THE CATECHOLAMINE HYPOTHESIS: BEFORE AND THEREAFTER

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I have been associated with Harvard University and the Massachusetts Mental Health Center (MMHC), a teaching hospital Of Harvard Medical School, for virtually all of my career. I received my AB summa cum laude from Harvard College in 1955, where I was elected to Phi Beta Kappa in my junior year, and my MD cum laude from Harvard Medical School in 1959- Then I broke free for a year from 1959-1960 to serve as a medical intern at the University of California Hospital in San Francisco, before returning for my residency training from 1960-1963 in psychiatry at the Massachusetts Mental Health Center.

I came to the Massachusetts Mental Health Center, intending to become a psychoanalyst. However, during my first year of residency, the antidepressant drugs, phenelzine (a monoamine oxidase inhibitor) and imipramine (a tricyclic antidepressant), were just being introduced at MMHC for the treatment of depressed patients. When I became aware of the remarkable clinical effects of these antidepressants compared to psychotherapy alone (which, with the exception of electroconvulsive treatment, had been the only treatment for depressed patients until that time), it became clear to me that I had to learn more about the possible mechanisms of action of these clinically effective antidepressant drugs.

Fortunately, Milton Greenblatt, the assistant superintendent at MMHC, was in the process of developing a small research unit for the study and treatment of depressed patients, and he asked if I would be willing to become the chief (and at that point, the only) resident on this research ward. This was a wonderful opportunity that I could not refuse. The ongoing research on this unit enabled me, in collaboration With Gerald Klerman, to conduct a study comparing the effects of phene1zine and imipramine on the excretion of vanillylmandelic acid (VMA), a major metabolite of norepinephrine, in depressed patients. Since the conversion of norepinephrine to VMA requires the enzyme monoamine oxidase, the aim of this study was to determine whether, in clinical use, phenelzine (a monoamine oxidase inhibitor) would, in fact, inhibit monoamine oxidase as reflected by a decrease in the urinary output of VMA. In addition to a placebo comparison group, this study also included a comparison group of patients treated with imipramine, which is not a monoamine oxidase inhibitor, and which was, therefore, not expected to produce a change in VMA.

While there was no change in VMA output in patients treated with placebo, as my co-investigators and I had hypothesized, VMA was markedly reduced in patients treated with phenelzine. We were very surprised, however, to find that treatment with imipramine also produced a decrease in VMA (Schildkraut et al.1964) the unexpected finding that treatment

with imipramine decreased VMA led to my thoroughly the rather limited basic pharmacological literature pertaining to these antidepressants and, thus, developing an expertise in the emerging field of neuropsychopharmacology. As a result, Seymour Kety invited me to become an associate in his Laboratory of Clinical Science at the National Institute of Mental Health (NIMH) upon completion of my residency in 1963. I went on to NIMH to spend the next four years of my career (1963-67) extending my clinical research m neuropsychopharmacology on Jack Durell's clinical research unit, and beginning my career in basic neuropharmacology, collaborating with Saul Schanberg in Irwin Kopin 's neuropharmacology laboratory.

The first study I performed at the NIMH was an attempt to replicate my research on the effects of imipramine on VMA excretion and to extend into other aspects of not-epinephrine metabolism. In that first study, my collaborators and I confirmed that imipramine decreased VMA excretion. Moreover, we also observed that normetanephrine (the O-methylated metabolite of norepinephrine), which was thought to derive from norepinephrine that was released into the synapse, was increased and that increase seemed to be temporally related to the clinical antidepressant effects of imipramine in these imipramine-responsive patients (Schildkraut, Gordon, Durell 1965a). This was of considerable interest, since Julius Axelrod had previously discovered that the major mechanism for inactivating norepinephrine released into the synapse was by reuptake of that norepinephrine into the presynaptic neuron of origin, and that imipramine blocked this reuptake.

