

# The mystery of Depression.

Dr. Luis Risco Neira <sup>1</sup>

<sup>1</sup>. Psychiatry Department, Bipolar Disorders Unit, Universidad de Chile.

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The first descriptions of melancholy are almost as old as medicine itself. The weary appearance, the empty look, the lack of interest and movement, appearing to be out of this world; a world that the rest of us mortals share, full of small, insignificant incidents that still catch our attention, and goals that are often nothing more than irrelevant lights and shadows that still make us strive in a captivating and essentially trivial world, which is absolutely foreign to those affected by what the ancients called melancholy. It also finds continuity and has always existed in the profound and brilliant descriptions of what we now call depression.

For centuries, the challenge was to unify criteria to refer to melancholy. There were several types, clinical configurations, and evolutionary forms. What seems obvious to us today, knowing that depression has various clinical forms, and is much more than just different nosographic approaches, is an immeasurable achievement. Thus, observations about the different types and factors involved in its presentation and evolution needed separate observation and research efforts. Monopolar and bipolar depressions, postpartum depressions, seasonal depressions, single-episode depressions, those with psychotic symptoms consistent or not with mood, those determined preferentially by temperament, and those that are not. The brief and recurrent ones... in short, the various clinical forms of what we have called depression have been increasingly described and already are established conceptual heritage.

However, we are far from knowing what really causes depression. Waves of etiological hypotheses have passed through clinical and academic environments - let us remember the

monoaminergic theory, those related to the psychosomatic organization of the family, those related to the metabolism of protein kinases, to mention a few - and they have remained, with the passage of time, as if they had been nothing more than a fad, a wave that has left everything more or less the same as before.

The powerful emergence of neuroscience in recent decades has been an unavoidable encouragement in the fight to clarify the mystery about the etiology of what we call depression. First of all, we have admitted that depression, rather than being a specific clinical condition with specific causes, determinants, and treatments, actually seems to be a kind of syndrome; in the sense that similar clinical configurations can be a consequence of different etiologies. A relevant example is depressions that are refractory to any commonly known therapeutic measure and that respond only to supraphysiological thyroid hormone loads. Is it a psychiatric condition triggered by endocrinological factors, or an endocrinopathy whose most obvious clinical appearance is depression? In the case of depressions triggered over time by the absence or detriment of ambient light, which improve with light therapies using a photon load to supply the retina with light; could it be a type of depression in which chronobiological factors are triggered or is it rather the manifestation of a chronopathy, an area of unexplored pathologies?

Surely, we could continue citing examples of this nature, which can illustrate a starting point for neuroscience research. They would better define a conceptual essential platform, which in order not to be trapped within the remains of the following old concepts that have kept us comfortable in this

regard for a long time: depression is a syndrome, a final common pathway, of several hindered or disturbed neural processes, which are prior to the ones we have considered until today to be primarily involved in the evolution of depression. The path of phenotyping various subgroups, both in clinical and laboratory terms, both in terms of state and trait markers, and in terms of “natural” evolution and response to treatment; seems for now to be the most promising or, perhaps, the only moderately viable one nowadays going in that direction. Research is aiming in that direction, and the proof of this is that pharmaceutical companies are no longer trying to create new molecules based on the monoaminergic theory of

depression, as they have done until now, but they rather are committed to opening new treatment paths aimed at the “primary” causes of depressive processes, whether we can find endocrinological, inflammatory, related to neuropeptides, or specific hormonal profiles, etc.

Let us hope that these investigations bear fruit soon. Whatever it is in terms of origin, what we call depression is a condition that causes immense suffering, fatality rates that are far from being negligible, and is still a mystery for clinical doctors, almost as much as it has been for those who recognized and described it in the history of medicine... this devastating and unholy disease, which we still call depression today.

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**Correspondence:**

Dr. Luis Risco-Neira

Email: [lrisco@uchile.cl](mailto:lrisco@uchile.cl)