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# Autism: Genetics or Epigenetics?

**Alexander B. Poletaev*[1, 2], Boris A.Shenderov[3]**

[1]MRC "Immunculus" Moscow, Russia
[2]P.K.Anokhin Res. Inst. of Normal Physiology RAS, Moscow, Russia
[3]Research Institute of Epidemiology and Microbiology after G.N. Gabrichevsky, Moscow, Russia
**a-b-poletaev@yandex.ru*

**Abstract:** *Autism is gradually becoming an epidemic. The frequency of birth of children suffering from this disorder today is one case for every 60–80 infants, compared with 1:10000 approximately 40–50 years ago. This confirms that most cases of autism are not associated with disorders of the genome (genetic disease epidemics do not occur) and allows you to think about a progressive deepening of problems of the environment as the basis of the pathogenesis of most cases of autism. Environmental pressure may barely noticeable for an adult, but this could disturb the development of a fetuswho is less stable. A variety of environmental factors that may be involved in the pathogenesis of autism (industrial and agricultural pollutants, heavy metals, pathogenic bacteria) may cause persistent changes in the immune system of a pregnant woman.Immune deviations are manifested in the form of changes in the production of biologically active autoantibodies and cytokines. We can assume the same type of final outcomes (equifinality) from the action of different environmental factors, due to the fact that they all cause similar changes in the production of molecules of autoantibodies and cytokines influencing the development (morphogenesis and functional maturation) of different cells of the fetus.Moreover, transplacental transfer of excess of some maternal autoantibodies of IgG class leads to 're-wiring' of the immune system of the fetus (by mechanisms of maternal immune imprinting), which could be an additional factor in the pathogenesis of autism.It is noted that the environment-induced immune changes are mostly adaptive for the mother;however, for the unborn child, they can often be the factors of pathogenesis. Discuss the possibility of the study of repertoires of maternal autoantibodies forthe predictionof normal or abnormal development of the foetus and the birth of the new born with congenital disordersthat are not caused by gene defects.*

**Keywords:** *autism, environmental factors, maternal immune deviations, autoantibodies, opiate system, nutrition*

## 1. INTRODUCTION

The total incidence of genetic diseases, i.e. diseases based on genetic or chromosomal defects of any kind, is approximately 2–4%. These figures are characterised by a pronounced stability and little change over the decades [Ginter, 2003]. Accordingly, it is difficult to imagine the possibility of raising the issue of the epidemic of one or another genetic disease. The situation is different in the case of autism.

In the forties of the last century, Leo Kanner and Hans Asperger first described autism as a nosologically distinct rare form of neurological disorders in children [Kanner, 1943; Frith, 1991]. From the forties to the mid-eighties, autism met approximately 4children out of 10,000. However, by 2000, this rate increased to 67 per 10,000 [Ritvo et al., 1989].In California, where the prevalence of autism is lower than that in the whole of USA, between 1987 and 2003 the increase in the number of autism cases amounted to 634% [Ka-YuetLiuet al., 2010]. According to the recent estimates ofthe Center for control and diseases prevention (CDCP), from 2002 to 2008, there was a 78% increase in the incidence of autism, under the age of approximately one case per 88 children [CDC, 2012]. Moreover, if initially, in the 70s, 80s, 90s years, the growth of these numbers could be attributed to the increased alertness of parents and teachers, along with some expansion of the diagnostic framework, in recent years, this explanation is not tenable. Continued year-to-year growth of the incidence of autism gives rise to thepossibility tothe talk about thisreallybeing an observed epidemic [Ka-Yuet Liu et al., 2010]. Simultaneously, these data suggest against a recently dominant view about autism as a genetic disease and give further support to the epigenetic[1] views on the nature of autism.

[1)]The term of EPIGENETICS goes far beyond the phenomenon of methylation of genomic DNA on cytosine. Talking about epigenetic changes, we have to understand any modification influenced on functional activity of

