

Lapin I P & Oxenkrug G F. Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect. *Lancet* 1:132-6, 1969.

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The authors suggested the involvement of tryptophan and its metabolites, serotonin and kynurenes, in the mood-elevating component of antidepressant effect. [The SCJ® indicates that this paper has been cited in over 350 publications.]

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In 1967 I became a postgraduate student of I.P. Lapin, who headed the first (and at that time the only) Department of Psychopharmacology in the Soviet Union. He was looking for somebody with expertise in adrenals, and I had just published a paper on adrenal function in ovariectomized breast cancer patients. Lapin suggested that I start by reviewing the biochemical pharmacology of depression and was patient enough to wait for two months until I felt more or less ready to begin experimentation.

At that time, the catecholamine (CA) hypothesis of depression dominated the literature, but Lapin had already observed the potentiation of central serotonergic effects by imipramine in the cat and in the frog. He asked me to pay particular attention to serotonin. I was surprised to find that almost all arguments in favor of CA involvement in depression and in the mechanism of antidepressant action were applicable to serotonin as well. Lapin responded: "Why don't we write a serotonin hypothesis?" and I continued in the library for two more months. We used to discuss our ideas almost every day in his office, and very often we were so excited that we spent long, white, Leningrad nights with tea in discussions at his home.

We sent the manuscript to the only psychiatric journal in the Soviet Union (*Zhurnal Nevropatologii*

i Psikhiiatrii imeni S.S. Korsakova [Moskva]), but it was obvious that it would take (at least) two years for it to be published. (As a matter of fact, we did not hear from the editor for three years, and then the manuscript was returned to us "because of the cleaning of the journal portfolio.") To save mailing time, we decided to try Europe rather than the US. We chose *Lancet* because of its heading "Hypothesis." Thanks to Lapin's fluent English, we had no problem with the translation, but it was difficult to find a typist with a Latin typewriter. We were lucky: it took only six months to obtain the "special permission" from Moscow to send our manuscript to England. I took it to the main post office, and very soon we were holding galleys printed on very thin paper. They trembled in our hands. The hypothesis appeared in the January 18, 1969, issue, having narrowly missed being published in 1968, the year when it was really written.

The paper was very well accepted everywhere except in the Soviet Union; even several years after publication, one of our colleagues was requested to omit the reference to our *Lancet* paper from his manuscript because "the readers of Korsakov's journal were used to the CA hypothesis and were not prepared yet for the serotonin one!" I guess the main reason for the frequent references to our paper was that it appeared at the right time; apparently many researchers were about to express hypotheses very similar to ours. Besides, the honeymoon with the CA hypothesis was almost over in the late 1960s (as happened later with the serotonin hypothesis). For clinicians, the main factor was the ability of serotonin precursors (tryptophan and 5-hydroxytryptophan), but not of CA precursor (DOPA), to alleviate depression.

It is noteworthy that we never had any intention of replacing the CA hypothesis with the serotonin one; in fact, we proposed that serotonergic activation is associated with a thymoanaleptic (mood-elevating) effect in depressed patients, while CA-ergic activation is associated with overcoming psychomotor retardation.

What we did stress was the role of tryptophan rather than one of its metabolites, 5-HT, in mood regulation. At least two aspects of this approach still warrant study: the neurotropic activity of the tryptophan metabolites, kynurenes,^{1,2} and the role of (pineal?)-hypothalamic-pituitary-adrenal (and/or gonad?) dysfunctions in the integration of the serotonin and kynurene pathways of tryptophan metabolism into the "vicious cycle" in depression.

1. Lapin I P. Kynurenes as probable participants of depression. *Pharmacopsychiatry* 6:273-9, 1973.

2. ———. Structure-activity relationships in kynurene, diazepam and some putative endogenous ligands of the benzodiazepine receptors. *Neurosci. Biobehav. Rev.* 7:107-18, 1983.