Thomas A. Ban: Neuropsychopharmacology in Historical Perspective Education in the Post-Psychopharmacology Era

Thomas A. Ban: Mental health (Psychiatry) and pharmaceuticals in a historical perspective*

Introduction

Developments that led to the birth of the drug industry began with John Dalton's (1766 – 1844) postulation that the elementary units of all matter in the universe are indivisible and indestructible atoms in 1808 (Dalton 1808) and Friedrich August Kekulé's (1829–1896) formulation of the theory that allowed for the determination of the chemical structure, i.e., the bonding order of all of the atoms in a molecule, almost 50 years later (Kekulé 1856).

Instrumental to further development was William Henry Perkins' (1838-1907) 1856 discovery of aniline purple, the first artificial dye in history (Brightman 1956; Golin 1957). Modifications of his process led to the development of many dyes and the emergence of the dye industry in the middle of the 19th century, e.g., Bayer and Ciba (1859), Geigy and Sandoz (1862) (Menzie 1983). By the end of the 19th century, some of these dye companies, e.g., Ciba (1890), Bayer (1896), extended their activities to the development of drugs (Healy 1997, 2002).

The legal underpinning of companies dealing with drugs was the same legislation as for dyes or any other products. The roots of this legislation were in the British Corporate Law which, in 1844, passed the control of Corporations from the Government to the Court (Joint Stock Corporation Act) with a subsequent 1855 decree (Limited Liability Act) that protected investors' personal assets from the consequences of their corporate behavior (Harris 2000; Hunt 1936).

First set of drugs

The rapidly growing pharmaceutical industry during the second half of the 19th century had a major impact on the development of the different medical disciplines and especially of psychiatry through the introduction of several centrally acting drugs. By the end of the 1890s subcutaneously administered morphine (Shorter 1997; Wood 1855), along with apomorphine and hyoscine (scopolamine) were extensively used in the control of excitement, agitation and aggression; potassium bromide (Shorter 1997; Lockock 1857), for relieving restlessness, anxiety and tension; and chloral hydrate (Liebreich 1869) and paraldehyde (Cervello 1882) for calming and inducing sleep.

The judicious use of this first set of drugs in psychiatry provided day- and night-time sedation and allowed the replacement of physical restraint by pharmacological means (Ban 2011; Lehmann and Ban 1970). The control of behavior allowed for the collection of information and study of patients throughout their illness. It was with the use of the newly collected information that by the end of the first quarter of the 20th century psychopathology, the discipline that deals with the symptoms and signs of mental illness (Feuchtersleben 1845; Jaspers1913) and psychiatric nosology, the discipline that deals with the rules of separating subpopulations within mental illness and classifying these subpopulations (Cullen 1769; Jaspers 1913; Sauvages 1768). It was during this period -- between 1850 and 1900 -- that academic psychiatry was born with more than 20 academic departments established in German-speaking universities alone (Shorter 1997).

Simultaneously, with the introduction of the first set of centrally acting drugs, the "amnestic syndrome," characterized by memory disturbance (Wernicke 1881; Korsakoff 1887) was separated from "dementia," characterized by progressive deterioration of all mental faculties (Bayle 1826); Pick's disease (Pick 1892), a "pre-senile dementia" (Binswanger 1898), from "senile dementia" (dementia senilis) (Krafft-Ebing 1872); and the "endogenous psychoses," i.e., mental pathologies without identifiable pathological anatomy (Möbius (1893) from the "organic dementias," i.e., mental pathologies with identifiable pathological anatomy (Bayle 1826)

It was also during this period that Emil Kraepelin (1856–1926), in the sixth edition of his textbook published in 1899, shifted emphasis from "cross-sectional," syndromic manifestations, to the "course "and "outcome" of mental pathology and divided the "endogenous psychoses" into

"manic-depressive insanity" with an episodic-remitting course and "dementia praecox" with a continuous course that leads to "psychic invalidity" (Kraepelin 1899).