## 2. GENETIC AUTISM

The term ‘autism’ includes disorders characterised by an array of typical manifestations, the most visible of which is the lack of communication and social interaction, a tendency to behavioural stereotypes and a range of other disorders. Cases of autism can differ substantially in terms of the severity of behavioural (neurological) disorders. A small portion showsoutwardly similar behavioural disturbances in children, namely the autistic symptoms that accompany a number of clinically defined genetic syndromes that are not quite rightfully referred to as ‘genetic autism’.For example, autistic symptoms are typical for approximately 10% of the patients with Down syndrome; however, these symptoms are considered nothing more than a symptom that may occur in some patients diagnosedwith‘down syndrome’. Slightly more autistic symptoms observed in patients suffering from tuberous sclerosis (in 15–20% of cases) or the syndrome of Martin-Bell aresynonymous with the syndrome fragile X-chromosome (typical 20–40% of patients). Most often, the typical symptoms of autism are observed in the Rett syndrome (more than 90% of patients). It is more correct to consider such cases (with the possible exception of Rett syndrome)from the standpoint of the main diseases, due to a specific genetic syndrome, but not to allocate them in separate forms or subtypes of autism. Along with these, there is the ‘pure’ genetic autism, which can be identified as a separate nosological form, based on certain genetic defects [Bobylova, Pechatnikova, 2013]. Perhaps as one of the genetic forms of autism, it is advisable to include Rett syndrome, albeit with some reservations.Rett syndrome is due to thefaulty gene MECP2, localised in the X chromosome. The encoded protein binds to the methylated CpG sites, which leads to compaction of chromatin and stable repression of certain genes of the neurons [Hendrich&Tweedy, 2003]. The Rett syndrome affects girls. Up to 6–18 months, the child develops normally, then there is regression of acquired motor and language skills, seizures; the growth of the head stops, appears typical, aimless, movements of the arms become repetitive, and other changes similar to autism are observed [Yurov, 2004].

Overall, genetic autism, apparently should be classified as a separate, fairly rare group of monogenic diseases. The set of such forms a ‘family’s autism’, is not more than 2–3% of all cases of autism and have nothing to do with growing over the last 30–40 years of the epidemic of autism. The epidemic, which is fuelled by epigenetic external factorsis introduced into our everyday life in a technological civilisation. Whether the individual is under the influence of such factors or not is in no way determined by the genome.

Therefore, the words of Robert Deth can be repeated: ‘…the worship of the MYTH that autism is a genetic disease, does a disservice to those who could be successfully treated, and diverts attention from exploring the real causes of disease’ [quoted on Treating Autism Publications http://www.autismtreatment.org.uk/wp-content/uploads/2014/03/Medical-Comorbidities-in-Autism-May-20131.pdf].

In passing, we note that in the North American Amish[2]community, which essentially rejectsthe innovations of civilisation, the frequency of autism cases in 2005 did not exceed 1 in 10,000 children; whereas in the whole of USA, this value was 1 case per 166 children according to the CDC in 2005 [Olmsted, 2015]. Features of life of the Amish can hardly influence the frequency of gene mutations and chromosomal abnormalities, but can significantly reduce the risks of exposure to the environment on the conditions of the pregnant body (though not eliminate them completely – we all live on the same planet).

## 3. THE SINGLE NUCLEOTIDE POLYMORPHISM OF GENOMIC DNA AND AUTISM

The main tools of evolutionary variability are random, and for the most part, neutral point mutations involvemainly the non-coding region of the genome. Tangible expression of such mutations are so

the molecules DNA, RNA and proteins. These modifications can be induced by many external influences that do not affect the nucleotide sequence of the genome. Changes can occur at the stages of transcription, translation, or implemented in the form of post-synthetic modifications of protein molecules (phosphorylation, glycosylation, adenylation, acetylation, ubiquitinylation, etc.).

[2)]Living in the USA and Canada, the most conservative followers of the sects of Mennonites (‘the Protestant believers’). The Amish consciously reject the ‘blessings of civilization’, including electricity and running water in the house, various chemicals and drugs used in household and agriculture, abandoning the use of pharmacological drugs, vaccination, etc.

called SNP (Single Nucleotide Polymorphism); this is the result of transitions (replacement of G and T to C), transversions (replacement of G to A and T to C) or deletions of single nucleotides [Conrad et al., 2006].

Using genome wide screening (GWAS), it is possible to identify SNP variants (which are quite numerous), occurring with increased frequency in the genomes of many children with autism [Anney et al., 2012]. However, the prognostic significance of these findings is rather small and can hardly be used clinically. The fact is that a randomly occurring single-nucleotide polymorphism only in a small subset of cases can influence the expression of certain macromolecules (e.g., enzyme, receptor, transport proteins). This, in turn, may lead to minimal changes of metabolism, and reduce the overall resistance of the organism to external influencesto some extent (usually slightly). It is clear that reducing the general resistance of the organism in the conditions of constant environmental pressure, to some extent, will increase the risk of any disease — from the risk of influenza, to postponingmyocardial infarction, and to increasingthe probability of the birth of an autistic child. Suchreduction of the total resistance refers only to the general nonspecific resistance, and does not imply anincreased predisposition to any particular disease.

