

Barry Blackwell: Pioneers and Controversies in Psychopharmacology

Chapter 13: The Anxiety Enigma

The Anxiety Enigma in Controversies

Preamble

This chapter, written in 2014 remains true today. Its message is reinforced by the philosophy of Frank Berger (Chapter 10), the work of Karl Rickels (Chapter 13) and most of all the skill and duplicity of the pharmaceutical industry in garnishing the rewards of American infatuation with pills skillfully advertised for new anxiety diagnoses that the DSM system created, (Chapter 18). As I write this preamble *The New York Sunday Times* (December 17, 2017) sits beside me advertising Professor Ronald Siegal's 24 lecture series on CD, "*The Science of Mindfulness: A Research Based Path to Wellbeing.*" Founded on work by the Harvard psychology professor (Siegal, 2009) it is promoted for "Its application to a wide range of issues, psychological, social and medical... joining ancient wisdom practices and scientific methodology in forging new possibilities for living." The promise of Mindfulness Meditation is that it is available directly to the public at an affordable cost without the parsimony of the medical insurance companies.

Time alone will tell to what extent "anxiety" is an existential manifestation, a medical disorder or an invention of the drugs that suddenly arrived to treat it.

Reference:

Siegal RD. *The Mindfulness Solution: Everyday Practice for Everyday Solutions.* Guildford Publications, 2009.

THE ANXIETY ENIGMA

By

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Anxiety has become such a commonplace word in both culture and medicine that it is difficult to view it as “mysterious or puzzling” (*enigma*, Oxford English Dictionary – OED). But viewed through the lens and across the trajectory of my 50-year career the word seems apposite. This essay examines a brief history of the term, its semantics, its nosology and natural history, the evolving and contemporary role for medicine or other forms of therapy and its putative philosophical or existential purpose.

The concepts of “stress” and “anxiety” span mainly from the 20th century into the present. A recent book, *“Emotions and Health”* (Carrera 2013), focuses on the negative dimensions of feeling described in medicine from the 13th century; melancholy, fear, anger, revenge and sadness are included but not anxiety. Another book, *“The Age of Stress: Science in Search of Stability”* (Jackson 2013), focuses on stress alone and traces this from Hans Selye, who coined the term. Selye was born in 1907, graduated from Prague University as a doctor of medicine and chemistry at age 22 and emigrated to the United States in 1931 where his prolific research and writings laid the basis of psychosomatic medicine. Only six years later in 1937, Frank Berger graduated in medicine from the same university with strong interests and accomplishments in both pharmacology and microbiology, migrating to the United States in 1947 and going on to develop the first drug to treat anxiety. Both these pioneers in work on anxiety may also have been exposed during their training to Freud’s theories. By 1896 Freud had abandoned hypnosis and neurology and coined the term psychoanalysis. In the 24 volumes of his collected works anxiety is used in the titles for the first time in Volume XX (1925), *“An Autobiographical Study, Inhibitions, Symptoms and Anxiety”* (Strachey 1976), but Pichot (1999) traces Freud’s occasional use of the term to beginning in 1895. Freud’s treatment and theories were accessible to medical students. In 1901 an internist, Kahane, who joined Freud’s Wednesday discussion group with two other medical doctors published *“An Outline of Internal Medicine for Students and Practicing Physicians”* which described Freud’s work in positive terms (Rose 1998). A more focused discussion of semantics relevant to anxiety appears later in this essay.

The seven-year hiatus between my matriculation to Cambridge University (1954) and graduation as a physician from Guy’s Hospital (1961) formed the serendipitous seedbed for modern psychopharmacology. First chlorpromazine (1952), then meprobamate (1955), iproniazid

(1957), imipramine (1958) and chlordiazepoxide (1960), each discovered and introduced for the treatment of psychosis, anxiety and depression. During five years of residency training (1961-1967) lithium was introduced for prophylaxis in bipolar disorder (Blackwell 2014a). Coincident with completion of my training as a psychiatrist, the basic therapeutic repertoire for all the major psychiatric disorders became available. While the number of compounds with similar effects would proliferate they added complexity, expense and novel side effects, but little genuine progress over the ensuing four decades --1970-present.