Early on in my career at NIMH, I became aware that there was very little cross-talk between the clinical psychiatrists and the basic neuropharmacologists, and it appeared to me that there was a need for a review of the psychiatric implications of the ongoing neuropharmacological studies of norepinephrine and other catecholamines. Thus, I came to write a paper entitled, "The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence," published in 1965 (Schildkraut 1965b) which would come to set the agenda for biological research on depression for the next 25 years. This paper, which crystallized a new way of thinking about mood disorders and pushed forward a paradigmatic shift in the understanding of their pathophysiology and putative etiology, has become the most frequently cited of all articles ever published in The American Journal of Psychiatry and "one of the most cited papers in psychiatry" (Healy 1997) at the time it was published, "The Catecholamine Hypothesis" captured the imagination of the field, demonstrating how pharmacology, by providing a bridge linking neurochemistry and clinical psychiatry, could offer a rational approach to research in clinical neurosciences Moreover, on a broader scale, These ideas eventually reached the popular culture and helped lessen the stigma of psychiatric illness, by promoting the awareness that depressions are medical illnesses and that many mental disorders are related to "chemical imbalances."

This article was selected as a "Classic Article in Neuropsychiatry" (Neylan 1995a), and reprinted in the Journal of Neuropsychiatry and Clinical Neuroscience in 1995 (Neylan 1995b), the first year that this series was published the Journal. David Healy, in his book, The Psychopharmacologists Ill (2000) wrote "More than any Other paper, Joe Schildkraut's

Catecholamine Hypothesis defined the psychopharmacological era. One may quibble with the details of the hypothesis, but the paper was foundational — the 1960s equivalent to Freud's The Interpretation of Dreams" (Neylan 1995a).

Following up on Julie Axelrod's Work, in my research at NIMH, my colleagues and I (in Irv Kopin's laboratory) found that, in animals, a variety of tricyclic antidepressant drugs blocked the reuptake of not-epinephrine into the presynaptic neuron of origin, while simultaneously increasing brain levels of normetanephrine. Moreover, we found that acute administration of these drugs appeared to slow the release of norepinephrine from the brain (Schanberg, Schildkraut and Kopin 1967; Schildkraut et al. 1967). In further studies, we went on to show that the major metabolite of normetanephrine in rat brain was the sulfate conjugate of 3-methoxy4-hydroxyphenylglycol (MHPG) (Schanberg et al.1968).

In 1967 I returned to the MMHC and joined the faculty of Harvard Medical School as an assistant professor of psychiatry. I became an associate professor of psychiatry in 1970 and a full professor of psychiatry in 1974. Upon my return to MMHC I founded the neuropsychopharmacology laboratory, which some years later developed a subcomponent, the psychiatric chemistry laboratory, which functioned as a clinical laboratory under the aegis of the department of pathology at the New England Deaconess Hospital. One of the goals of the neuropsychopharmacology laboratory was to develop a program of research to explore the mechanisms of action of antidepressant drugs. Initially, I had planned to study the neuropsychopharmacological effects of long-term administration of tricyclic antidepressant drugs, since chronic administration is required to achieve clinical antidepressant effects, and virtually all of the previous studies of the neuropharmacology of these antidepressants involved acute administration. Thus, after all laboratory assays had been standardized, my first major study was to compare the effects of acute and chronic (three weeks) administration of imipramine on the turnover and metabolism of norepinephrine in rat brain.

In these studies, my colleagues and I confirmed the earlier findings that the release of not-epinephrine from rat brain was decreased after a single administration of imipramine. During long-term administration (three weeks) of imipramine, however, the release of norepinephrine from brain gradually increased (Schildkraut, Winokur and Applegate 1970b). In that paper, we suggested that these findings may help to explain why antidepressant effects are observed clinically only after long-term treatment with imipramine; and in further studies, we went on to confirm and extend these findings (Schildkraut et al. 1971). Moreover, in these studies, my colleagues and I observed that both acute and chronic administration of imipramine blocked the pre-synaptic neuronal uptake of norepinephrine and shifted its metabolism from intraneuronal deamination to extraneuronal O-methylation.