In the same year as Kraepelin's 1899 textbook was published, an alternative classification was presented by Carl Wernicke (1848–1905) (Wernicke 1899). By adopting Wilhelm Griesinger's (1817–1868) extension of "reflex" activity of the brain to mental activity and to its pathology (Griesinger 1845), Wernicke (1900) perceived and classified the different forms of mental illness as "hyperfunctioning"; "hypofunctioning" or "parafunctioning" in the "psychosensory-afferent"; and "intrapsychic central" or "psychomotor – efferent "component(s) of the "psychic reflex" (Franzek 1990).

One of the first attempts to link mental activity and its pathology to the functioning of the brain was Karl Wernicke's. It was based on contemporary scientific contributions which were to become the structural foundation of neuroscience, i.e., the detection of "multipolar cells" in the cerebral cortex by Camillo Golgi (1843–1926) (Golgi 1874); the recognition that the "neuron" is the morphological and functional unit of the nervous system by Santiago Ramón y Cajal (1852–1934) (Cajal 1894); and the demonstration that the "synapse" is the functional site of transmission from one neuron to another by Charles Scott Sherrington (1857-1952) (Sherrington 1906; Shorter 2005).

Second set of drugs

By the dawn of the 20th century drugs became an integral part of treatment in psychiatry. The first legislation to protect the public from their potential toxic effects, was The Pure Food and Drugs Act (PFDA) enacted by the US Congress in 1906. With the PFDA, demonstration of "safety" and "purity" became pre-requisites for releasing a substance for clinical use. To meet PFDA requirements all active ingredients of the substance must be listed on the label of the container in which the drug is packaged. Enactment of the PFDA was instrumental to the founding of the Food and Drug Administration of the United States (Young 1989).

Developments in psychiatry (opened by the introduction of the first set of drugs during the second part of the 19th century) continued during the first half of the 20th century. In 1907 Alois Alzheimer (1864-1915) described Alzheimer's Disease (AD) and separated AD from the other

"presenile dementias"; in 1909, Karl Bonhoeffer (1868-1948) separated the "exogenous psychoses," induced by toxic agents from the "endogenous psychoses"; in 1910 Kart Jaspers (1883-1969), "abnormal (personality development)" that was to become the subject matter of "abnormal psychology" from "psychopathological process," the subject matter of "psychiatry; in 1916 August Wimmer (1872-1937), the "reactive psychoses" precipitated by psychological trauma from the endogenous and exogenous psychoses; and in 1925, Karl Kleist (1879–1960), the "cycloid psychoses" from "manic-depressive psychosis" (Kleist 1925, 1928).

Simultaneously with this development, discoveries relevant to the molecular substrate involved in neuronal processing (transmission) began with Henry Dale's (1914) demonstration of acetylcholine (ACh) release at parasympathetic nerve endings and Otto Loewi's (1921) recognition of the changes in the adjacent cells of the ACh release. After the introduction of chromatography, research in the 1930s shifted to the brain from the periphery with the demonstration of the presence of the necessary enzymes for ACh synthesis in the cerebral cortex (Quastel, Tennenbaum and Wheatley 1936), and the isolation of ACh, the first substance identified which qualified for a neurotransmitter, from brain homogenates (Stedman and Stedman 1937).

Pharmacotherapy in psychiatry in the early years of the 20th century remained restricted to the control of behavior with the employment of centrally acting drugs. The armamentarium of these compounds was extended with the introduction of barbiturates, a series of centrally acting sedative drugs derived from barbituric acid (Baeyer 1863), and complemented with the introduction of amphetamines, a series of centrally acting stimulant drugs derived from phenylethylamine (Edeleano 1887). From the approximately 2,500 different barbiturate preparations, with different lipid solubility and duration of action, about 50 found a place in clinical practice as hypnotics, sedatives, anticonvulsants, general anesthetics, etc. (Lehmann and Ban 1970). From the different amphetamine preparations, one, racemic amphetamine, was introduced in the treatment of narcolepsy by Prinzmetal and Blumberg (1935), and another, dextroamphetamine, for calming hyper-excitable-hyperactive children by Bradley (1937). But despite the many drugs introduced, there were more and more psychiatric patients with "organic" and "functional" psychoses hospitalized in larger and larger psychiatric institutions.

