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The biological background of psychiatry

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Different aspects of psychiatry in the sense of it being a biologically based science are discussed by the author.

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To what extent is psychiatry a science, if it is a science at all?

If we define science, in the Popperian sense, as a set of hypotheses that may be proved true or false, psychiatry fulfils the criterion of being a science only partially. Similarly as other divisions of medicine, psychiatry is in part science, in part art, in part – ideology. Some of its branches, as analytical psychiatry, are definitely not a science. Biological psychiatry, which attempts to answer questions in the frame of modern neurobiology, may attempt to be science. Millennia of development of our civilisation were needed to secure the position of a part of psychiatry as a science in the modern sense.

The main problem of applying scientific methodology to psychiatric research lies in the fact that humans differ considerably from each other, mentally even more than physically. A psychiatrist, psychologist or sociologist deals with a set of such diverse personalities that their characteristics are very resistant to a meaningful treatment with mathematical tools and objective methodology. Generalisations based on such divergent material, a set of irreproducible objects, were for a long time regarded as completely unjustified. Thus, up to the 1970's the American science rejected the view that this parts of knowledge about man that is the topic of psychiatry could be restrained by scientific methodology. The work of a psychiatrist, similarly as the work of an artist, would rely on intuition, the skilful insight into the patient's psyche, and experience of previous therapeutic successes and failures. Owing to that psychiatry from its beginning for a long time there was rather the description of cases. Also, the attitude to the mentally ill changed with time, an important turning point being in 1795, when

Philippe Pinel (1745-1826) removed the chains from the inmates in the psychiatric institution of Salpetriere.

Spiritual or physical causes of psychiatric diseases?

At the dawn of civilisation, in ancient Egypt, Assyria and Babylon, psychic diseases were believed as inflicted by evil deities. The belief in the role of demons, present also in the Old and New Testament, survived very long. However, the medicine and philosophy of ancient Greece allowed for somatic origins of psychic disorders. According to Hippocrates a mental disease resulted from the imbalance among the four fluids: blood, phlegm, yellow bile and black bile. The views that mental diseases have physical causes are also encountered in the Middle Ages, where among therapeutic measures besides exorcisms there appear various herbal infusions, and also trepanation of the skull and removal of the "stone of insanity."

The concept of the biological causes of mental diseases was adversely influenced by the concept of radical dualism of spiritual and carnal substances, introduced in the first half of the 17th century by René Descartes (1596-1650). According to it, the soul and body, which meet only in one point located inside the pineal gland, exist independently. The psychiatric illness, the disease of the soul, therefore lacks a biological content.

However, shortly after Descartes, the biological approach to psychiatric illness reappears: Thomas Sydenham (1624-1689) carries out autopsies of the psychiatric patients' brains and discerns between diseases caused by general brain disease and diseases in which the brain appears normal, and the illness is caused by disturbances of the "animal soul." Sydenham classified also the causes of mental diseases as "remote" (impairment of function), immediate (disorders of animal soul) and antecedent (faulty disposition of animal soul).

A further step in the direction of biological psychiatry was the concept of Franz Joseph Gall (1758-1828), who assumed that the brain contained separate personality shaping organs that were present in specific areas. The development of these organs would influence the structure of the cranium, so that the development of an organ would be determined from the shape of the skull. Those concepts, later modified by Johann Gaspar Spurzheim (1776-1832) and George Combe (1788-1858), were the base of the first biological psychiatry concept – phrenology. Phrenology was found to be a total failure as a method for predicting of personality traits from the shape of the skull, but the seeds of the idea of a link between brain anatomy and psychic functions were proven to be viable.

Integrity of the brain is necessary for mental health

The medical world was convinced to appreciate the importance of the brain for psychic functions by the celebrated case of an American railway labourer, Phineas P. Gage, in 1848. Owing to the premature explosion of dynamite the metal shaft was blown through his jaw, palate and skull, destroying a part of temporal lobes. Surprisingly, Gage survived, but his personality was dramatically changed. "The animal soul

since the accident dominated the human soul of Gage."

A view that mental diseases are brain diseases even if not always specific brain changes may be correlated with a definite psychic disturbance was advocated by an eminent German psychiatrist Wilhelm Griesinger (1817-1868). As a professor of neurology and psychiatry in Berlin, Griesinger initiated the studies on brain anatomy and pathology. His results, concomitantly with the discovery of the brain speech centre by Paul Broca (1824-1880) in 1861 in Paris paved the road for the school of brain psychiatry of Theodor Meynert (1833-1892) in Vienna and Carl Wernicke (1848-1905) in Wrocław, which attempted to find cerebral localisation for psychical functions.