Another goal of my research was to determine whether various subtypes of depressive disorders showed differences in the output and metabolism of norepinephrine. Since my earlier studies had shown that MHPG was the major metabolite of in norepinephrine rat brain (Schildkraut et al. l973), in a preliminary study my colleagues and I compared levels of urinary MHPG in patients with manic-depressive illness, depressive phase (i.e., bipolar

disorders), and patients with unipolar chronic characterological depressions. In this preliminary study, we observed that urinary MHPG levels were significantly lower in depressed patients with manic-depressive illness than in depressed patients with unipolar chronic characterological depressions (Schildkraut et al. 1978a). This preliminary study led us to develop a program of research that we called "Toward a Biochemical Classification of Depressive Disorders." The findings from this research on the biochemical pathophysiology of depressive disorders were reported in a series of papers published from 1978 to 1989 (Schildkraut et al. 1978a; Schildkraut et al.1978b; Schatzberg et al. 1978; Schatzberg et al. 1980; Schatzberg et al. 1982; Gudeman et al. 1982; Rosenbaum et al. 1983; Samson et al. 1985; Schatzberg et al. 1985; Schatzberg et al. 1989).

In the first of these studies, we examined the differences in levels of urinary MHPG and other catecholamine metabolites in a series of patients with various clinically defined sub-types of depressive disorders: manic-depressive depressions, schizoaffective depressions, unipolar endogenous depressions, unipolar nonendogenous depressions, and schizophrenia-related depressions (Schildkraut et al. 1978a). Urinary MHPG levels were significantly lower in patients with bipolar manic-depressive and schizoaffective depressions than in patients with unipolar nonendogenous depressions, in patients with unipolar endogenous depressions, we observed a wide range of MHPG levels, with some patients showing low levels comparable to those seen in patients with bipolar manic-depressive depressions, and others showing urinary MHPG levels that were higher than those seen in patients with unipolar nonendogenous depressions. (It is possible that some of those patients with low levels of urinary MHPG may have, in fact, been patients with bipolar disorders who had not yet experienced their first episode of mania.)

In addition to levels of urinary MHPG, my colleagues and I also measured urinary norepinephrine, epinephrine, and various other metabolites of these catecholamines, including VMA, normetanephrine, and metanephrine. Further biochemical discrimination among these clinically defined subtypes of depressive disorders was obtained using an empirically derived multivariate discrimination equation based on these biochemical data (Schildkraut et al 1978b). Multivariate discriminant function analysis was applied to the data on catecholamines and metabolites obtained from an initial series of patients with bipolar manic-depressive depressions and unipolar nonendogenous (chronic characterological) depressions. The terms available for computer entry into this equation included: norepinephrine (NE), normetanephrine (NMN), epinephrine (E), metanephrine (MN), vanillylmandelic acid (VMA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and various sums and ratios of these terms. Based on these terms, a discrimination equation was generated in a stepwise procedure, where the variable selected by the computer for entry into the equation at each step was the one with the largest contribution to discrimination, when the information shared with items already entered was partialed out. Thus, this empirically derived equation was determined by an analytic procedure that was not influenced by the investigators (Schildkraut et al 1978b).

The equation for what we termed the "Depression-type" (D-type) score was of the form:

$$D\text{-type score} = C_1 (MHPG) - C_2 (VMA) + C_3 (NE) - C_4 (NMN + MN)/VMA + C_0$$

These four terms were selected from the terms available to the computer because each made a statistically significant ($p<.01$) contribution to the discrimination between bipolar manic-depressive depressions and unipolar nonendogenous (chronic characterological) depressions. No other terms added significantly to the discrimination obtained from these four terms, and the overall accuracy of discrimination was highly significant. In developing the metric for this equation, a value of O was assigned to bipolar manic-depressive depressions, and the value I was assigned to unipolar nonendogenous depressions. Therefore, in the application of this equation, D-type scores less than 0.5 are associated with bipolar manic-depressive depressions and D-type scores greater than 0.5 are associated with unipolar nonendogenous depressions.

This equation was then applied to data on urinary catecholamines and metabolites in an independent series of 33 depressed patients who were studied after the derivation of this equation, and whose biochemical data, therefore, had not been used to derive the parameters of the equation. In this validation sample, all of the patients with clinical diagnoses of bipolar manic-depressive or schizoaffective depressions had D-type scores below 0.5. In contrast, all of the patients with diagnoses of unipolar nonendogenous depressions, as well as all patients with schizophrenia-related and unclassifiable depressions had D-type scores above 0.5 (Schildkraut et al. 1978b).

