

## Human development XV: The biochemical hypothesis for the etiology of the mental diseases is not substantiated

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### Abstract

We review the understanding of the etiology of the mental diseases, which has changed considerably during the last two decades. We consider the results from psycho-neuro-pharmacology and the derived historical, biochemical hypotheses for the mental diseases, and find that they have not been substantiated. We analyse the biochemical hypothesis of the diseases depression and schizophrenia and find that the standard biochemical hypotheses are not substantiated. We suggest a mechanism for the pasifying effect of the antipsychotic drugs. When it comes to the etiology of the two most common mental diseases both of these seem to be caused by disturbed psychosexual development, causing a degenerated intent, in accordance with Bleuler's classical description and understanding of schizophrenia. We present a psychobiological and more holistic models of the mental diseases and their etiology, which we find more plausible than the historical, biochemical and genetic models.

**Keywords:** Quality of Life, QOL, holistic biology, theoretical biology, clinical holistic medicine, public health, human development.

### Introduction

All transmitter systems known so far are present in both rats and humans; they must therefore be considered to be very stable in an evolutionary perspective (1). But here are significant differences also in the vertebrate brains; it looks as if man to a much higher degree than animals is in control of his fundamental mental functions such as attention, sleep, and motor activity. In man all these functions are under control of the will and are assumed to be ruled from the cerebral cortex. This is in accordance with the known development of the cerebral neocortex and

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above all the fronto-orbital lobes. Because mental diseases such as depression and schizophrenia are hardly found in animals, it seems reasonable to believe that mental diseases are caused by regulation from the cerebral cortex rather than deregulation in one or several of the ascending systems. The rational-mechanical interpretation of reality favours the hypothesis of a defect in the ascending systems, while the energetic-informational interpretation of reality favours a complex cerebral deregulation. Research has concentrated on the ascending systems, partly because of the documented effect of the antidepressants and the neuroleptics. However little is known about the descending, neural systems.

Seen from a rational interpretation of reality we think it is natural to assume, that mental diseases are caused by an inherited, mechanical defect in the brain such as a defect in an enzyme or a receptor. When psychopharmacological drugs were invented, they were seemingly able to reduce many of the symptoms of mental illnesses, i.e. the hallucinatory behaviour of schizophrenic patients. The mentally ill patients became much more calm and easier to care for, and members of the patients family often appreciated the results of the treatment, in spite of the rate of cure was rarely found to be significantly improved compared to the traditional methods of psychotherapy and holistic therapy. Especially the obedience of the patients was often radically improved, and the lack of resistance and the cooperation was seen as important signs of improvement.

This led to a number of hypotheses, as it was assumed that the effect of the drugs was a simple compensation for specific defects behind the mental diseases. This interpretation has, however, in spite of many years of research and thousands of published papers not lead to the expected full understanding of the aetiology of mental diseases; quite on the contrary mental illness and human brain function seems more mysterious and hard to understand from a chemical perspective than ever.

This paper provides arguments to reject the hitherto proposed simple hypotheses about a link between biochemical, molecular defects and mental disease. For instance, in spite of a great scientific effort neither schizophrenia nor depression has been linked to such defect genes or other specific

biochemical defects; and this fact was clear to researchers already in 1989 (2).

### *Psychoneuropharmacology and the biochemical hypotheses of the etiology of mental diseases*

Almost every drug that affects the brain does so in terms of influences on synaptic transmissions (3). Antidepressants and neuroleptics as well as several other types of psychotropic drugs often work on one or more ascending mono-aminergic transmitter system (with serotonin (5HT), norepinephrine (NE) or dopamine (DA) as transmitter), whose nuclei are present in the brain stem or the diencephalon. Pharmacological interaction with systems with acetylcholine (Ach) or gamma-aminobutyrate (GABA) can, however, also give a similar effect. Reserpin was the first antipsychotic drug that were shown to empty the monoamines from their storage vesicles, making them accessible to degradation by mitochondria-tied monoamine oxidase. The discovery of such compounds lead to the formation of the hypothesis of genetically specified dysfunction in these systems as a possible cause of schizophrenia, and serotonin and norepinephrine of depression.