Psychoanalysis versus biological psychiatry

The development of psychiatry as a science was halted at the beginning of 20th century by concepts proposed by Sigmund Freud (1856-1939) and his followers: Alfred Adler (1870-1937), Carl Gustav Jung (1875-1961), Otto Rank (1884-1939), Karen Horney (1885-1952), and Sandor Rado (1890-1972). Freud applied for therapeutic purposes a method of free associations and analysis of dreams, which he named the psychoanalysis in 1896. Using it, he found that the diseases of his patients – obsessions, phobias, and hysteria symptoms – are caused by unconscious remembering of early illicit sexual encounters. Freud's followers attributed much less importance to sexual experience, but their concepts similarly strongly emphasise the role of unconsciousness in the genesis of psychiatric disorders. The development of psychoanalysis reduced the interest in biological psychiatry and led to pronounced antagonisms between biological and analytical psychiatrists. Regardless of how effective the psychoanalytical method would be, its scientific character should be categorically denied, as its main statements were suppositions that could not be proved to be false, and Freudian concepts in a large part based on introspection. In cases when psychoanalysis attempted to predict something it frequently missed the point. Thus, e.g., according to classical Freudian psychoanalysis, the aggressive reactions would release tension and lead to catharsis. In reality aggressive behaviour augments when unopposed.

Psychoanalysis had its greatest successes in the USA, where it was introduced in 1909 at the Psychological Conference held on Clark University, Worcester, Massachusetts, and developed further in the thirties, after massive immigration of Jewish physicians from Germany and Austria. At that time no medical license was required in the USA to set up a psychoanalytical practice.

It should be added that biological psychiatry had its spectacular failures in the first half of the 20th century. Particularly mentioned here should be psychosurgery, with leucotomy introduced and propagated in Europe by Antonio Caetano de Abreu Freire de Egas Moniz (1874-1955), and in the USA by Walter Freeman (1895-1972). In spite of rewarding Moniz with the Nobel Prize in 1945, leucotomy, for most of the patients brought about tragic consequences, and this kind of psychosurgery must be regarded as a terrible mistake.

Neurobiology as a base for biological psychiatry

The most important issue for biological psychiatry is the understanding of the functioning of the brain. The neuronal theory of Santiago Ramon y Cajal (1852-1934) and the studies on transmission of the nervous signal, initiated by the classical experiments of Otto Loewi (1873-1961) in 1920's became a base for biological understanding of psychical processes and their pathological disturbances. We know now that the human brain contains approximately 100 billion neurones that communicate among themselves chiefly with chemical signals – neuromediators. Neuromediators released from nerve ending (or sometimes from the axon) travel, usually across the synaptic cleft, to the dendrite or soma of another neurone, when they bind a specific receptor. That binding initiates a cascade of intracellular events, which, eventually, lead to a transient and rapid change of the membrane potential of the post-synaptic neurone, and slowly developing more persistent changes in the function of its genome.

Research in neurobiology was frequently honoured with the Nobel Prize. In 1904 the Nobel Prize winner was Ivan Petrovitch Pavlov (1849-1936), who initiated biological studies on higher nervous functions (though his prize was awarded for work on the physiology of digestion). In 1906 Nobel Prizes were awarded for work on the structure of the nervous system to two eminent though hating each other neurologists, Ramon y Cajal and Camillo Golgi (1844-1926). In 1936 for the results that are the base for our understanding of the principles of transmission in the nervous system the Nobel Prize was awarded to Otto Loewi and Sir Henry Hallet Dale (1875-1968). For the final formulation of the theory of chemical neurotransmission the Nobel Prize of 1970 was given to Julius Axelrod (1912 -), Sir Bernard Katz, (1911-), and Ulf Svante von Euler (1905-1983). A great discovery for biological psychiatry, the evidence for the existence of "two souls in one brain" was awarded with the 1981 Nobel Prize for Roger Wolcott Sperry (1913-1994) for his research on the split brain. Finally, at the end of the 20th century Nobel Prizes were awarded for basic research on the role of dopamine, a neurotransmitter involved in schizophrenia, Parkinson's disease and drug abuse to Arvid Carlsson (1923-), for the work on transmission of the signal from the membrane receptor to the cell nucleus for Paul Greengard (1925-), and for elucidation of the neurobiological mechanisms of memory to Eric Kandel (1930-).