The 9 patients with unipolar endogenous depressions had a wide range of D-type scores, with several below 0.5 and, clearly, in the range observed in bipolar manic-depressive or schizoaffective depressions. Thus, D-type scores below 0.5 may conceivably help to identify from within the overall group of unipolar endogenous depressions, those patients with a biochemical similarity, or predisposition to bipolar manic-depressive (or schizoaffective) disorders, even though the patient may not have a history of prior overt episodes of hypomania or mania. This D-type equation may provide an even more precise discrimination among biologically meaningful subtypes of depressive disorders than does the level of urinary MHPG alone. Thus, it is intriguing to speculate that the discrimination equation, by including the contribution or various urinary catecholamine metabolites of peripheral origin, may be correcting for the fraction of urinary MHPG that derives from the periphery, rather than the brain (Schildkraut et al. 1978b).

In a further study, data on 24-hour urinary levels of catecholamines and metabolites were determined in 114 depressed patients. For each patient, a D-type score was calculated from the previously derived D-type equation of all biochemical measures obtained D-type Scores provided the highest sensitivity and specificity for separating bipolar manic-depressive/ schizo-affective depressed patients from all remaining patients (Schatzberg et al. 1989).

In the early 1990s John Mooney and others in my research group examined pretreatment 24-hour urinary MHPG levels and D-type scores as possible predictors of antidepressant responses to either imipramine or alprazolam (Mooney et al. 1991). In the case of imipramine, the responders had significantly lower pretreatment urinary MHPG levels ($p = .002$) and D-types scores ($p<.001$) than did nonresponders. In contrast, responders to the antidepressant effects of

alprazolam had significantly higher pretreatment urinary MHPG levels ($p<.05$) and D-type scores ($p=.001$) than did nonresponders. For each antidepressant treatment, D-type scores appeared to provide a better separation of responders from nonresponders than did urinary MHPG levels alone. These findings show that D-type scores, which were initially derived to separate bipolar manic-depressive depressions from other subgroups of depressive disorders, also appear to predict differential responses to certain antidepressant drugs in patients with unipolar depressions. Thus, this observation extends the potential clinical utility of the D-type equation and enhances the heuristic value of this empirically derived equation as a theoretical model that may provide clues concerning the underlying biochemical pathophysiology of catecholaminergic neuronal systems in patients with depressive disorders.

In another aspect of our research, John Mooney and I reconceptualized the inactivation and metabolism or norepinephrine released into the synapse. This led to a reformulation of the mechanisms of action of norepinephrine reuptake inhibitor antidepressant drugs. On this basis, we developed a proposal for a rapidly acting antidepressant. Working through the Harvard Medical School Office of Technology Licensing and Industry-Sponsored Research, we filed a provisional patent application on March 16, 2000, and a final patent application on March 16, 2001. This United States Patent NO. US 6,403,645 B2, entitled "Antidepressant Effect of Norepinephrine Uptake 2 Inhibitors and Combined Medications Including Them" was approved on June l, 2002 (Schildkraut and Mooney). This patent proposed that normetanephrine or other inhibitors of the extraneuronal monoamine transporter (uptake 2) in brain would speed up the clinical antidepressant effects of norepinephrine-reuptake-inhibitor antidepressant drugs.

Over the years, in the research of the neuropsychopharmacology/psychiatric chemistry laboratory, John Mooney has also spearheaded a program of research concerning biochemical methodologies and basic neuropsychopharmacological studies (Mooney et al. 1981a; et al. 1981b; Mooney et al. 1982; Mooney et al. 1985; Mooney et al. 1988; Mooney et al. 1998).

