

Antonio Egidio Nardi  
Rafael Christophe R. Freire  
*Editors*

# Panic Disorder

Neurobiological and  
Treatment Aspects

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*To Andrea*  
A.E.N.

*To Ana Catarina*  
R.C.R.F.



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## Foreword

Needless to say, I am immensely gratified to be asked to write the foreword to this volume, which exemplifies the multiple, burgeoning approaches to the understanding of panic.

Your editors' historical approach refers to ancient descriptions of the panic attack and the various attempts to develop an understanding of anxiety related conditions. They state that, "In 1954, Mayer-Gross associated anxiety disorders to hereditary, organic and psychological factors, dividing them in simple anxious states and phobic anxious states. In 1959, Donald Klein observed that patients with these disorders responded favorably to imipramine, a tricyclic antidepressant."

Naturally, the protagonist of this event has a more detailed and complicated recollection. Our concern in the late 1950s was to understand the effects of this new agent, imipramine. European studies stated it to be an antidepressant, so our expectation was that it would be a super cocaine and blow the patients out of their rut. At Hillside Hospital, a psychoanalytic hospital, the premium treatment was psychoanalytic psychotherapy without medication. The average length of stay was 10 months. After the failure of therapy, the patient was voluntarily referred to the Department of Experimental Psychiatry where the senior scientist was Max Fink MD and I was a very junior associate. Max and I were confirmed anti-diagnosticians since all the excellent studies of the 1950s indicated gross diagnostic unreliability. Psychoses could be barely discriminated from neuroses and that was about it. Therefore, it seemed foolish to attempt to fit medications to diagnoses.

So our first effort was a pilot trial trying to treat the entire range of patients that had not responded to treatment with psychoanalytic psychotherapy, chlorpromazine or imipramine. Our results led to a tentative classification based upon response to medication [1, 2]. We noted that several patients, plagued by anxiety attacks, had not responded to chlorpromazine, considered the most potent anti-anxiety agent, but had responded during treatment with imipramine. We were not sure if these patients might have been depressed. We looked therefore for nondepressed patients with manifest anxiety to see if imipramine had specific anti-anxiety effects, independent of their effects on depression.

The first patient that met our criteria was incessantly complaining of his fears of being alone, traveling, and dying. He demanded that he be accompanied at all times. His hospitalization was initiated by his family. They were no longer able to put up with his demands for constant reassurance and having a



companion at all times. Yet, he was not depressed. He was radically pessimistic about his fate but also had a lively interest in his circumstances, took pleasure in gossip, spoke well, ate well, slept well, and laughed at jokes.

He was placed on imipramine 75 mg daily to be weekly increased by 75 mg. He remained in psychotherapy. I examined him before the clinical open trial. The patient stated that by being placed on medication the doctors had given up on him. I also weekly interviewed the therapist, the supervisor, and the ward staff. The first 2 weeks were negative. The patient bitterly stated the medication had done him no good, and his therapist, supervisor, and ward staff agreed. His therapist indicated that he saw signs of loose associations and was sure the patient was actually psychotic. Perhaps pseudo-neurotic schizophrenia, a recently fashionable diagnosis applied to seemingly neurotic patients who did not respond to therapy. The supervisor felt that the therapist had not gone deep enough but did not elaborate.

After the third week of treatment, the patient, therapist, and supervisor remained in pessimistic agreement. Nothing was happening.

Most of the ward staff persisted in negative evaluation, but one nurse claimed that he was better, pointing out that for the past 10 months the patient had run to nursing station 3–4 times a day, saying that he was dying and had not done that for the past week. Previously, they had held his hand, told him for the thousandth time that his heart was fine and that it was just his terrible anxiety. After 20 min, he left quite dissatisfied to reappear 6 h later and go through the same routine. Other nurses said this was unimportant since whenever you talked to the patient, it was the same litany of complaints.

Discussing this with the patient, I mentioned that he seemed to be better.