The monoamine systems (5HT, NE, DA) are supposed to be the primary site of action of many psychotropic drugs and have therefore been the subject of intensive research activity. But in spite of this the precise nature of the exact relation between the monoamine systems, the mental effect of the drugs, physiology, and behaviour is still not understood in details. Because of their great diversity the monoaminergic systems can be assumed to attend to general regulatory functions. The function of the serotonergic systems is the least understood. They seem to function through a neural inhibiting tonus especially to the limbic system, correlated to muscle tonus. Dopaminergic systems possibly regulate motor activity and the activity of thoughts. Regulation of outwardly directed attention is possibly connected to the noradrenergic systems.

### *Model examples of mental disorders*

Depression and schizophrenia can be seen as examples of mental illness, which is the heavy workload in any psychiatric centre or practice. Depression is characterized by constantly bad mood, self-disapproval, a low self-confidence, and a negative self-image (4). Schizophrenia most frequently occurs at the age 15-35 years and is characterized by lack of zest for life and disorganization of logical thought most often together with auditory hallucinations and paranoid delusions (5), together with emotional flattening and social withdrawal (comp. Bleuler 1911). Depressed and schizophrenic patients constitute far the greatest part of the mentally ill patients. These two mental diseases will be the subjects of the further discussion in this paper, because they represent the best known and investigated mental disorders existing today.

## **Depression**

### *The inheritance of affective diseases*

Studies of monozygote twins showed that if twins grow up together, the concordance as regards depression is higher for monozygote twins (33-79%) than for dizygote twins (54%) (6). A concordance of 79% in the heaviest cases showed that even in these cases monozygotic twins have a considerable freedom to develop in their own way despite having the same genes and living in the same environment.

*Studies of adoption.* A study of 29 adopted bipolar depressive patients showed that 31% of the patients had adoptive parents who suffered from affective diseases, in contrast to only 9% of the biological parents. In the case of non-depressive adopted children 2% of their adoptive parents suffered from affective diseases. These data, reviewed by (7) suggested that the environmental factors dominate in the ratio 2:1 against the “early factors”, at least in this case. A simple mendelian inheritance seems unlikely. We hypothesize that intrauterine information transmitting interactions between the mother and child are responsible for the remaining cases not explained by genetics and environment.

Most affective diseases have a cyclic nature, most notably bipolar depression that hardly tallies with a genetic defect or a descending cerebral dysfunction. In the well-known “winter-depression” the light factor seems to play a key role.

It seems that environmental factors as well as genetic factors and other early factors, of which we favour intrauterine information transmitting interactions, play a role in the development of depressive diseases. As there is a very close contact between mother and child in utero, and adopted children of course spend their foetal lives in their mother’s womb, twin studies are not able to distinguish between the two kinds of factors.

*The effectiveness of antidepressants compared to placebo.* For many years it was thought that antidepressants were more active than placebo, but around year 2000 the understanding of the active placebo effect led to re-investigation and comparison of the most efficient antidepressants (the tricyclic antidepressant) with active placebo, and quite chocking it was found that these drugs, being the most potent antidepressant drugs known, was not at all better than placebo (8). Before that it was generally believed that app. 65% of non-psychotic depressive patients respond to imipramin, while app. 30% responds to placebo; all heterocyclic antidepressants had the response figures of 65-75% after one month treatment compared to 20-40% response to placebo. Generally speaking, the worse a depression is, the better the antidepressant fares compared to the passive placebo (7), but this difference is obviously annihilated when it comes to active placebo.

The above-mentioned old studies were conducted in a way that opened up to criticism. Even a 50% reduction in the Hamilton rating score (9) were clinically called a response, but in fact this was only a mild relief of symptoms. More importantly most researchers only included patients that completed the experiment, but did not inform about how many patients that did not complete the experiment – and they did not count these as non-responders, what most of them perhaps were. Moreover it was rarely told how many patients the subjects are chosen from, and there were serious problems with the criteria for election for the experiment. Only patients that do respond positively to the drugs were included in most of the studies, creating a tremendous bias: “Most of

the controlled clinical studies exclude patients who have not responded to antidepressants in the past" (10). In most cases the studies report no results of the duration of the recovery or of the frequency of relapse, and long-term follow-ups are extremely rare. So it is easy to see to day how the inefficient, antidepressive drugs were artificially turned into active and valuable drugs by the research that was almost always paid for by the pharmaceutical industry.