Since the 1980s, I have been involved in the development of Harvard's Commonwealth Research Center (CRC), sponsored by the Massachusetts Department of Mental Health and based at the Massachusetts Mental Health Center. The mission of the CRC was to develop a program of biologically-based research on the psychopathophysiology of severe and persistent mental illnesses, including schizophrenia and the depressive disorders. For many years, in its initial phase of development, I served as chair Of the CRC scientific advisory board. And I subsequently served as senior mentor to its director, Alan Green and other members of the CRC. In the course of this evolution, my laboratory became an integral component of the Commonwealth Research Center, and in 1998 I assumed the position of rounding director of the neuropsychopharmacology/psychiatric chemistry laboratory and appointed Alan Green as its director. Employing the research strategy that I termed the "pharmacological bridge" (Schildkraut 1970a), Alan Green and I, working with his colleagues and members of the neuropsychopharmacology/psychiatric chemistry laboratory, focused our research on the neuropsychopharmacology of clozapine (Green et al. 1993; Green and Schildkraut 1995; Green et al. 1999). This close mentoring and collaborative endeavor came to an end in November, 2002,

when Alan left MMHC to become chairman of the department of psychiatry at Dartmouth Medical School.

A former editor-in-chief of the Journal of Psychiatric Research, I am the author of over 200 scientific publications. My pioneering research on the neurochemistry and neuropharmacology of depressive disorders has been recognized with many awards and prizes including: the Anna Monika Foundation Prize for Research in Endogenous Depressions in 1967, the first year that this international prize was awarded; the Hofheimer Prize for Research from the American Psychiatric Association in 1971 ; the William C. Menninger Memorial Award from the American College of physicians in 1978; a Lifetime Achievement Award from the Society of Biological Psychiatry in 1996, presented at the Society's Annual Meeting to "seminal founding scientists in the field"; and the Award for Research in Mood Disorders from The American College of Psychiatrists in 1999.

For the past twenty years, I have also been exploring the inter-relatedness of depression, spirituality and artistic creativity, and my work on this subject has appeared in leading peer-reviewed journals (Schildkraut 1982; Schildkraut and Hirshfeld 1995; Schildkraut, Hirshfeld and Murphy 1994). In 1993, I organized and chaired a symposium on "Depression and the Spiritual in Modern Art: Homage to Miro" that was held at the Miré Foundation in Barcelona. John Wiley & Sons, Ltd., published the proceedings of this symposium in 1996 in a volume entitled, Depression and the Spiritual in Modern Art: Homage to Mirö, that I edited with Aurora Otero, then president of the Catalan Society of Psychiatry (Schildkraut and Otero, eds 1996).

I plan to continue this line of research on the inter-relatedness of depression, spirituality and artistic creativity during my retirement.

(Joseph L Schildkraut was born in Brooklyn, New York, United States, in 1934. He received his MD from Harvard Medical School, Boston, Massachusetts, United States, in 1959. Currently Schildkraut is professor, department of psychiatry, Harvard Medical School, and founding director emeritus, psychopharmacology, Psychiatric Chemistry Laboratory, Massachusetts Mental Health Center, Boston, Massachusetts.)

REFERENCES:

Green AI, Alam MY, Sobeiraj JT, Pappalardo KM, Waternaux C, Salzman C, Schatzberg AF, Schildkraut JJ (1993). Clozapine response and catecholamines and their metabolites. Psychiat Res 46:139:149.

Green AI, Schildkraut JJ (1995). Should clozapine be first line treatment for schizophrenia? The rationale for a double-blind clinical trial in first episode patients. Harv Rev Psychiat 3:1-9.

Green AI, Zimmet SV, Strous RD, Schildkraut JJ (1999). Clozapine for comorbid substance abuse disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiat 6:287-296.

Gudeman JF, Schatzberg AF, Samson JA, Orsuluk PJ, Cole JO, Schildkraut JJ (1982). Toward a biochemical classification of depressive disorders VI: platelet MAO activity and clinical symptoms in depressed patients. Am J Psychiat 39:630-633.

Healy D. (1997). The Antidepressant Era. Cambridge University Press. pp. 15.5-161.

Healy D (2000). The psychopharmacologists Vol III. London/New York: Oxford University press.

Mooney JJ, Chao FC, Orsuluk PJ, Schildkraut JJ (1981a). An approved method for the recovery of mitochondrial monoamine oxidase from human platelets using colchicine and nitrogen decompression. Biochem Med 26:156-166.

