 31 discordant pairs had other affected first-degree relatives; in a study of MZ twins with psoriasis there was no difference in risk to first-degree relatives of concordant twins as compared with risk in relatives of discordant twins (Brandrup, 1984). These findings are closely analogous to those in schizophrenia mentioned above (Gottesman & Bertelsen, 1989).

It is not difficult to see why incomplete penetrance should be so characteristic of autoimmune diseases when one considers the chain of events needed to generate the particular clones of cells required for a specific autoimmune reaction (Adams *et al*, 1987). Consider the following sequence: an infectious (or other antigen-releasing or antigen-modifying) process triggers a specific immune response, leading to a series of random somatic mutations and somatic combinatorial events, which are the mechanisms for generating diversity in every immune response (Hood *et al*, 1985). In those who are genetically susceptible (and, therefore, have a germline immune response repertoire which requires fewer mutations or recombinations to create a self-reactive clone), this antigen-driven random chain of events can ultimately lead to production of pathogenic clones specific for one or more self-antigens. Because such a chain is dependent on several random events, there is uncertainty whether the end-point is ever reached, how long it will take to be reached, and what form the end-point will take in terms of pathology. In pureline (genetically identical) NZB mice, which virtually all develop autoimmune haemolytic anaemia, we have observed the age of onset to be widely variable even in large groups housed together in the same cage so as to provide uniform exposure to environmental factors.

In MZ twins who become concordant for autoimmune diseases, there is often a lengthy discordant period between the time of onset for the first twin and the time of onset for the second twin. For example, in a series of MZ twins concordant for diabetes mellitus, the discordant period was four years or greater in 28% of cases and greater than 10 years in 10% (Barnett *et al*, 1981). This may be compared with Fischer's series of MZ twins concordant for schizophrenia, where discordant periods ranged from 1–29 years, the discordant period being four years or greater in 5 of 10 pairs and greater than 10 years in 2 of the 10 pairs. The effect which random events have on outcome of an autoimmune disease process in individuals with identical germline immune response repertoires is graphically demonstrated (provided the observation is not due to a chance coincidence) in a report of MZ twins both developing thyroid autoimmunity, but with opposite symptoms. One developed hyperthyroidism caused by autoantibodies stimulating the thyrotrophin receptor, and the other developed hypothyroidism caused by autoantibodies blocking the thyrotrophin receptor (Ilicki *et al*, 1990).

The season-of-birth effect

Although small, this effect seems robust, having been studied in tens of thousands of subjects. Most of the proposed explanations involve seasonal infection of the developing foetus. It is possible that such infections could lead to long-term alterations in the developing immune response repertoire through the mechanism of immune tolerance. There are several precedents for this. For instance, lymphocytic choriomeningitis virus infection in developing mice leads to permanently impaired immunity to that virus (Buchmeier *et al*, 1980). This also seems to be the explanation for subacute sclerosing panencephalitis in man, involving persistence of the measles virus in people unable to mount an effective immune response

against it (Himmelhoch *et al*, 1970). There is a season-of-birth effect in Japanese encephalitis. People born at certain times of the year are more susceptible to this virus in later life, but the differential effect is only seen in those born in severe encephalitis epidemic years (Miura *et al*, 1977). An excess of winter birth dates has also been reported in diabetes mellitus (Jongbloet *et al*, 1988), the insulin-dependent form of which is believed to depend on autoimmune processes triggered by diverse viral infections.

Triggering by infection

Of particular interest is evidence suggesting that certain infectious processes may trigger schizophrenia, or increase susceptibility to it at a later date. Mednick's studies (Mednick *et al*, 1988) suggest that intrauterine exposure to certain strains of influenza A virus may increase risk of development of schizophrenia in adult life. An attempt has been made to identify specific binding sites that influenza viruses might use in the brain (Laing *et al*, 1989). The rationale was that neurotropic strains of influenza virus might bind specifically to some kind of brain receptor and interfere with its function. Brain proteins were separated electrophoretically, transferred to a membrane (Western blotting), the membrane was probed with live neurotropic virus, then a specific rabbit antibody against the virus was used to detect bound virus immunochemically. A negative control experiment containing no virus revealed that the antivirus antibody itself bound directly to a 37 kilodalton brain-specific protein. So, the rabbits, immunised with highly purified influenza A virus, had produced an autoantibody against a brain protein. In order to test whether this was a common property of rabbit antisera to influenza viruses, 23 different antisera were tested. The only ones that gave a positive result were those raised against A/NWS and A/WSN neurotropic viruses, A/New Jersey '76 (the notorious Fort Dix swine influenza), and A/Bellamy, which also bears an antigenic relationship to the swine influenza viruses of the 1920s era.

