Obsessive-Compulsive Disorders: A Serotonergic Hypothesis

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Historically, obsessions and compulsions have been mentioned in the religious and nonscientific literature for centuries. Obsessive-compulsive features are not only present in individuals, but constitute an important part of collective rituals and ceremonies including magic and superstition (Meyer, 1968).

The purpose of this paper will be focused on the medical aspects of obsessions and compulsions with much less emphasis on the psychosocial approach.

In the United States of America, obsessions and compulsions are usually classified under the label of anxiety neurosis in spite of the fact that anxiety is only one of the symptoms. In addition, anxiety may be an effect rather than a cause in the pathology of obsessive-compulsive disorders. Besides, obsessions and compulsions are not uncommon in other neuropsychiatric entities. Thus, we have proposed classifying all those syndromes whose main symptomatology include obsessions and compulsions under the term obsessive-compulsive disorders (OCD).

Among them, the most important and common one is obsessive-compulsive neurosis, also known as obsessive-neurosis, anancastic neurosis, psych-asthenia, or "folie du doute" of the French school and hereby denominated as true obsessive-compulsive disorders.

Obsessive-compulsive disorders are a group of entities characterized by two main groups of symptoms: (a) **obsessions** manifested by unpleasant, intrusive thoughts, images, or melodies that dwell in the mind and cannot be repelled; and (b) **compulsions,** described as an urge to perform an act.

The three fundamental elements of these disorders are: (1) **an iterative trend,** that is to say, the repetition of a movement until it is perfectly executed; (2) **the omnipotence of the thought** by which the patient believes that by the mere act of thinking he may modify the course of events; and (3) **the doubt,** characterized by the inability to make decisions.

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Obsessive-compulsive symptoms may be divided into: (1) ideational, and (2) motor.

(1) **Ideational symptoms,** doubting, magical thinking, worrying, counting, dwelling of thoughts, images or melodies, rigid thinking, repetitive questioning, et cetera.

(2) **Motor symptoms: (a) routine activities** (Le., double checking, cleaning); (b) **bizarre activities** (i.e., self-mutilation); (c) **physiological activities** (i.e., vomiting, urinating, eating, drinking) (Stevko et al., 1968), "needle freaks" (compulsive self-injection) (Levine, 1974); and (d) **nonsensical acts:** repetitive going to bed or getting up; taking several baths, repetitive dressing and undressing; hand washing, tapping, touching, abnormal movements, jumping and oral habits (lip biting, tongue twisting, clenching and gritting of teeth) (Pridgeon and Halpert, 1969).

Aggressive behavior inwardly or outwardly directed is another common symptom that, if severe, minimizes the primary disorder (OCD) and misleads the psychiatrist in the diagnosis. Additional symptoms include verborrhagia or an urge to talk incessantly, changes in speech pattern (Weintraub and Aronson, 1974), stammering, stuttering, echolalia (Kornyey, 1975), spastic dysphonia (Aronson et al., 1968); hypergraphia or compulsive writing (Waxman and Gesch-wind, 1974); compulsive self-induced photic epilepsy (Robertson, 1954; Rail, 1973; Mosovich, 1974) or compulsive eating as an epileptic manifestation (Green and Rau, 1974). Physical examination of patients may yield soft neurological symptoms including extrapyramidal signs and oral dyskinesia. Abnormal EEC tracings were reported in 48 percent and borderline in 29 percent out of 110 cases.(lnoue, 1973). In another study (Sugiyama, 1974), EEC was utilized to determine considerable heterogeneity-at the nosological level. Finally, sexual maladjustment (Weissmann, 1969) and family disturbances complete the various syndromes.,

Every individual from childhood on experiences at various times of his life obsessive-compulsive symptoms. However, to speak of a pathological entity, the diagnosis has to be based on the intensity and frequency of the symptoms and the need of the individual to be treated. The premorbid personality of obsessive-compulsive disorders comprises self-centered, obstinate individuals with very rigid thinking, sometimes known as "man of reason," with a high-verbal and low-performance I.Q. and a short attention span (Dayan, 1977).