Mooney JJ, Chao FC, Orsuluk PJ, Adler SA, Schildkraut JJ (1981b). Platelet monoamine oxidase activity in psychiatric disorders: the application of a technique for the isolation of free platelet mitochondria from relatively small blood samples. J Psychiat Res 16:163-171.

Mooney JJ, Horne WC, Handin RI, Schildkraut JJ, Alexander RW (1982). Sodium inhibits both adenylate cyclase and high affinity ^{3}H-labeled p-aminoclonidine binding to α_2-adrenergic receptors in purified human platelet membranes. Mol Pharm 21:600-608.

Mooney JJ, Schatzberg AF, Cole JO, Samson JA, Gerson B, Pappalardo KM, Schildkraut JJ (1991). Urinary MHPG and the depression-type score of differential responses to antidepressants. J Clin Psychopharm 1l:339-343.

Mooney JJ, Schatzberg AE, Cole JD, Kizuka PP, Schildkraut JJ (1985). Enhanced signal transduction by adenylate cyclase in platelet membranes of patients showing antidepressant responses to alprazolam: preliminary data. J Psychiat Res 19:5-75.

Mooney JJ, Schatzberg AE, Cole JD, Kizuka PP, Salomon M, Lerginger J, Pappalardo KM, Gerson B, Schildkraut JJ (1988). Rapid antidepressant response to alprazolam in depressed patients with high catecholamine output and heterologous desensitization of platelet adenylate cyclase. Biol Psychiat 23:543-559.

Mooney JJ, Schatzberg AF, Cole JO, Samson JA, Gerson B, Pappalardo KM, Schildkraut JJ (1991). Urinary MHPG and the depression-type score of differential responses to antidepressants. J Clin Psychopharm 1l:339-343.

Neylan TC (1995a). Classic articles in neuropsychiatry. Introduction to the series. J Neuropsychiatry 7:102.

Neylan TC (1995b). Pathophysiology of affective disorders: Joseph J Schildkraut's catecholamine hypotheses. J Neuropsychiatry 7:523-533.

Rosenbaum AH. Maurta T, Schatzberg AF, Orsuluk PJ, Jiang N-S, Cole JO, Schildkraut JJ (1983). Toward a biochemical classification of depressive disorders VII: urinary free cortisol and urinary MHPG in depressions. Am J Psychiat 140:314-318.

Samson JA, Gudeman JE, Schatzberg AF, Kizuka PP, Orsuluk PJ. Cole JO, Schildkraut JJ (1985). Toward a biochemical classification of depressive disorders VIII: platelet MAO activity in subtypes of depressions. J Psychiat Res 19:547-555.

Schanberg SM, Schildkraut JJ, Breese GR, Kopin IJ (1968). Metabolism of normetanephrine H3 in rat brain: identification of conjugated 3-methoxy-4-hydroxyphenylglycol as the major metabolite. Biochem Pharmacol 17:247-254.

Schanberg SM, Schildkraut JJ, Kopin IJ (1967). The effects of psychoactive drugs on norepinephrine-H3 metabolism in brain. Biochem Pharmacol 16:393-399.

Schatzberg AF, Orsuluk PJ, Rosenbaum AH, Maruta T, Kruger ER, Cole JO, Schildkraut JJ (1980). Toward a biochemical classification of depressive disorders IV: pretreatment urinary MHPG levels as predictors of response to imipramine. Comm in Psychopharm 4:441-445.

Schatzberg AF, Orsuluk PJ, Rosenbaum AH, Maruta T, Kruger ER, Cole JO, Schildkraut JJ (1982). Toward a biochemical classification of depressive disorders V: heterogeneity of unipolar depressions. Am J Psychiat 139:471-475.

Schatzberg AF, Rosenbaum AH, Orsuluk PJ, Rohde WA, Maruta T, Kruger ER, Cole JO, Schildkraut JJ (1978). Toward a biochemical classification of depressive disorders III: pretreatment urinary MHPG levels as predictors of response to treatment with maprotiline. Psychopharm 75:34-38.

Schatzberg AF, Rothschild AJ, Gerson B, Lerbinger JE, Schildkraut JJ (1985). Toward a biochemical classification of depressive disorders IX: DST results and platelet MAO activity in depressed patients. Br J Psychiat 146:633-737.