## 4. EPIGENETIC AUTISM

Through painstaking analysis of hundreds of articles on autism, published during the period 1971 – 2010 in the most prestigious medical journals, D. A. Rossignol and R. E. Frye [2012] came to the following conclusions:

1. Only in 6–15% of the cases, autism isdirectly related to genetic defects; according to others this is in less than 3% of the cases [Treating Autism Publications, http://www.autismtreatment.org.uk/wp-content/uploads/2014/03/Medical-Comorbidities-in-Autism-May-20131.pdf].
2. In 85–95% of the cases, the development of autism is independent of the defects of the genome and is related to epigenetic factors.
3. Among the latter, the leading role is played by immune deviations and inflammatory processes. Then follow the toxic effects of the environment, oxidative stress and mitochondrial dysfunction.

Half a century ago, the formation of autism was associated with the infringement of the symbiosis between mother and foetus, difficult childbirth, and with the influence of harmful external factors. All this suggests a multifactorial pathogenesis of the disease [Mahler, 1955; Mahler, 1958]. It is interesting that the results of today's studies confirm these early suspicions, and allow usto return to the old views on a new turn of the spiral.

It would be a mistake to think that epigenetic autism, which we allocate a separate group of inborn disorders to, is not related to the characteristics of the genome of the individual. The formation of autism, its severity, and the manifestations in each case, of course, depend on the individual features of the genome (like all other biological manifestations of our life in the norm, and sickness). These features determine the efficiency of expression of many thousands of enzymes, transport proteins, antibodies and other macromolecules that regulate a lot of intracellular and intercellular events and interactions.In the end, memory and learning, and cognitive function in general, as well as overall energy metabolism, muscle activity or features of digestion are based on the regulation of expression of the molecules encoded in the genome and post-genomic (post-synthetic) modifications caused by external factors to the genome influences.

Epigenetic autism refers to polyfactorial diseases, for which, in addition to a certain genetic background, one must have some environmental influences and factors. It is clear that information about such influences is not contained in the genome in principle [Poletaev et al., 2014]. The role of external factors, the impact of which on pregnant woman, can lead to the formation of anautistic child, can lead tovery different environmental hazards. In some cases,thesemay be heavy metals, in other cases, pesticides or herbicides, in somechronic inflammation, acute infectious diseases and many other external influences. Theimportant or even decisive factor may be the persistent changes in the microbiome of women preparing for pregnancy or already pregnant. Such changes may be due to nutrition deficiencies, abuse of antibiotics or some other poorly studied influences on extremely complexbiocenosis, which we habitually and not quite correct call the 'human body' [Shenderov, 2014].Characteristically, such outwardly unrelated factors, such as disturbances in the composition of normal (symbiotic) intestinal microflora, or the various toxic environmental factors, or chronic

inflammation, or acute bacterial and viral infections, are characterised by a fundamental feature:the ability to induce along-lasting change in the immune system of a pregnant woman [Poletaev et al., 2014].

The response of the immune system to any (infectious, toxic) biologically significant impacts to the environment is versatile and results inshifts in the production of many antibodies and cytokines. Therefore, the medium-induced immune changes can simply and reliably detect persistent shifts in the production of many natural autoantibodies [Poletaev, 2013] and/or by changes in the serum concentrations of several cytokines (the latter is less easily and reliably due to its high lability and the low concentration of cytokines).

## 5. Critical Periods of the Foetal Development in Relation to Autism

The timing of embryogenesis and fetogenesis, accounting for primary interference effects, can play a very important role. Therefore,the development of autism, apparently, is determined by the influences that affect the relatively early stages of the prenatal period, i.e. they are attributable to the critical periods that are important for the formation and further development of many primordial organs and tissues. Perhaps this explains the typical for autistic children the poly-systemic disorders.

In passing, let us note that epigenetic autism should be viewed as a group of inherited, intrauterine emerging multisystem diseases, which affect the nervous system as well as pathological changes in stomach, small and large intestines and other organs of the digestive system; besides, they have frequent changes in the lungs, pelvic organs, kidneys and adrenal glands [Rossignol, Frye, 2012; Poletaev et al., 2014]. It is therefore not surprising that the mortality from different somatic causes of children with autism is 3–10 times more (depending on severity of autism) or higher than the mortality among children who are not autistic of the same age groups [from Treating Autism Publications.http://www.autismtreatment.org.uk/wp-content/uploads/2014/03/Medical-Comorbidities-in-Autism-May-20131.pdf]. If changes in the organism of pregnant woman start later (if damaging impacts have not been seen in the early, but in more later stages of gestation), this leads to more selective disordersin the developing nervous system and does not affect or has a negligible effects on other organs and systems, critical periods of development, which was completed earlier. For example, some preliminary data suggest that the relatively late effect (for example, flu in the second half of pregnancy) may cause the development of not autism but rather schizophrenia-like disorders.