*The hypothesis of depression.* Around 1990 research of the effect of antidepressants led to a fundamental revision of the earlier hypotheses. Most researchers seem to agree that the simple hypothesis of depression as caused by lack of monoamines was not verified. This hypothesis was partly based on the assumption that the drugs worked through an increased supply of transmitter substances (NE and 5HT) in the synapses in a clinical time variance of the effect of between 7- 45 days (7), a much longer time than the quickly induced biochemical effect. Moreover drugs e.g. iprindol and mianserin, that are not reuptake- or MAO-inhibitors in a significant way were found to be as efficient as the classical drugs. In addition amphetamine, which is a reuptake-inhibitor, cannot effectively be used in the treatment of depressions.

Studies of monoamine-turnover in laboratory animals, long term treated with antidepressants or electroshock, showed no significant deviation from normal. The influence of the reuptake-blocking seems to be submitted to a feedback-regulated mechanism exerting its effect through auto-receptors.

None of these findings are sufficient in themselves in order to reject the hypothesis, "but together they provide a powerful argument for its re-examination and suggest that antidepressants act in a more complex manner than that envisaged by the monoamine deficiency hypothesis of depression" concluded Elliot and Stephenson in 1989 (4).

*Psychotherapy, holistic therapy and depression.* Since 1975 great methodological and technical improvements have been made, including improvement of methods of evaluating 1) the condition of the patient, 2) the qualifications of the therapist, 3) the contents of the therapy and 4) the improved situation of the patient. Central coordination of therapist training and evaluation programs has apparently resulted in a minor revolution in this area.

The results are mixed, but some researchers have concluded that there are large differences in effectiveness between the different therapies (9).

Recent research has documented that depressed patients were helped better by psychotherapy than by psychiatric standard treatment (11-13). One of the best predictors for response to interpersonal therapy is a pathological picture indicating endogenous depression!

It seems reasonable to conclude, that mental factors are of tremendous importance concerning affective diseases (14,15). We interpret the existing data in the following way: Mental illnesses are caused primarily by psychological factors, not by genes, as genes cannot be changed by psychotherapy. More efficient than psychotherapy alone is the combination of psychotherapy and bodywork, and holistic therapy like clinical holistic medicine, also including work with philosophy of life and sexuality (16-25).

## Schizophrenia

### *The inheritance of schizophrenia*

Evidently schizophrenia is not randomly distributed within a population, but is more frequent within exposed families than in the population as a whole ( $p < 0.001$ ) (26). In recent twin studies the concordance between pairs of twins growing up together is larger between monozygote (31-78%) than between dizygote twins (6- 28%). These studies also show that 22-69% of monozygote twins growing up together do not both develop schizophrenia (ibid.). This points towards a dominant influence of environmental factors. Since several investigations have shown that monozygote twins to a far higher degree than dizygote twins share the same environment, friends, and attitudes of their parents and teachers (ibid.), the greater concordance might as well be attributed to these environmental likenesses.

Studies have found a significantly higher occurrence of schizophrenia among children adopted by schizophrenic parents and among adopted children, whose biological parents were schizophrenic, compared to the average population. In some studies no significant difference was found, however. Studies of monozygote twins not growing up together were of much greater value than studies of monozygote twins

growing up together. The adopted children have, however, often spent a smaller or larger time together with the mother, and in all circumstances they had had the opportunity to adapt to the mother within the womb. The information transmitting interactions have had the time to work.

What is transferred from one generation to the next is not a simple tendency towards the development of schizophrenia, not even a non-specific tendency towards the development of psychiatric diseases, but a tendency towards bad psychosocial functioning, "These findings provide an increasingly complex, but informative, picture of the nature of transmitted liability to schizophrenia" (26).

Since 1916 it has been known, that schizophrenia does not follow a classic Mendelian inheritance pattern, thus, it is obvious to imply a polygenic inheritance. Models for polygenic inheritance, however, are flexible, because they are very difficult to falsify.

From all this, it seems that the studies of adopted monozygote children could suggest the importance of "early factors", but it is not known, whether these are of a genetic or an intrauterine nature. In addition, it is evident, that environmental factors play a great role.

*Hypotheses for schizophrenia.* Several hypotheses for schizophrenia have been proposed, but the dopamine hypothesis seemed for many years to be the only transmitter hypothesis, that could not be definitively falsified (see historical review in (5)). The dopamine hypothesis was founded in the effect on dopaminergic systems of many of the original neuroleptics. The hypothesis says that schizophrenia is caused by a (genetically inherited) hyper-activity of the dopaminergic system.