These data suggest that some strains of influenza have the ability to initiate specific autoimmune responses against brain-specific antigens. Perhaps the best example of an infection triggering an autoimmune process against the brain is Sydenham's chorea, which develops in approximately 15% of cases of acute rheumatic fever. Acute rheumatic fever is a late sequel in about 3% of those infected with group A streptococci, can involve joints, heart, brain, and skin, and is attributed to immune responses against streptococcal antigens which are cross-reactive with host antigens, although the precise mechanism has not been delineated (Bisno, 1985). Husby *et al* (1976) found autoantibodies against the caudate nucleus and subthalamic nuclei in patients with Sydenham's chorea, and it seems likely that these may have pathogenic significance.

Triggering by drugs

There are numerous examples of autoimmune diseases which are triggered by drugs which bind to cell surfaces, presumably through a hapten-carrier mechanism. For example, methyldopa, levodopa, and nomifensine can all have as an adverse reaction initiation of haemolytic anaemia, hydralazine can trigger SLE, and D-penicillamine can trigger myasthenia gravis (McQueen, 1987). A statistical association has been reported between specific types of drug abuse and a clinical diagnosis of schizophrenia, but whether there is a causal relationship or whether schizophrenic patients have a greater propensity to abuse certain types of drug as a result of their illness is not clear (Turner & Tsuang, 1990).

Triggering by physical injury

A two- to threefold increased risk of 'schizophrenia-like psychosis' was reported in a study of 15 000 brain-injured war veterans (Davison, 1987). Furthermore, Wilcox & Nasrallah (1986) provided data which suggested an association between childhood brain injury and catatonia. Is it valid to exclude psychosis initiated or maintained by a known organic factor from the diagnosis of schizophrenia? Physical injury is a well known trigger of some autoimmune diseases. Perhaps the most spectacular example is sympathetic ophthalmia. In this condition physical damage to one eye can lead months or years later to an autoimmune attack on the other eye (Duke-Elder & Perkins, 1966). Presumably, release of antigen from damaged tissue provides a stimulus to the immune system which normally it would not encounter.

Dissociation of schizophrenia and rheumatoid arthritis

A tantalising finding, which remains unexplained, is the virtual mutual exclusion between schizophrenia and rheumatoid arthritis, which is a presumed autoimmune disease (Mellsop *et al*, 1974; Osterberg, 1978). It has been suggested that a similar dissociation exists between schizophrenia and another autoimmune disease, IDDM (Finney, 1989). A possible

explanation for these observations is that a gene (or genes) which increases the risk of one of these diseases decreases the risk of the other. There are precedents for such a mechanism. For example, the histocompatibility antigen HLA-DR2 causes a 130-fold increased risk of narcolepsy, a 2.7-fold increased risk of MS, and a 13-fold increased risk of Goodpasture's disease (Tiwari & Terasaki, 1985). However, this same antigen confers a 10-fold decreased risk of IDDM, and a 25-fold decreased risk of pemphigus vulgaris in the Japanese population (Tiwari & Terasaki, 1985). Clearly, the chances of a person with narcolepsy developing IDDM must be greatly reduced.