Psychobiology "on-line" or peeping into the brain's work

The first non-invasive method of brain function investigation, electroencephalography, was invented in 1930's, but it was not suitable to study more complicated, localised brain functions. Thus for a long time after its introduction the problem of validity of using the results obtained on dead brain tissue (usually of rats) to interpret the processes taking place in the living human brain was disputable.

The problem, which a quarter of a century ago seemed impossible to solve, was overcome by the introduction of brain imaging techniques: positron emission tomography (PET) and nuclear magnetic resonance (NMR). With these techniques it could be proven that several psychiatric disorders have neuroanatomical basis. Thus, NMR studies demonstrated anatomical deficits in the brains of autistic patients, and that those deficits are sometimes present also in the cerebellum, a structure usually not

regarded as participating in cognitive functions. PET studies on glucose utilisation by neurones permit us to measure objectively the degree of activity of localised brain areas, showing its considerable decrease in Alzheimer's disease and depressive states, and elevations in mania.

Fascinating results were obtained by studying the activity of neurone groups in various areas of the cerebral cortex during the performance of psychic functions. For example, it could be established that early-formed memory traces in the sensory cortex are rapidly transformed (in the process known as consolidation) in more permanent traces in the frontal cortex. Our methods permit us today to attempt studying consciousness from the neurobiological point of view, while thirty years ago consciousness was regarded as a field of study of psychologists and divagations of philosophers.

Neurobiological basis of psychopharmacotherapy

The predominant majority of psychotropic drugs now in use work by interaction with brain neurotransmitter systems.

Two disseminated neurotransmitter systems, involving approx. 95% of neurones, are the systems in which the role of neurotransmitters is played by amino acids. They are the excitatory glutamatergic system and inhibitory GABAergic system. It is presently thought that the glutamatergic system is responsible for conductance of the prevailing majority of organised information flowing in the central nervous system, while other neurotransmitters serve only to control it and modulate excitation. The GABAergic system, consisting mainly of inter-neurones, controls other neurotransmitter systems. It may also exert indirect excitatory influence by inhibiting other GABAergic neurones (inhibition of inhibition results in excitation). Inadequate activity of the GABAergic system causes various disturbances of psychical state, e.g., anxiety. Thus, many anxiolytics are the compounds that activate the GABA receptor complex.

Important neurotransmitter systems responsible for defined psychic and neurological functions are the cholinergic and dopaminergic systems. The cholinergic system, particularly its rostral part, projecting from the forebrain basal ganglia, is the most anterior large system carrying out information to the cerebral cortex. It is involved on the processes of attention, learning, and memory. Its activity declines with age due to extinction of cholinergic neurones, resulting in main cognitive symptoms of ageing. Premature degeneration of the cholinergic system leads to Alzheimer-like dementia. The caudal part of the cholinergic system together with the dopaminergic system controls the activity of the striatum. Shifting of the balance between these two systems leads to motor disturbances. Most frequent is the deficit of the dopaminergic system, which results in the development of Parkinson's disease. The second part of the dopaminergic system, with neurones present in the ventral tegmental area, projects onto the limbic system and cerebral cortex. Deficits of this system may lead to substance abuse, the hyperactivity in the frontal cortex – to schizophrenia.

A particular role in the regulation of the action of the brain is played by central state systems: noradrenergic and serotonergic. Both consist of a very small number (less that 500,000) of extensively branched neurones (five million nerve endings to

a neurone) that innervate vast areas of the cerebral cortex and subcortical structures. Noradrenaline in the brain plays a similar role as in the autonomic nervous system – it is an ergotropic neurotransmitter, stimulating the organism to active interaction with the environment. Serotonin, on the other hand, plays a role analogous to that of acetylcholine – it is a trophotropic neurotransmitter that activates metabolic processes, conservation of energy, reproduction, feeding and other activities important for the survival of an individual and the species. Disturbances of these systems cause, among others, mood disorders, particularly depression, obsessive-compulsive disorders and social phobia.

The above-mentioned neurotransmitter systems, using so-called classical neurotransmitters, are modulated by neuropeptidergic systems, discovered only in 1970's. There exist only few neurones containing a neuropeptide as the only chemical signal: usually neuropeptides coexist with a classical neuropeptide and modulate their action.