## 6. Regressive Autism

Approximately in 25–30% of cases of autism, the parents and paediatricians noted that initially the child's development was almost normal, but later (usually at age 1–2.5 years) suddenly a regression occurred. As a result, during a short period of time, the child loses the majority of previously acquired skills, including verbal communication, and appears to display stereotypic behaviour, and other pathological symptoms. The regression was preceded in most cases by an acute infectious disease, intoxication, vaccination or some other external events. If thisis so,is regressive autism per se not contrary to propositions about the inherent nature of the disorder?

We believe that this is not a controversy, and the situation is explained by the fact that in some cases a newborn can develop almost normally even with certain deviations formed in the prenatal period.Through a variety of compensatory mechanisms until then, he may not have or almost does not have any obvious clinical manifestations.In other words, for a long time, the disease remains hidden, i.e. it is in itslatent form. However, this situation is not sustainable, and any additional external event may be the final straw that leads to the failure of compensation, i.e. transfer disease from a hidden (latent) form in a clear, with all its typical manifestations. For this reason, most the children (normally formed and without latent violations) neither the flu or other infectious diseases or vaccination, almost never lead to regression previously formed social-communicative and language skills.But in the small number of cases of the same factors leading to clinical manifestation of until that, compensated deviations and to 'appearance' of previously undiagnosed, hidden disease.

## 7. The Immune System as an Interface between Organism and Environment

The immune system, as well as the nervous system is designed to ensure the safety of contacts between the organism and the environment. Both systems are evolutionary adapted to the perception of incoming information, its processing (integration), storing and playback. Both systems accumulate an individual experience (not inherited), and provides a more prompt and adequate reaction of the organism on the repetition of previously meeting incoming signals.

The nervous system is specialised for perceiving and processing the information incoming mainly in the form of signals of physical nature (visual, auditory, mechanical, thermal stimuli). In turn, the immune system responds to the information coming in the form of different chemical stimuli, including viral and bacterial antigens (exogenous), and endogenous, end-products related to the functioning of cells and tissues of the own organism. In other words, the immune system can be considered as a peculiar interface, mediating the physiological reactions of an organism in response to the chemical factors coming in from the external and internal environment.It is clear that any toxins, pollutants or microbial antigens, long-term supplied to the body in a certain excess, will inevitably cause changes in the immune system of the individual, sometimes very persistent.Range of reactions of the immune system to a variety of chemical factors is rather limited in form. In all cases, these reactions most visibly manifest themselves in changes in the production of cytokines (pro-inflammatory and anti-inflammatory) and antibodies (autoantibodies).At the physiological level, these reactions manifest in the form of the successive phases of the sanogenic process: the development of local inflammation, activation of the ground clearance of the body from the excess of dying cells and potentially harmful exogenous and endogenous products, and in the stimulation of regeneration and functional recovery processes. These immuno-physiological processes are protective (adaptive) in essence. But in some cases, for example, because deviated regulation, caused by too intense or too prolonged external influences, the originally adaptive immuno-physiological processes turn into its opposite and can become pathogenic ones. Most often, the negative effects of abnormal activation of the immune system is observed in pregnant women with all sorts of unwanted external influences on the fragile systemsof the mother and the foetus.

## 8. Altered Immune Reactivity of Mother and its Influence on the Development of a Foetus

It should be noted that the increased serum levels of autoantibodies with different organ and tissue specificity are universal defensive reactions of a human organism, induced by pathological changes of any etiology and any location. Increased production of these molecules provides an activation of the clearance of damaged organs and tissues [Poletaev, 2014]. Environmental problems characterised by prolonged excessive accumulation in the environment (and therefore in soil, water, food) a variety of toxins and pollutants that can cause pathological changes in different tissues, organs and systems of the human body [Dotsenko, 2006]. In addition, many pollutants directly influence the state of the immune system, and induce abnormal changes in the production of many cytokines and antibodies. In the situation of pregnancy, we meet with a highly dialectical situation. The mother-foetussystemrepresents a single quasi-organism [Poletaev, 2014]. Organ and tissue disturbances in the maternal compartment of this quasi-organism, even subclinical, accompanying activation of apoptosis or necrosis, will induce adaptive (with point of view the maternal compartment) increasing of production of autoantibodies according to cellular-tissue specificity [Hare et al., 2013; Poletaev, 2014]. However,sanogenic immuno-physiological reaction of women organism, which manifested in increased production of autoantibodies ofclass IgG to antigens in the affected organs and tissues may be pathological, in relation to the foetus. Especially in cases where enhancement produces ‘neuro-tropic’, ‘pancreas-tropic’, ‘pulmo-tropic’, ‘cardio-tropic’, etc.autoantibodies, appears excessively long and/or too intense. Chemical pollution of the environment, may be accompanied mostly by a long but not very intense changes in the body. On the contrary, acute infectious diseases may be a cause significantly more short, but more intensive changes in production of different autoantibodies [Poletaev et al., 2007]. Under normal conditions, transported maternal antibodies are involved in the pre-programming of the emerging immune system of the unborn child (the phenomenon of maternal immune imprinting [Poletaev, 2008; Lemke, Lange, 2009]. However, one should take into account that the antibodies are biologically active molecules, and prolonged abnormal increase in the production of any of them could cause harm to the foetus.