These symptoms may have a gradual onset, characterized by attacks or spells that later on become permanent. Moreover, fluctuations in frequency and intensity and symptom substitution may be present. Some of the obsessive-compulsive symptoms (OCS) may be masked due to psychological compensatory mechanisms (i.e., inability to make decisions indicates an obsession to make the perfect decision). Therefore, a patient may come to consultation complaining that he cannot achieve his goals in life as he cannot assume responsibilities, hold a job, et cetera. Patients will repeat questions over and over again in order to be sure that they have correctly understood the answers. Repetitive questions will confirm their lack of self-confidence; this continuous doubting is very characteristic of obsessive-compulsive disorders. Patients are unable to modify structures or patterns of life, and an attempt to do so may precipitate a panphobic reaction. Sometimes the obsessive-compulsive disorder is monosymptomatic and may resemble pure paranpia.

Unless the, compulsion is performed, overwhelming anxiety pervades the individual! Contrariwise, if the task is carried out, the patient obtains relief from his anxiety. As a consequence of giving in to these obsessions and compulsions because of his incapacity to stop them from occurring, the patient becomes depressed or angry.

It is important to notice that in spite of the bizarreness of his acts, reality testing remains intact all along, helping to rule out a psychotic syndrome.

Moreover, the need for symmetry that some of these patients express (i.e.,

proper distribution of various objects on tables, arrangements of pictures on walls, et cetera) should be emphasized. Sameness and compulsions similar, to those described in Kanner's syndrome (Simons, 1974) are not unusual. Some patients will manifest a compulsion to equalize the stimulus whether it be external or internal. This phenomenon, described as unilateral hyperschematia, was attributed to psychogenic factors (Critchley, 1968), but this may not be so.

It is not uncommon to find severe hysterical traits that, if present, are detrimental for a good prognosis (Ver-beek, 1975.

Obsessive - compulsive disorders should not be mistaken for the obsessive-compulsive symptoms that may accompany certain forms of psychoses. Furthermore, the proteiform symptomatology of obsessive-compulsive disorders may lead to a misdiagnosis (e:g., character neuroses, Dongier, 1971). Therefore/a thorough examination of the patient becomes imperative.

The psychological symptomatology of obsessive-compulsive neurosis Was magisterially analyzed by Freud and disciples, mainly by Sandor Rado. They have described the magic component of thought process and the main phenomenon: the compulsion ("Zwang"), which, for them, is the result of an aggressive-destructive pattern.

Consequently, the physiopathology of obsessive-compulsive disorders was usually explained within the psychoanalytical context based on the anal or anancastic personality and recently in terms of learning theories (Wolpe, 1958)', or as a phenomenon of depersonalization (Goppert, 1960).

Organic theories of obsessive-compulsive disorders were never elaborated in spite of the fact that obsessive-compulsive symptoms are present in many neuropsychiatry entities which have a well-established organic pathology (see Table 1). Some of these neuropsychiatric illnesses include: encephalitis, Parkinsonism, Parkinson's disease (Jellife, 1932; Schilder, 1938; Schwab et al., 1951; Parsons, 1977), and pica due to iron

TABLE 1 Syndromes with Obsessive-Compulsive Symptoms

1. True Obsessive Compulsive Disorder
2. Gilles de la Tourette
3. Anorexia Nervosa
4. Aggressibn — Self-Mutilation — Anorexia
5. Lesch-Nyhan
6. Parkinsonism
7. Epilepsy
8. Psychosis and Mental Retardation

deficiency (Crosby, 1976). In addition,, obsessive-compulsive symptoms are observed as a side effect of levodopa administration to Parkinson patients (Anden et al., 1970), or after its discontinuation (Sack, 1977). They are also present *in* dysponesis as a result of a disturbance in the limbic system (What-more and Kohli, 1968), in hyperpraxia (Mehegan and Dreifuss, 1972), and in headbangers (Williams et al., 1972). Furthermore, obsessive-compulsive symptoms have been observed in the compulsive writing and drawing of the Interictal Behavioral Syndrome of temporal lobe epilepsy (Waxman and Gesch-wind, 1975), carbon monoxide poisoning, brain infections, and epidemic neuraxitis (Mira y Lopez et al., 1954). It has been stated that genetic factors may set a predisposition to obsessive-compulsive disorders (Inouye, 1972). We have seen evidence of this in families of OCD patients where other members also suffer from the same disorders.

In psychosomatic illnesses, some forms of tics, torticollis spasticus, and other types of motor disturbances are related to obsessive-compulsive phenomena (Beck, 1973).

There are several syndromes where obsessive-compulsive symptoms are indigenous to the primary illness.