“Who told you that?,” he snarled. “A nurse” I stuttered. “What do they know?,” he dismissed. When I asked him about not running to the nursing station, he seemed puzzled, and quickly affirmed that he was anxious as ever. Pressed about the change in his behavior, he finally noted, “I guess I learned that they can’t do anything for me.” I questioned, “You mean after 10 months you learned just this week?”

“Well, you have to learn sometime,” he replied, thus anticipating the development of cognitive behavioral therapy.

It became clear that the run to the nursing station was precipitated by an attack. What confused me was that the overwhelming crescendo of the attack was considered the worst anxiety but imipramine took the top off, while leaving marked anxiety behind. It seemed reasonable that a medication would be most effective at the moderate level of illness rather than the worst form. It was at that time I realized that anxiety was heterogeneous and that the anxiety attack should be called something else, to distinguish it from ordinary chronic anxiety, itself considered an inappropriate manifestation of fear. Notably, the chronic anxiety persisted. This led to my renaming the attack as a panic attack. It also seemed, by reviewing detailed histories, that the phobic manifestations only occurred after the onset of repeated panic attacks. The phobias of these hospitalized patients were limited to situations where, if they had a panic attack, they couldn’t get to help. This was not due to conditioning since these patients often refused to fly, although they never had a panic attack on an airplane. It was the possibility that paralyzed them. They were not afraid

of dogs, or thunder, or heights. Also, it became apparent that the time between repeated panic attacks and phobic manifestations was very variable. Some patients withstood the attacks for many months while others folded up immediately and became housebound.

In general with repeated attacks, chronic anticipatory anxiety developed about when the next panic attack would happen. This led to severe travel limitations by ensuring that help was always easily available. It could be radically diminished by a companion. The propensity for chronic high levels of anticipatory anxiety, unleashed by the panic, seemed an independent component of the phobic development. A final confusing note was the frequent history of separation anxiety disorder that became manifest when school was required, leading to the misnamed school phobia. These children were not afraid of school. School was a forced separation from their mother and they were overwhelmed, which they explained by concern for the mother's welfare." Maybe she got sick," they would whimper. However they usually got over this and did not have panic attacks during this period. At sometime later, frequently when they had to change schools or move the separation anxiety would recur. Panic attacks occurred rarely before puberty and raised the suspicion of cerebral dysrhythmia. Later we found that Panic Disorder waxed and waned.

These early observations were followed by a series of controlled trials regarding panic disorder and separation anxiety disorder [3–8].

However, an independent placebo controlled trial confirming the anti-panic effect of imipramine awaited Sheehan and Ballenger [9], two nervy, smart residents at Massachusetts General Hospital, part of the Harvard empire. Hillside Hospital had no academic links and nowhere near Harvard's prestige.

This necessary independent study took place about 17 years after our initial presentations to a largely dismissive world. At Yale a senior psychoanalyst explained that these phobic patients did not travel because that requires walking the streets and since they had an unconscious desire to be streetwalkers (prostitutes) they couldn't do it. He thought imipramine must be a chemical straight jacket. Others were not as articulate but just as disbelieving.

The publication of DSM-III was also in 1980. By including Panic Disorder in a manual for clinical diagnosis, it legitimized research in Panic Disorder, which took off after 1980. That research in psychiatry requires the prior development of a clinical category is illogical. However, that this should lead to rejection of clinical categories, as in the NIMH RDoC program, is glib and misleading [10].

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Donald F. Klein

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## Preface

This book was carefully edited to condensate the accumulated knowledge on panic disorder produced by a network of very productive researchers at this subject in recent years. This network includes distinguished professors and renowned researchers who enthusiastically participated from Brazil, United States, Italy, Spain, United Kingdom, Mexico, and Switzerland.

We present several aspects of panic disorder including historical aspects, neurobiology findings, connections with the respiratory and cardiovascular systems, pharmacological and nonpharmacological treatments, psychopathology and genetics, among others.

We recommend it to anyone who has an interest in anxiety and panic disorder, specially psychiatrists, clinical psychologists, postgraduate students, and researchers in this area.

Rio de Janeiro, Brazil

Rafael Christophe R. Freire  
Antonio Egidio Nardi



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