Features of the reaction of pregnant woman induced by certain pollutants and pathogenic viruses and bacteria, as well as features of the immune response, will largely be determined by the characteristics of the genotype of the individual woman.It is essential to note that this causes changes in production of cytokines, that is highly labile molecules (half-life most of them do not exceed the minutes-tens of minutes) and almost does not penetrated the placenta, are unlikely to be very noticeable to the foetus. In contrast, changes in production and serum content of many autoantibodies, particularly autoantibodies of the class IgG, the half-life of which in vivo amounts to weeks and which actively transported from mother to foetus through the placental barrier may be highly significant [Poletaev,

2008]. Different persons would create more or less dangerous anomalies in the production of different variants and combinations of antibodies, more pathogenic or less pathogenic in relation to one or another primordial organ of the foetus. Such individual features of reactivity will ultimately determine the outcome of the pregnancy, as well as the degree of compensation or, on the contrary, the clinically manifesteddecompensation of inborn abnormalities of the future child.

In relation to the pathogenesis of autism, as well as referring to the development of new approaches to its prevention and correction, the main question is,can the effects of toxins, pollutants, infectious agents and other environmental factors involved in the development of autism, be implemented (mostly) through induced changes in the immune system of a pregnant woman? Or immune changes are very important, but only as one of the other important components of the pathogenesis of autism? Obviously, the answer is fundamentally important, not only in academic terms, but also in purely practical terms. The first option of response, prevention and correction of health status of expectant mothers may be mainly targeted to correct the immune system activity. Whereas the second variant of the answer to this question, impliesan extensive complex set of additional measures aimed at selective correction of some extra-immune mechanisms, including restoration of certain metabolic links. In any case, all these corrective measures should be performed before planned pregnancy and be targeted to the most efficient recovery of the parameters of homeostasis-homeorhesisof the woman's organism that are critical in relation to the outcome of the future planned pregnancy.

## 9. CONCLUSION

The available information does not allow us to make an unambiguous conclusion about the relative contribution of the immune and extra-immune disturbances in the development of autism and requires serious experimental and clinical study. However, the foregoing arguments allow us, as it seems, to assume the following sequence of major events leading to the development of epigenetic autism:

1. Long-term negative impact of toxic chemical agents and/or infectious antigens on the organism of women of childbearing age.
2. Induction of persistent immune changes (along with other functional and metabolic changes?)
3. Pregnancy on a background of previously generated immune changes (variant: induction of the critical immune changes, during the earlier of pregnancy)
4. Immune-dependentmalformation of the brain structures as well as the developmental deviations in other organs and systems of the foetus.
5. The birth of a child with (a) decompensated, (b) partially compensated, or (c) a latent autism. *NB*: it must be borne in mind that the clinical manifestation of previously latent disease in children group (c) can be triggered, in particular, by procedures of preventive vaccination.

Probably, the proposed scheme will require additions and refinements. First, this may relate to the role and significance of extra-immune events (components) in the pathogenesis of autism. However, it is doubtful that the proposed scheme will be fully revised. The widespread increase in the incidence of autism, acquired in the past 15–20 years, the nature of the epidemic and possibly a pandemic, clearly requires a rapid development of measures of prevention. It is important to understand that any remedial measures, if any, will be directed only to help the victims (even the most effective), and areunlikely to halt the further spread of the epidemic.

We believe that, to date, considerable convincing evidence suggests that the immune system plays an important role in the pathogenesis of autism, and some autoantibodies may be used as molecular markers of this pathology. Accordingly, it is hoped that the specialised immunochemical methods for the analysis of such markers will soon be able to be applied for the mass screening of infants and diagnosis of autism in the first months of a child's life. An equally important task will be organisation of wide screening of women planning pregnancy to identify persons and early correction of persons at risk.

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**Conflict of Interest**

The authors declare that they have no Conflicting interests.

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