The second set of drugs with an impact on the development of psychiatry were thiamine (Jansen and Donath 1926), penicillin (Fleming 1929) and nicotinic acid (Elvehjem, Madden,

Strong and Wooley 1937). The introduction of nicotinic acid and penicillin led to the virtual disappearance of psychoses due to cerebral pellagra (Fouts, Helmer, Lepkovsky and Jukes 1937) and cerebral syphilis (Stokes 1944); and of thiamin, to a marked decrease in the prevalence of amnestic syndrome due to Wernicke's (1881) disease (cerebral beri-beri) (De Wardener and Lennox 1947). By the end of the 1940s there were major changes in the diagnostic distribution of psychiatric patients in mental hospitals with a shift in prevalence of patients from "organic psychoses" to "functional psychoses." A contributing factor to the change was the decrease in hospitalized epileptics after the introduction of diphenylhydantoin, an effective anticonvulsant, developed by Putnam and Merritt at Harvard University, and marketed by Parke Davis and Company in the late 1930s (Putnam 1970).

Introduction of the second set of drugs in psychiatry coincided with the advent of physical therapies such as "insulin coma" (IC) (Sakel 1935), pharmacologically induced convulsions by camphor or pentetrazol (Meduna 1937) and "electroconvulsive therapy" (ECT) (Cerletti and Bini 1938). By providing effective treatments in the functional psychoses (schizophrenia, depression and mania), physical therapies, together with the rapidly emerging social therapies, played a major role in extending the site of psychiatric practice from mental institutions to general hospitals.

Third set of drugs

After the enactment of the Pure Food and Drugs Act, drug legislation for more than 50 years, from1907 to 1961, was restricted to the separation of prescription from over the counter medications.

The third set of drugs with an effect on the development of psychiatry (in chronology of discovery of their therapeutic effects) were lithium for mania (Cade 1949), chlorpromazine for schizophrenia (Delay and Deniker 1952), reserpine (Bleuler and Stoll 1955; Kline 1954), meprobamate for anxiety disorders (Berger 1955; Tone 2009), imipramine for depression (Kuhn 1957), iproniazide for depression (Loomer , Saunders and Kline1957) and chlordiazepoxide for anxiety disorders (Wick 2013).

Introduction of the third set of drugs and with it a psychopharmacological era in psychiatry was triggered by the success of chlorpromazine (CPZ), an aminopropyl phenothiazine, developed

originally for the potentiation of general anesthesia by Rhône-Poulenc, a French pharmaceutical company. The substance became available for clinical use in psychiatry in 1952 and was found to be more effective than any of the drugs used in the past for controlling excitement, agitation and aggression. In addition, it relieved the intensity of psychotic symptoms such as delusions and hallucinations. Yet CPZ was received incredulously by academic psychiatry, and especially by the psychoanalytic establishment of the United States, Great Britain's social psychiatrists and Germany's phenomenological psychopathologists. Academic psychiatry in the Soviet Union was ready to discount it as a gimmick of exploitation by Western capitalism. Despite the resistance of the psychiatric establishment, treatment with CPZ spread around the world and in a few years it transformed disturbed wards and the psychiatric service. Moreover, its commercial success stimulated the pharmaceutical industry to develop drugs with psychiatric indications (Ban 2006, 2007).

Psychopharmaceuticals, an industry of little economic consequence previously, quite suddenly mushroomed into a billion-dollar business. By the end of the 1950s, 12 "psychotropic drugs," a term, coined by Ralph Gerard in 1957, were introduced for the treatment of psychoses: CPZ, methotrimeprazine, prochlorperazine and thioproperazine by Rhône Poulenc; reserpine by CIBA; thiopropazate and trifluprομazine by Searle; perphenazine by Schering; thioridazine by Sandoz; trifluoperazine by Smith, Kline and French; chlorprothixene by Lundbeck; and haloperidol by Janssen. There were also three drugs introduced for the treatment of anxiety: hydroxyzine by Pfizer, meprobamate by Carter-Wallace and Wyeth and chlordiazepoxide by Rochr; and seven drugs for the treatment of depression: imipramine (IMI) by Geigy; iproniazid and isocarboxazid by Roche; nialamide by Pfizer; phenelzine by Warner-Chilcott; tranylcypromine by Smith, Kline and French; and amitriptyline (AMI) by Merck, Roche, and Lundbeck (Ban 1969; Usdin and Efron 1967).