While compounds affecting neurotransmission form the main body of present psychotropic drugs, more and more attention is recently paid to the possibility of modulation of processes taking place within the neurone after stimulation of receptors, i.e., manipulation of the intracellular signal cascade, formation of transcription factors and induction of lasting changes on the genome of neurones. Those lasting changes, cased by adaptation processes, are responsible for the persistent action of psychotropic drugs. We presently know that antidepressant and antipsychotic drugs that act at the receptor level owe their therapeutic action to the fact that their prolonged administration leads to genomic changes.

Psychotropic drugs are the success of biological psychiatry

The biological approach to psychiatry was eventually justified by introduction in 1950»s of the psychotropic drugs effective in schizophrenia and depression. Although the first neuroleptic drug, reserpine, had been used in ancient Indian Ayurvedic medicine and described in the literature in 1930's, the breakthrough in treatment of schizophrenia was the discovery of chlorpromazine. Jean Delay (1907-1987) and Pierre Deniker (1917-1999) introduced it in 1952 as the first antipsychotic agent. The main mechanism of action of drugs of this class consists in the blockade of dopamine receptors of D2 class (receptors D2, D3, and D4) in the frontal cerebral cortex. Its blockade of D2 receptors in the striatum leads to unwanted side effects such as post-drug Parkinsonism and tardive dyskinesia. Presently introduced atypical neuroleptics, such as clozapine, olanzapine, and risperidon, block, in addition, serotonin 5HT2 receptors, and probably owing to that they do not produce extrapyramidal effects.

Other psychotropic drugs were antidepressants – inhibitors of monoamine oxidase, discovered serendipitously during treatment of tuberculosis with iproniazid (Nathanial Kline, 1916-1983), and tricyclic antidepressants introduced as neuroleptics, with imipramine as the prototype compound (Roland Kuhn, 1912-). The drugs of both those groups similarly, though due to different mechanisms, elevated the concentrations of noradrenaline and serotonin in the vicinity of receptors. Presently it seems that drugs

specifically inhibiting serotonin reuptake, such as fluoxetine, paroxetine or citalopram may in some cases be more advantageous as they are devoid of some unwanted receptor actions (e.g., cholinolytic). Recently there are drugs being introduced that simultaneously inhibit the reuptake of serotonin and noradrenaline, without affecting neurotransmitter receptors. Two of the drugs of this group recently introduced are venlafaxin and milnacipran.

Another important group of psychotropic drugs, presently most frequently prescribed, are anxiolytics of the benzodiazepine group, introduced in the years 1960-1963. They activate the benzodiazepine receptor, a component of GABA1 receptor complex, and in this way increase the inhibitory activity of GABA-ergic system.

Recently attention had been paid to procognitive drugs – medications enhancing the memory processes and slowing down – unfortunately partially and transiently – the effects of extinction of cholinergic neurones in dementive states. Particularly effective in this group are inhibitors of cholinesterase that augments the action of acetylcholine.

Intensive studies are also carried out on drugs, which could be helpful in the treatment of substance dependence, particularly those attenuating craving, the main cause of relapse. A drug effective in fighting tobacco smoking is the recently introduced bupropion; in alcoholism beneficial effects were reported for naltrexone and acamprosate.

It should be added that while introduction of modern psychotropic drugs is possible due to the development of neuroscience the introduction of these drugs and their use as investigator tools immensely helped in understanding of some basic neurobiological mechanisms.

Are biological psychiatry and psychopharmacotherapy sufficient?

The progress of our knowledge about the material basis of the brain's work and increasingly effective modification of these processes with psychotropic drugs is of utmost importance for the modern psychiatry. Owing to them the steady increase of the number of institutionalised patients in mental hospitals and asylums, existing till the 1950's in spite of the development of psychoanalysis, was reversed. There are no doubts however, that psychotherapy is an inherent part of treatment in the psychiatric inpatients and outpatients, and the work of a psychiatrist cannot be reduced to writing prescriptions. The great diversity of personalities, mentioned at the beginning, makes individualisation of doctors' approach a necessity. We are also aware now that the frontier between soul and the body is volatile: emotions in strictly defined manner cause neurochemical changes in the brain, and conceivably in many cases psychotherapeutic approach may achieve the same results as the use of chemical substances. The advantages of simultaneous psychotherapeutical and pharmacological approach could be particularly clearly seen in the treatment of substance abuse, where intensive psychotherapy evidently decreases the relapse rate in addicts treated with pharmacological agents.

Doubtless, the progress in psychiatry is being achieved due to the development of methods of biological psychiatry as well as to the increasing understanding that co-operation of pharmacological, physical and psychological methods is the base of

the therapeutic success.

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