The hypothesis came in different versions each considering one of several possibilities with regard to the function of DA in the psychotic brain. Either there was too fast a DA-metabolism, or a too large a receptor sensitivity (5). Unfortunately for the believer in the dopamine hypothesis, post mortem studies or other studies did not provide evidence for an increased DA-turnover in the brain of people with schizophrenia. An up regulation of D2-receptors as a consequence of the administration of neuroleptics in the brain of schizophrenics was not found. There is still no positive evidence for occurrence of changed D2-frequency in untreated schizophrenics. Thus there

is no evidence for any molecular hypothesis for schizophrenia, not even for the dopamine hypothesis. This is in agreement with the fact that schizophrenia occurs in episodes - a fact that is very difficult to explain in terms of a defect in a transmitter system. The earlier mentioned simple hypotheses about schizophrenia as caused by simple biochemical defects or disturbances were around 1990 abandoned in favour of more complex explanations of the brain function.

From 1990 to 2008 came a large series of Cochrane metaanalysis analysing the effect of all kinds and types of antipsychotic drugs on a number of different illnesses and mental states (27-103). Quite surprisingly it was found that every time an antipsychotic drug was tested against placebo, the patients' mental state was not found to be significantly improved. Behaviour was still found to be modified, but the effect of the behaviour was just pacification, not an improvement. Hallucinations and other symptoms of mental illness was not at all relieved by the drugs, which does not deserve its name "antipsychotic medicine" anymore, as the drugs are not at all antipsychotic, only tranquillising the patients. It was also documented in these studies that the adverse effects of the drugs were very severe; they basically took the patient's energy and autonomy away, thus giving the obedient and more socially acceptable picture of an improved patient, that from an existential perspective was actually losing his quality of life as a sad consequence of the treatment.

The Cochrane analyses finally made it impossible to believe in the biochemical hypothesis of schizophrenia and the other psychotic mental illness; they were simply not substantiated.

*Negative and positive symptomatology.* The subdivision of schizophrenics into a positive and a negative symptomatology has a long history and seems to be supported by morphological studies (104). The positive symptoms are hallucinations, delusions and some types of thought disturbances as derailment, neologisms and incoherency. The negative symptoms are lack of function in a number of areas, such as social withdrawal, weakened affect, reduced motivation, psycho motor retardation, and poverty of speech.

It was around 1990 commonly understood, that the negative symptoms are not disappearing by use of

neuroleptics, but only with the Cochrane studies systematic exploration of the effects of the drugs on the positive effects was it documented that the positive symptoms were not improved either.

There is clinical evidence showing that negative symptoms may be connected with too low a dopamine activity. It is known that Parkinson disease is often associated with social withdrawal and deflated affect. Large doses of neuroleptics may trigger the negative symptoms, besides motor inhibition, while chronic l-dopa administration, which counteracts neuroleptics, sometimes is able to alleviate deflated affect, withdrawn emotions, and apathy.

This means that schizophrenic patients can be divided into a "hyper-dopaminergic" group with positive symptoms, and a "hypo-dopaminergic" group with negative symptoms. The words "hyper" and "hypo" refer to the pharmaceutical compensation that seems to remove the symptoms, and not necessarily to the DA-activity of the patients. The variance in neuropsychological state cannot in itself support a biochemical hypothesis for schizophrenia.

Taken all together it is clear today that the biochemical hypothesis for schizophrenia is in no way substantiated.

## Discussion

The passive placebo effect seems to be the same for anti-schizophrenic (antipsychotic drugs) as for antidepressants (5); the active placebo effect is only known for the antidepressant drugs, as nobody yet has investigated this with the antipsychotic drugs. The psychological and sexual factors seems to be dominant in schizophrenia as well as in depression. In studies of neuroleptics, the fact that 2 of three or more were non-responders showed that the brain has a great adaptive capacity to compensate these dating influences of the neuroleptics.

It has been known for a long time that the side effects of neuroleptics closely resemble Parkinson's disease, which is known to be associated by the decay of dopaminergic neurons; the strongest evidence for the dopaminergic effect is the fact that the clinical efficiency of many neuroleptics is closely correlated to their displacement of 3H-spiroperidol and 3H-haloperidol from D2-receptors (5,104). When it was

shown, that there was a good correlation between the clinical efficiency of neuroleptics and D2-binding, it seemed reasonable to assume that neuroleptics worked through the D2-receptor. Today a whole new generation of neuroleptics with quite different affinity profiles (27-103,105) have been created. Among the newly identified neuroleptics are compounds that by thorough clinical testing has been shown to be as effective as the old ones, while they on the whole have no affinity to DA-receptors (e.g. clozapin; less tested is flulerlapin, and BW 234 U). These compounds are all found to be "effective" in animal models. It has been shown, that they in general are clinically effective, since it is no longer possible to associate neuroleptic activity with D2-binding. Hence there is no pharmacological evidence, that psychosis is associated with the DA-systems (5). Webster and Jordan concluded in 1989: "The controversy over neuroleptic treatment and the state of D2-receptors remain unsolved." To day this is finally solved: The illness called schizophrenia is not at all connected to the D2-receptors.