Correlation of age of onset within families

Crow & Done (1986) analysed age-of-onset and time-of-onset data derived from five major studies of families in which there were two or more siblings affected with schizophrenia, in order to test their 'contagion' hypothesis. Their analyses revealed that in every study (a) age of onset showed a strong correlation between siblings, and (b) the mean age of onset was earlier in the younger than in the older sibling. Initially, they interpreted these findings as being compatible with the contagion hypothesis, that is, that the disease is transmitted from one sibling to the other, or that both are subjected to the same pathogen at the same time. Further analysis led Crow & Done to ascribe these remarkably consistent findings to 'ascertainment bias' – selective under-inclusion of illnesses of later age of onset in younger siblings – but we are unconvinced by their reasoning. They concluded that "contagion could account for the findings only if the postulated infectious agent were latent for a period approximately equal to the mean age difference between siblings". An auto-immune mechanism would, of course, account for such a latent period between infection and symptoms.

We have analysed age-of-onset data from several studies of autoimmune disease. Analysis of Bartels' (1941) study of sibling pairs with Graves' disease revealed that both the age-of-onset correlation between siblings and the age-of-onset shift in younger siblings apply in this disease also (Fig. 1). Spinner *et al* (1968) found a striking age-of-onset correlation in sibling pairs with idiopathic (autoimmune) Addison's disease and hypoparathyroidism, and our reanalysis of Kaplan's (1984) data for sibling pairs with SLE shows a similar age-of-onset correlation (Fig. 1).

Haldane (1941) pointed out that a genetically determined disease would be expected to manifest

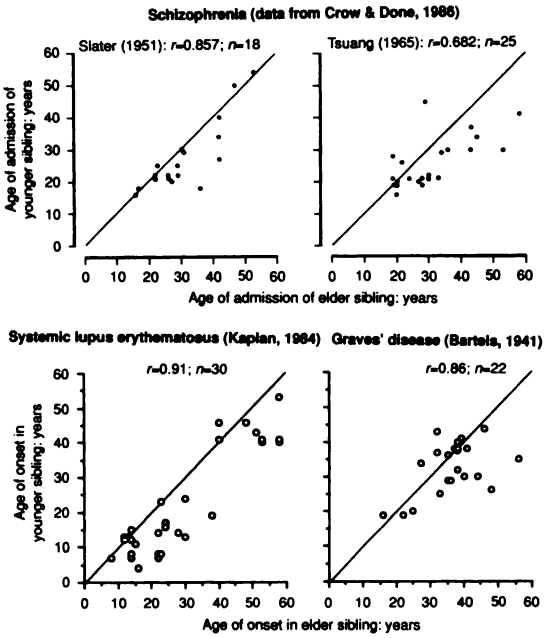

Fig. 1 Correlation of age of onset (or first admission) in sibling pairs: comparison of schizophrenia with two autoimmune diseases. n = number of sibling-pair comparisons; r = correlation of the age of onset of the disease within sibling pairs – the higher the value of r, the greater the chance that familial (both genetic and non-genetic) factors are influencing the age of onset. Note that superimposed on this highly significant correlation ($P<0.001$ in each case) in every study is a strong trend for the younger sibling to develop the disease at an earlier age, as indicated by the excess of points falling below the line $x=y$. At least in the case of SLE this is unlikely to be due to earlier detection of the disease in the young sibling, because in 50% of these cases it was the younger sibling who first presented with the disease. The trend in each disease is compatible with both siblings being exposed to an infectious trigger at the same point in time. The two examples from the five cited by Crow & Done were selected to match the number of sibling pair comparisons in the Graves' disease and SLE samples.

itself at approximately the same age in siblings sharing the same gene. If ages of onset show a wide range in unrelated individuals, this may indicate the occurrence in the population of more than one – perhaps several – genes, all capable of producing what is superficially the same disease. Our interpretation of the data for autoimmune diseases is that within families there is a tendency for similar germline immune response repertoires to require similar sequential mutational or combinatorial steps to produce the particular pathogenic clones needed for disease to ensue. Between families such germline repertoires presumably vary quite widely, thus giving rise to considerable variation in the number of sequential steps – and, therefore the time needed – for a triggering event to lead to expression of disease.

The tendency for disease onset to be at an earlier age in younger siblings could be explained by the fact that younger siblings will be exposed at a younger age than older siblings when any infectious trigger comes into the family. Therefore, they are likely to develop the disease at a younger age on average – even though the latent period (possibly several years) between exposure to infectious trigger and expression of disease may tend to be similar within families because of the similar genetic predisposition.