Schatzberg AF, Samson JA, Bloomingdale KL, Orsuluk PJ, Gerson B, Kizuka PP, Cole JO, Schildkraut JJ (1989). Toward a biochemical classification of depressive disorders X: urinary catecholamines, their metabolites, and D-type scores in subgroups of depressive disorders. Arch Gen Psychiat 46:260-268.

Schatzberg AF, Orsuluk PJ, Rosenbaum AH, Maruta T, Kruger ER, Cole JO, Schildkraut JJ (1980). Toward a biochemical classification of depressive disorders IV: pretreatment urinary MHPG levels as predictors of response to imipramine. Comm in Psychopharm 4:441-445.

Schatzberg AF, Orsuluk PJ, Rosenbaum AH, Maruta T, Kruger ER, Cole JO, Schildkraut JJ (1982). Toward a biochemical classification of depressive disorders V: heterogeneity of unipolar depressions. Am J Psychiat 139:471-475.

Schildkraut JJ (1970a). Neurochemical studies of the affective disorders: the pharmacological bridge. Am J Psychiat 127: 358-360.

Schildkraut JJ (1965b). The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiat 122: 509 - 522.

Schildkraut JJ (1982). Miró and the mystical in modem art: problems for research in metapsychiatry. Am J Soc 4:2-20.

Schildkraut JJ, Gordon EK, Durell J (1965a). Catecholaminergic metabolism in affective disorders; I, Normetanephrine and VMA excretion in depressed patients treated with imipramine. J Psychiat Res 3: 213-228.

Schildkraut JJ, Hirschfeld AJ (1995). Mind and mood in modern art I: Miró "melancholic." Creativity Res J 8:139-156.

Schildkraut JJ, Hirschfeld AJ, Murphy JM (1994). Mind and mood in modern art II: depressive disorders, spirituality and early deaths in the abstract expressionist artists of the New York School. Am J Psychiat 151:482-488.

Schildkraut JJ, Klermann GL, Hammond R, Friend DG (1964). Excretion of 3-methoxy4-hydroxyphenylglycol (VMA) in depressed patients treated with antidepressant drugs. J Psychiat RCS 2; 257-266.

Schildkraut JJ, Koeler BA, Grab EL, Kantrowich J, Hartmann E (l973). MHPG excretion and clinical classification of depressive disorders. Lancet l:1251-1252.

Schildkraut JJ, Mooney JJ inventors; President and Fellows of Harvard College assignee Antidepressant effect of norepinephrine uptake 2 inhibitors and combined medications including them. US Patent 6,403,645 June 1, 20026.

Schildkraut JJ, Orsuluk PJ, LaBric RA, Schatzberg AF, Gudeman JF, Cole JO, Rohde WA (1978b). Toward a biochemical classification of depressive disorders II: application of multivariate function analysis to data on urinary catecholamines and metabolites. Arch Gen Psychiat 35:1436-1439.

Schildkraut JJ, Orsuluk PJ, Schatzberg AF, Gudeman JF, Cole JO, Rohde WA, LaBric RA (1978a). Toward a biochemical classification of depressive disorders I: differences in urinary MHPG and other catecholamine metabolites in clinically defined subtypes of depression. Arch Gen Psychiat 35:1427-1433.

Schildkraut JJ, Otero, eds (1996). Depression and the Spiritual in Modern Art: Homage to Miró Chinchester. John Wiley & Sons Ltd.

Schildkraut JJ, Schanberg SM, Breese GR, Kopin IJ (1967). Norepinephrine metabolism and drugs used the affective disorders: a possible mechanism of action. Am J Psychiat 124: 600-608.

Schildkraut JJ, Winokur A, Applegate CW (1970b). Norepinephrine turnover and metabolism in rat brain after long-term of imipramine. Science 168:867-869.

Schildkraut JJ, Winokur A, Drasoczy PR, Hensle JH (1971). Changes in norepinephrine turnover in rat brain during chronic administration of imipramine and protriptyline: possible explanation for the delay of onset in clinical antidepressant effects. Am J Psychiat 27:1032-1039.

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