The considerable time-elapse, before the effect of the neuroleptics occurs, points to a complex interaction between drug and brain. As the discontinuation of the drug rarely leads to an immediate aggravation of symptoms, it is evident, that the effects of the drugs cannot be explained by a simple interaction between a drug and a transmitter system.

Neuroleptics have not improved during the past 50 years (28) and while patients' mental health according to the many new Cochrane metaanalysis stays totally unaffected their bodies suffers. A vast fraction of the patients get serious side effects, such as tardive dyskinesia and tardive psychosis, the consequences of which are still uncertain. In spite of intensive studies the patients that selectively respond to these drugs have not been characterized (106).

Finally there is no clinical evidence that neuroleptics should be more active against schizophrenic psychoses than against any other kind of psychosis (107). Therefore there is no reason to limit the DA-hypothesis to schizophrenia; it should comprise all kinds of psychoses. Discontinuation of neuroleptics rarely seems to result in acute aggravation of the schizophrenic symptoms. The

schizophrenic symptoms seem to arrive in episodes, a detail that proposes a very complex mechanism.

One of the strangest arguments of the 80'ies, interesting for its historical value, is that the pharmacological effect is due to adaptation to the drug. This hypothesis is of course not plausible, because adaptation should lower the effect of the neuroleptics, not increase them, but in the 80'ies researches in antipsychotic drugs often suspended all reason to prove what they believed was true. But this is not so rare in science.

### *A suggestion of the mechanism of psychopharmacological drugs*

The key problem in understanding the mechanism of antidepressants and neuroleptics seems to be the great time delay of their effect. The pharmacological effect takes a few hours, the central nervous system adaptation to this effect presumably takes a few days, but the clinical effect often takes a month or more. The hypothesis of adaptation at receptor level as a mechanism behind the clinical effect does not seem plausible given the time discrepancy. The pharmacological effect of antidepressants generally seems to be an augmentation of synaptic activity, where neuroleptics (e.g. reserpine) may induce depression.

About 1990 it seemed reasonable to assume, that antidepressants respectively neuroleptics compensated a hypo-activity respectively a hyper-activity in the brain as a whole, not at any specific site of action for a specific drug. This compensation could give the complete neural system a "push" in the right direction towards normal function and normal interpretation of reality. According to this interpretation the time delay of the clinical effect was seen as inertia in the adaptation at the higher (mental) levels of the brain.

We suggest that the cognitive content of mental disease corresponds to a large number of considerations and decisions that take a long time to accumulate in one's model of reality in the brain. This inertia in the change of perception of reality leads to the time delay in any treatment of depression and schizophrenia, whether it is done by pharmacological means or by electro shock (ECT), psychotherapy and holistic therapy.

But the most obvious hypothesis for the function of the drugs is much simpler: Poisoning. As time goes by, and the patients lose energy due to severe poisoning, the behaviour becomes more and more obedient, passive and without the initiative and rebellion that characterizes autonomous beings. The psychopharmacological drugs are simple socializing the patients by depriving them of their life energy. This interpretation seems to be in almost perfect accordance with the findings of the Cochrane studies of antipsychotic drugs.

### *The etiology of depression and schizophrenia*

In 1990 it was found that depression could be counteracted through interaction with many different transmitter systems. This pointed towards a complex mechanism and not a simple one tied to a single transmitter system. Reuptake in itself could also be excluded as a mechanism, because cocaine and amphetamine did not act as antidepressants. Compensatory up regulation of beta-receptors was often seen, but not always (107), thus this could not be the general regulation mechanism. Adaptation to a drug, including receptor adaptation through increased sensitivity, was suggested as a mechanism. This did not seem likely, because such an adaptation should eliminate the disturbance and thus decrease rather than increase. In this way reduce instead of increase the effect of the antidepressants. It seems absurd to suppose that such an adaptation should give a whole new effect as for example to alleviate a depression. An adaptation to a psychotropic drug normally takes about four days (108), whereas the effect of antidepressants often does not assert its effect before about six weeks (7).