Rejection of the 'contagion hypothesis' has led Crow to develop alternative hypotheses – particularly the 'retrovirus/transposon hypothesis' and the 'pseudo-autosomal locus hypothesis'. These provocative hypotheses have generated interesting and controversial data (Crow *et al*, 1989; Curtis & Gurling, 1990) and from that point of view represent an important contribution. We note with interest that several studies have demonstrated that the children of diabetic fathers have a higher risk of developing IDDM than do children of diabetic mothers (Warram *et al*, 1984; Tillil & Kobberling, 1987). Furthermore, a study of IDDM in multiplex families (Field, 1989) found that fathers transmitted the disease-associated allele DR4 to their offspring significantly more frequently than did mothers. Possible mechanisms suggested for this phenomenon include: differences in disease penetrance depending on the sex of the parent contributing the predisposing gene; the lower frequency of recombination between linked loci in men than in women, resulting in increased frequency of transmission of predisposing combinations of alleles from fathers than from mothers; pre- or post-zygotic selection, including selective loss of foetuses that are genetically susceptible to IDDM, or alternatively the protection of susceptible foetuses from the subsequent manifestation of disease by exposure to a diabetic mother during gestation (Tillil & Kobberling, 1987; Field, 1989). It occurs to us that if such protection occurs, it could be due to development of anti-idiotypic clones by the foetus responding to placentally transferred anti-islet cell antibodies. Perhaps such mechanisms provide as likely an explanation as the 'pseudo-autosomal locus' one for the observations cited by Crow *et al* (1989), suggesting that schizophrenia may in some cases be preferentially transmitted from father to son.

In view of the large number of diseases which are now known or suspected to be due to autoimmune processes triggered by diverse (and perhaps ubiquitous) infections and other antigen-releasing or antigen-modifying processes, it would seem premature to rule out a potential role for post-natal infections just because the data do not fit a simplistic notion of 'viral infection = disease'. The known or suspected risk factors for schizophrenia, including family history, season of birth, obstetric complications, assault by infection, head injury, or drugs, do appear compatible with an initial trigger setting in motion a sequence of random events acting on an underlying genetic predisposition, similar to that seen in diverse autoimmune diseases.

Possible autoimmune mechanisms in schizophrenia

What mechanisms are there whereby autoimmunity could be involved in some forms of schizophrenia? If schizophrenia involves overactivity in dopaminergic pathways, then several mechanisms seem plausible, including autoantibody-mediated stimulation of post-synaptic receptors, blocking or reuptake of neurotransmitter, potentiation of release of neurotransmitter – or perhaps a combination of these, reminiscent of the modes of action of amphetamine. Some of these possibilities have been investigated (Knight & Pert, unpublished), but technically it is extremely difficult and it has not been done exhaustively. Many groups have looked for anti-brain antibodies using a wide variety of techniques, and many such antibodies have been reported (DeLisi *et al*, 1985; Knight *et al*, 1987). However, few of the techniques used have anywhere near the degree of sophistication likely to be necessary in order to discriminate between pathogenic and non-pathogenic autoantibodies. The anti-acetylcholine receptor antibodies in myasthenia gravis were only discovered because a competitive binding assay could be devised, and the thyroid-stimulating autoantibodies in Graves' disease can only be demonstrated using functional assays (Adams *et al*, 1987). In order to be meaningful, the 'signal' from such pathogenic autoantibodies needs to be distinguishable from the 'noise' created by commoner, non-pathogenic autoantibodies which appear to bear little relationship to symptoms. Standard immunological methods, including immunofluorescence, ELISA, and immunoprecipitation, lack sufficient specificity or sensitivity to make the necessary distinction.

Possible genetic susceptibility to an autoimmune cause of schizophrenia

If some forms of schizophrenia were autoimmune, then what genes might one expect to find involved? The cells of the immune system originate from

multipotent stem cells in the bone marrow. Lymphocytes develop along one or two paths – to become either B-cells, which give rise to antibodies, or T-cells, which perform various effector and regulatory functions. Evidence from the last six years indicates that the molecules of specificity in the immune system (the antibody molecules, the T-cell receptor molecules, the various histocompatibility antigens, and others) all share certain common elements.