Gilles de la Tourette's Syndrome, originally characterized by chronic involuntary movements, explosive-aggressive behavior (Moldofsky et al., 1974), utterances, echolalia, coprolalia, and self-mutilation (Van Woert et al., 1975) also shows obsessive-compulsive symptoms in 33 percent of the cases reported in the International Registry

(Abuzzahab and Anderson, 1973). However, a study conducted with Tour-ette patients in our laboratory showed the following: (1) a high incidence of obsessive-compulsive symptoms (89 percent); (2) involuntary movements are usually "thought out" (62 percent); and (3) an "urge" to tic (50 percent) (Yaryura-Tobias and Neziroglu, 1977).

In anorexia nervosa, obsessive-compulsive symptoms are a rather common finding (Halmi et al., 1973) where many patients describe the loss of appetite as an "urge" not to eat (Yaryura-Tobias, 1975). Moreover, in anorexia nervosa, Parkinsonian-like movements were also described (Needleman and Waber, 1976).

Recently, we have observed in 13 female patients what seems to be a discrete syndrome which is characterized by aggressive behavior, obsessive-compulsive symptoms, self-mutilation, sexual disorders, insomnia, and disturbances in the family constellation. Secondary findings in some patients included high pain threshold, abnormal EEC and glucose-tolerance curves. Nine had a past history of anorexia nervosa and four of psychosis. Clinically, this sample population shared obsessive-compulsive symptomatology as a predominant parameter and poor response to various forms of psychobiological therapies.

Other entities where obsessive-compulsive symptoms and self-mutilation are prominent are the Lesch-Nyhan Syndrome (Lesch and Nyhan, 1964) and the de Lange Syndrome (de Lange, 1933). In these and other syndromes where the population are children and self-injury a primary symptom, mental retardation and pain during the act of self-injury (Williams, 1974) differentiate them from our population.

The psychobiological treatment of obsessive-compulsive disorders has been generally directed to alleviate anxiety and depression as it was believed that obsessions and compulsions are the result of an anxiety state. In this regard, therapy is symptomatic and moderate in results. Psychoanalysis, individual psychotherapy, and hypnosis have not contributed much to the amelioration of symptoms. On the other hand, behavioral therapy has much more to offer (Roper et al., 1975; Marks et al., 1975) especially if a phobic component is present (Meyer, 1966).

Electroshock has been helpful on a transitory basis where the clinical use of retrograde amnesia produced by ECT has been reported to be more effective (Rubin, 1976). Other electrical therapies seem effective in monosymptomatic compulsions (Olson and Kelley, 1969; Kenny and Solyom, 1971). Psychosurgery has been used for the treatment of obsessive-compulsive disorders with various results (Pippard, 1955; Hassler and Dieckmann, 1967; Bridges and Goktepe, 1973; Mitchell-Heggs et al., 1977). The addition of behavioral therapy during the postsurgical phase appeared to be beneficial (Haaijman et al., 1977).

In compulsive eating, jejuno-ileost-omy has been reported to be helpful (Brewer et al., 1974).

Pharmacotherapy has been important in the treatment of obsessive-compulsive disorders primarily to control the anxiety and depression. For that reason, tri-cyclical and MAOI antidepressants, anxiolytics, and neuroleptics have been administered with various degrees of success. Among the neuroleptics, halo-peridol was found to be very effective if ritualistic compulsions are present (O'Regan, 1970), but negative results were also reported (Hussain and Ahad, 1970).

Of all the medication used to treat obsessive-compulsive disorders, Chlor-imipramine* (CLI), a tricyclical antidepressant, has been shown to have a strong anti-obsessive-compulsive effect (Fernandez and Lopez-lbor, 1967; De-Voxvrie, 1968; Capstick and Seldrup, 1973; Wyndowe et al., 1975; Yaryura-Tobias and Neziroglu, 1975; Yaryura-Tobias et al., 1976).

For the last three years, we have been using CLI in approximately 150 patients

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suffering from obsessive-compulsive disorders. Of this population, 90 were true obsessive-compulsive; 10 were psychotics with obsessive-compulsive symptoms; 41 had Gilles de la Tourette's Syndrome; and nine were patients with the aggressive behavior, self-mutilation, and obsessive-compulsive syndrome. Patients have been mostly characterized by the intensity and frequency of symptoms and the severity of their illness that made them socially disabled. Some of these studies included cross-over and double-blind methodology, and the results were statistically significant (Yaryura-Tobias et al., 1975, 1976; Yaryura-Tobias and Neziroglu, 1977).

The fact that other pharmacological agents are not effective for suppressing the primary symptoms of obsessive-compulsive disorders would indicate the specificity of CLI. Furthermore, the efficacy of CLI over the use of other psychobiological treatments suggests an organic pathology in certain forms of obsessive-compulsive disorders.