The long interval before the effect shows up indicated a very complex mechanism instead of a simple molecular mechanism. The same conclusion was indicated by the fact that about one third of the patients did not respond to antidepressants at all. The placebo effect – known today to account for the full effect (8) of the antidepressant drugs – caused by the expectations to a treatment, indicated an important mental factor. Inheritance studies suggested that a certain amount of genetic transmission could not be excluded. Spontaneous remission was well known in

patients with depression, but would not be likely in the case of a genetic programmed biochemical error. The periodical nature of manic depression (bipolar depression) was also difficult to connect to a genetic deficiency.

Today we know that psychotherapy is superior to drugs, and we know that the psychopharmacological drugs themselves are only giving positive effects through psychological mechanisms – the placebo effect.

The conclusion therefore is, that environmental factors are more important for the etiology of mental illness than genetic defects. As defect genes causing mental illness has never been found, the “early factor” seemingly important in the etiology of schizophrenia is more likely to be information-transmitting interactions between mother and child in and outside the womb. Inheritance studies showed that environmental factors played a decisive role in the etiology of schizophrenia. Early factors, such as genetic and/or intrauterine factors, were of minor importance. We hypothesize that information-transmitting interactions in utero and in early childhood were more important than genetic factors.

Studies of neuroleptics have shown a considerable placebo effect and a substantial group of non-responders, as is also the case in antidepressants. New generations of neuroleptics forced researchers around 1990 to reject the earlier assumption of schizophrenia was tied to the dopaminergic transmitter system. The long lapse of time before the effect manifest itself (7-30 days) corresponded badly with the time for the chemical effect (2 hours) or the time of adaptation at receptor level (a few days). Moreover, the episodic occurrence of schizophrenia makes it hard to maintain simple, molecular hypotheses for schizophrenia.

The positive and negative symptomatology seems to show, that schizophrenia covers a broad spectrum from “hypo“ to “hyper“ dopaminergic activity. Finally, neuroleptics assert their effect non-specifically against all psychoses, not only against schizophrenia.

All in all no evidence for any molecular hypothesis seems to have been found. On the contrary, there is clear evidence for the importance of environmental and psychological factors.

## Conclusions

We have the following final remarks after our review of the literature:

*Neuroleptics:* Almost hundred Cochrane metaanalysis seems to have documented that psychotic mental illness in general are not causally associated with the DA-systems, or any other transmitter system. The time-elapse from ingestion of neuroleptics to the effect occurs indicates that simple interaction between drug and transmitter system is not a plausible explanation. According to the receptor hypothesis concerning the effect of neuroleptics the pharmacological effect is due to adaptation to drugs, but we believe this is wrong, because adaptation should lower the effect of the neuroleptics, not increase them. It is most likely that the effect of antipsychotic drugs on behaviour – in our analysis seen as the reduction of the autonomy, libido and life energy from the patient, thus pacifying him or her and depraving the patient his basic life, is due to simple poisoning by the drugs. The Cochrane studies have systematically documented that compared to placebo; not a single type of antipsychotic drug did improve the mental state neither for the schizophrenics nor for other patients.

*Antidepressants:* In 1990 the pharmacological effect of antidepressants was used as argumentation of a biochemical hypothesis for depression linked to serotonin. This interpretation came into difficulties as the time delay of the clinical effect was seen as inertia in the adaptation to the drugs at the mental levels of the brain. A Cochrane study showed in 2004 that the most effective of the antidepressant drugs are not more effective than active placebo (8). Any hypothesis based on antidepressant drugs is therefore not substantiated.

*Etiology of the mental diseases in general:* Neither in the case of depression nor schizophrenia there seems to be evidence of genetic or molecular defects from the literature. Inheritance studies show a very important environmental factor, and a less important “early” factor, which may be due to genetic defects, but in our view far more likely, may be due to information transmitting interactions in the uterus.

The placebo effect seems to be what gives the effect of the psychopharmacological drugs; therefore it is hardly surprising that psychotherapy and holistic

therapy has been found to be more effective than psychopharmacological drugs. We conclude that the mental diseases have an etiology based on psychosexual developmental factors, not genetics.

A psychosexual etiology of the mental diseases is in accordance with recent research and opens up for psychodynamic (11-13) and scientific holistic therapy as the rational cure for mental diseases (16-25,109-130) and psychoform pain (131-133). It might also explain the most interesting connection between the sense of coherence and disease (134-140).

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