In fact it now seems probable that the genes for these diverse molecules have arisen from a single primordial receptor gene by a series of gene duplications and comprise what is called the immunoglobulin-gene superfamily (Hood *et al*, 1985). Between them the genes which code for these cell-surface molecules determine the basic substrate of the immune response repertoire with which we are born. However, throughout life that repertoire is constantly expanding and changing, partly as a result of infection (natural selection of clones that have the best fit) and partly as a result of somatic diversification by mutation and genetic combinatorial events in rapidly dividing lymphocytes. Of course, these mechanisms are inextricably inter-related. Genetic predisposition to a whole range of autoimmune diseases has been shown in the last few years to be influenced by combinations of these immune system genes. Two examples are insulin-dependent diabetes and MS.

In insulin-dependent diabetes, caused by an autoimmune attack on insulin-producing β cells in the pancreas, histocompatibility antigens DR3 and DR4 each confer a three- to fourfold increased risk (although there is some evidence that the DQ, rather than DR, locus is responsible), and in the presence of both the risk multiplies. HLA-DR2 is strongly protective (Svejgaard *et al*, 1986). There is evidence for increased risk of insulin-dependent diabetes conferred by certain C4 complement genes (Thomsen *et al*, 1988), immunoglobulin heavy-chain V genes (Field *et al*, 1986), and T-cell receptor β chain genes (Millward *et al*, 1987). MS shows involvement of the same combination of loci, with apparent involvement of HLA antigens (Haile *et al*, 1983), complement genes (Zhang *et al*, 1988), immunoglobulin heavy-chain genes (Salier *et al*, 1986), and T-cell receptor β chain genes (Seboun *et al*, 1989). Although HLA-DR2 confers a 2.7-fold increased risk of MS, most people who develop MS do not have that gene, and most people who are DR2 positive do not develop MS. This does not necessarily mean that there are aetiologically distinct forms of MS – although of course there could be. An infection-triggered autoimmune response could underlie all cases, but different genetic backgrounds and different environmental stimuli (e.g. cold-climate viruses) may alter the risk of such an unfortunate immune response developing in a given individual.

Immunogenetic studies in schizophrenia have a long history. Elston *et al* (1973) analysed blood group data for DZ twin pairs and provided a tentative indication of linkage between schizophrenia and the immunoglobulin heavy-chain marker Gm. McGuffin *et al* (1983) in a linkage study could not confirm this, but neither could they exclude it. Numerous studies of HLA antigens in schizophrenia have provided conflicting results, different studies finding different antigens involved. Unfortunately, enthusiasm for HLA studies waned before D-locus typing became widely available. A large study of D-locus antigens (Miyanaga *et al*, 1984) showed that HLA-DR8 conferred a fourfold increased risk of schizophrenia in Japanese subjects. Rudduck *et al* (1985) reported that the complement C4 BQO allele conferred a sevenfold increased risk of schizophrenia. It is interesting that of all the complement gene polymorphisms which exist, the one which showed this apparent association is the same one (the BQO null allele) that has been demonstrated in several autoimmune diseases (Alper *et al*, 1984). Further studies are needed in order to confirm or refute these findings in other populations.

Conclusion

Schizophrenia appears to have many features that would be compatible with an autoimmune basis. Direct evidence to support an autoimmune basis is fragmentary, but the autoimmune hypothesis is able to explain many features which confound other hypotheses.

We consider that there is justification for a large-scale linkage study using the full range of immunogenetic markers which have proven informative in autoimmune diseases. Concentrating on single-gene hypotheses may postpone full understanding of the genetic predisposition to schizophrenia. In addition to the strategies already being pursued, it would seem prudent to explore the possibility that the multiple genetic loci involved in determining the immune response repertoire produce an interactive concert which degenerates into the cacophony we know as schizophrenia after any of a number of environmental insults intrude. To test such a hypothesis would require expensive, full-scale international effort – but such an effort may be the most direct route to progress.

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