Simultaneously with the introduction of the third set of drugs in psychiatry and the first set of psychotropic drugs, there was a shift in the understanding of signal transduction in the brain from a purely electrical to a chemically mediated event, and by the end of the 1950s six neurotransmitters had been identified in the central nervous system: ACh, dopamine (DA), γ-aminobutyric acid, norepinephrine (NE), serotonin (5-HT) and substance P. Recognition of chemical mediation at the site of the synapse, coupled with the introduction of the

spectrophotofluorimeter (Bowman, Caulfield PA, Udenfriend 1955), an instrument with the resolution power to measure drug induced changes in the concentration of cerebral monoamines, such as NE and 5-HT involved in neuronal transmission at the synapse, triggered the development of neuropharmacology, the discipline that deals with the mode of action of psychotropic drugs (Ban 2004, 2006).

Development of neuropharmacology, the discipline dedicated to the study of the mode of action of centrally acting drugs, received great impetus in the mid-1950s by the demonstration that iproniazid increased, and reserpine produced a dose dependent decrease, of cerebral monoamines, such as NE and 5-HT, whereas a single dose of iproniazid produced a moderate elevation of same monoamines that lasted for three weeks (Pletscher, Shore and Brodie 1955, 1956; Besendorf and Pletscher 1956). Since treatment with iproniazid, a substance which blocks monoamine oxidase, the enzyme responsible for the breakdown of monoamines, was found to induce euphoria, a feeling of well-being in some tubercular patients (Flaherty 1952; Selikoff, Robitzek and Orenstein 1952), and treatment with reserpine was found to induce depressed mood in about 10% of hypertensives (Bunney and Davis 1965; Kline 1968), the possibility was raised that mood changes are mediated by 5-HT and NE. The postulation of a relationship between reserpine-induced depletion of monoamines and depression by Brodie, Shore and Pletscher (1956) led to the introduction of the reserpine reversal test in the pharmacological screening for antidepressants (Costa, Garattini and Valzelli 1960); and the postulation of a relationship between an assumed catecholamine (DA and NE) receptor blockade and the therapeutic effect of CPZ and haloperidol by Carlsson and Lindqvist (1963), lent support for the use of antagonism to dopamine agonists, such as amphetamine, in the pharmacological screening for antipsychotics (Janssen, Niemegeers and Schellekens 1965).

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In neuropsychopharmacology the effect of a psychotropic drug on mental illness is linked with the effect of the substance on brain structures involved in its mode of action. Hence, the detection of the mode of action of a psychotropic drug provides clues about the pathophysiology of the mental syndrome affected by the drug; and the identification of a treatment responsive form of illness to a psychotropic drug with a well-defined mode of action provides clues for the development of a pharmacologically based classification of mental illness.

Development of neuropharmacology, the study of the mode of action of centrally acting drugs, had a major impact on academic psychiatry. By adopting concepts about the molecular substrate of the brain that is affected by psychotropic drugs, the thinking in psychiatry shifted from psychodynamic (in the USA) -- or psychosocial (in the UK) -- to biological. In academic departments the old generation of psychoanalysts was replaced by a new generation of biologically

oriented psychiatrists, and psychodynamic interpretations about psychogenic etiology were replaced with neuropharmacological interpretations about the molecular substrate of mental illness. By the new generation of psychiatrists, i.e., for those entering the field since the 1980s, neuropharmacology is perceived as one of the basic sciences of psychiatry and psychopharmacology as the bridge between the mode of action and clinical indications of psychotropic drugs.

Since its inception in the second half of the 19th century, the pharmaceutical industry has had a major impact on the development of psychiatry. Successful control of behavior was instrumental to the development of academic psychiatry; causal treatments in the organic psychoses induced by pellagra and cerebral syphilis transformed the diagnostic distribution of patients in psychiatric hospitals; and the introduction of psychotropic drugs and the spectrophotofluorimeter led to the conceptualization of psychiatry as a discipline that is based on pathologies in neuronal processing in the brain which are expressed as pathologies in the processing of mental events (psychopathologic symptoms) and crystallized as distinct patterns of psychiatric disorders (nosological entities).

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