In animal experimentation, CLI is known to be a potent inhibitor of 5-hydroxytryptamine (5-HT) re-uptake with a lesser effect on the norepinephrine (NE) re-uptake (Carlsson et al., 1969). Moreover, it does not affect tryptophane binding, and of all the available antidepressants, it is the most specific inhibitor of serotonin (5-HT) re-uptake (Waldmeier et al., 1976). An inhibitory effect of CLI has been demonstrated in clinical use on 5-HT neurons in rat cerebral slices incubated in plasma from patients treated with CLI (Tuck and Punell, 1973). Inhibition of 5-HT re-uptake by CLI has been shown in vitro in preparation of the midbrain, hypothalamus region of the rat brain (Ross and Renyi, 1975). Thus, the existing evidence based solely on clinical trials is suggestive of a 5-HT disturbance in the pathology of obsessive-compulsive disorders.

It has been theorized that obsessive-compulsive behavior should be included within the spectrum of involuntary repetitive movements as being part of disorders where a hyperdopaminergic state has been shown (Carman, 1972). The gnawing compulsion syndrome in rats caused by apomorphine and dex-amphetamine administration (Ernst, 1967), amphetamine (Taylor and Snyder, 1970, 1971), and apomorphine combined with tricyclical antidepressants (Peder-sen, 1968) is a consequence of the stimulation of the dopaminergic neurons in the corpus striatum, yet the inhibition of the synthesis of dopamine did not alter the response in rats (Ernst, 1967); thus, it was concluded that apomorphine acted directly on dopaminergic receptors. Nevertheless, it has been shown that making more dopamine or 5-HT available equally leads to a greater apomorphine effect, indicating that the apomorphine-induced stimulation of the corpus striatum may be indirect in nature (Fekete and Kurti, 19/0). Therefore, it seems that the serotonergic system is also involved in the compulsive gnawing syndrome. This has been corroborated by the administration of the 5-HT precursor, 5-hydroxytryptophane, in rats pretreated with an MAOI, methisergide (Ernst, 1972), and the tryptophane hydroxylase inhibitor, p-Chlorophenylalanine (p-CPA) (Dadkar et al., 1976). Furthermore, the administration of p-CPA that depletes 5-HT induced compulsive sexual activity in normal and pinealectomized male rats (Tagliamonte et al., 1969). Moreover, an enhancement of dopaminergic and inhibition of cholinergic systems in the compulsive gnawing syndrome has also been postulated (Pedersen, 1967, 1968). Cholinergic stereotypes have been described by Schiflrring and Randrup (1968). And because of this, atrophine has been given to true obsessive-compulsive patients with good results (Korolenko et al., 1973).

Rats treated with trancylpromine and specific inhibitors of 5-HT re-uptake such as Lilly 110140 and 5-hydroxymethyl-tryptoline produced a hyperactive syndrome indistinguishable from that following trancylpromine and tryptophane; p-CPA pretreatment blocked the syndrome (Holman et al., 1976; Berg-mann et al., 1976).

An excellent review on stereotype and catalepsy has been written by Fog (1972). Animal behavior changes induced by amphetamines have produced repetitive movements of head and limbs. Stereotyped behavior takes different forms according to the species involved (rats, cats, monkeys, chimpanzees, and humans) (Randrup and Munkvad, 1972). Choreiform syndromes and pundning are seen in patients addicted to CNS stimulant drugs (Rylander, 1972). Obsessive-compulsive patients are very susceptible to motor disturbances due to phenothia-zine therapy.

The hallucinogenic agent, d-lysergic acid diethylamide (LSD), and CLI have been shown to have similar effects on the firing rate of serotonergic neurons located in the midbrain area (Aghajanian et al., 1968). Moreover, LSD directly inhibits impulse flow in 5-HT neurons (Gallager and Aghajanian, 1975). It has been reported that individuals with obsessive-compulsive characters are at higher risks for prolonged LSD effects (Saidel and Babineau, 1976). Contrariwise, LSD treatment for compulsions has been effective in one case (Brandrup et al., 1977).

The selectivity of CLI on 5-HT re-uptake and its efficacy for the treatment of obsessive-compulsive disorders indicates the possibility of a 5-HT disturbance. Other tricyclical antidepressants such as desipramine and amitriptyline show a pronounced selectivity for norepinephrine (NE) neurons (Snyder, 1972).

The stereotyped compulsive gnawing behavior is abolished by removal of the corpus striatum and can be elicited by direct implantation of dopamine into the corpus striatum (Ernst, 1967, 1969; Randrup and Munkvad, 1968).

Furthermore, most psychotropic drugs are not efficacious for the primary symptoms of obsessive-compulsive disorders, but are effective for the secondary symptoms of anxiety and depression. On the other hand, CLI suppresses the obsessions and compulsions and/or allows the patient to stop the obsessive thought or the urge to perform. Therefore, if CLI is so specific for the treatment of obsessive-compulsive disorders, and if its main pharmacological action is to block 5-HT re-uptake, it is possible to postulate a 5-HT involvement in the physiopathology of obsessive-compulsive disorders. We have shown in uncontrolled studies that the addition of oral L-tryptophane (x" = 3,000 mg per day) reduces the dosage of CLI almost in half. This corroborates previous studies of the potentiation of CLI by L-tryptophane in endogenous depression (Walinder et al., 1976). Moreover, we have reported the efficacy of L-tryptophane, niacinamide, and pyridoxine HCI in a group of true obsessive-compulsive patients (Yaryura-Tobias and Bhagavan, 1977). Thus, the therapeutic efficacy of CLI combined with L-tryptophane would again indicate a 5-HT disturbance in obsessive-compulsive disorders.

Further evidence to support this theory is given by the untoward effect of CLI administration (dry mouth, delayed ejaculation, arterial hypotension, loss of libido, hypersomnia, decreased urinary output, and psychotogenic effect), similar to some of the pharmacological actions of 5-HT.

The presence of soft neurological signs in obsessive-compulsive disorders in general and in true OCD, Tourette's Syndrome, and anorexia nervosa in particular, points towards an anatomical location of this group of syndromes. This proposition has been partly validated by psychosurgical procedures performed in patients suffering from true OCD, Tourette's Syndrome, anorexia nervosa, self-mutilation, and aggressive behavior. For instance, a positive usage of psychosurgery has been reported for the treatment of Gilles de la Tourette by stereotaxic elimination of rostral and medial intralaminar nuclei (Hassler and Dieckmann, 1970) or dentatotomy (Nadvornik et al., 1972) and in obsessive-compulsive illnesses by cingulec-tomy (Laitinen and Livingston, 1973) or anterior capsulotomy (Bingley et al., 1977). For anorexia nervosa, the upper mesencephalic reticulotomy and postero-medial hypothalatomy (Sano, 1960), leucotomy (Crisp and Kalucy,

1973) were performed with good results. In self-mutilation, "nasofrontal trac-tomy" and amygdalotomy have prevented further mutilation (Post and Schurr, 1977).

The hypothalamus appears to control some of the functions which are disturbed in the OCD patients. This regulatory activity of the hypothalamus includes sleep, sexual drive, thirst, glucose metabolism, appetite, and aggressive behavior. Interestingly enough, the two main neurotransmitters that are present in the hypothalamus are NE and 5-HT. As the clinical symptoms include at times extrapyramidal pathology, basal ganglia involvement should be taken into consideration. Furthermore, obsessive-compulsive disorders encompass not only ideational and motor but emotional behavior. In this regard, extensive work has been performed to identify brain sites with subjective emotional experiences (Heath, 1976). These areas are mainly found in the septal region, deep temporal lobe nuclei (hippocampus and amygdala) specific sites in the mesencephalic tegmentum, the cingulate gyrus, and in the fastigial nucleus of the cerebellum. Hence, it seems logical to suggest that obsessive-compulsive disorders may have an anatomical seat in the brain.

So far, the available evidence is in support of the view that the physio-pathology of obsessive-compulsive disorders is related to the hypothalamic-diencephalohypophysial suprarenal axis.

The biochemical mechanism of obsessive-compulsive disorders may involve the following:

(1) a norepinephrine-serotonin equilibrium
(2) an adrenergic-cholinergic equilibrium
(3) a defect in the metabolic pathway in any of the neurotransmitter systems (enzymes, coenzymes, precursors, et cetera). For instance, possible changes in the coenzyme, pyridoxal-5-phosphate, may be of importance as this coenzyme is involved in many of these pathways.

It seems that there is sufficient theoretical and clinical support to warrant investigating the etiology and physiopathology of obsessive-compulsive disorders from a biochemical point of view. For the time being, the positive clinical response to CLI therapy constitutes one potential step in the psycho-pharmacological approach to these disorders.

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