Although conceptually and clinically the impact of chlorpromazine on asylum care was dramatic (Callaway 2007; Rickels 2013) it was overshadowed in scope and public attention by an upsurge of drugs to treat the far more common symptom of anxiety. In her book, *"The Age of Anxiety"* (Basic Books, 2009), medical historian Andrea Tone details the changing tides of clinical, scientific, political, social, cultural and economic fact and opinion from the advent of meprobamate in 1955 to present times. My personal account of unfolding events is synchronized with the broader perspectives in Tone's scrupulously documented account.

Strange as it may seem in retrospect, prior to the release of meprobamate there was no widespread public or professional appetite for such a product. The manufacturer's own Gallup poll of 100 primary care physicians showed no enthusiasm or willingness to prescribe (Berger 2014). Nevertheless, Tone notes that within five years (1955-1960) meprobamate had been prescribed by three quarters of the physicians in America, success attributable to a climate of public approval for a stigma-free adjunct to "enhance the functioning of successful people," an affordable remedy for "the budget conscious and time strapped," readily available from primary care physicians as a tool to stifle the anxiety blamed for "a myriad of medical disorders." So, initially the drug was prescribed by general physicians for benefits perceived as primarily existential and medical, not psychiatric or biologically based.

Enrolled in University, I was oblivious to events occurring in America and, in retrospect, uncertain of their impact on British medicine or any potential import for my planned career. Personal concerns were more pressing; the second year at Cambridge marked a Rubicon and a point of no return was Organic chemistry. I failed this subject in high school and did so again during my first year at university. It was "three strikes and you're out," the major obstacle to becoming a doctor. My final attempt would be in 1955, after I obtained permission from my

college tutor to return for the summer session. This was a subject I found incomprehensible and I knew my chances were slender. The tutor greeted me kindly, sat me down and began, “Blackwell I know you failed the exam but there’s been a mistake, your name is published in the pass list. I believe you’ll make a good physician so I don’t plan to say anything” (Blackwell 2012).

This good fortune saved my career and fed an arrogant assumption that chemistry was redundant for medical practice, an opinion bolstered by becoming among the first of my Cambridge peers to receive a doctoral degree – in pharmacology and medicine. In the same month that I obtained my reprieve, April 1955, Frank Berger filed an application with the FDA in America for approval of meprobamate. Born 21 years before me (1913), Frank displayed an unusual aptitude for basic science in medical school. Concerned that his fellow students might fail pharmacology finals (it was two strikes and you’re out in Prague), he set about reading all the pharmacology texts and printed a student guide to the exam which he sold to support his tuition (Berger 2014). Following medical school Frank worked in microbiology research until March 1939 when Hitler invaded Czechoslovakia and he and his wife escaped to Holland, hoping to migrate to America. When their visa was revoked they arrived destitute in England without a medical license, no money, no friends and no job. His wife was pregnant and cared for in a Jewish shelter; Frank slept on park benches and local lock-ups, but eventually found work as a doctor in a refugee camp and then as a microbiologist. He developed a way of extracting penicillin from the liquid it was grown in and his publication in *Nature* (1944) led to a job at British Drug Houses where he worked on a non-toxic way to preserve penicillin. Among the drugs studied was mephesisin, a muscle relaxant with unusual “tranquilizing” properties in mice (Berger’s own term). In 1947 Frank and his wife migrated to America and two years later he was hired as research director for Carter Products (a subsidiary of Wallace Pharmaceuticals), the manufacture of “Carter’s Little Liver Pills.” It was their only product. Here Frank worked to develop a longer acting congener of mephesisin. This was meprobamate, marketed as Miltown, named after a small town close to where Frank worked (Berger 2014).

Suffice to say I was ignorant of these events or their impact, immersed in life as a medical student, playing vigorous rugby at the University level, rowing for my college, frequenting the local pubs and on my way to an indifferent Master’s degree in Natural Sciences.

At Guy's Hospital in London I captained the oldest rugby team in the world while gradually becoming absorbed in learning the basic skills of my profession in a series of intense three- to six-month student internships. I hardly noticed the unfolding revolution in psychopharmacology and remained blissfully unaware of the events in America which Andrea Tone describes: "The medical management of anxiety had gone mainstream. Miltown encouraged greater acceptance and dependence on lifestyle drugs. It stitched together patients, doctors and pharmaceutical companies in a web of psychotropic drug consumption, setting the stage for the massive expansion of the country's pharmaceutical armory."

Within this widespread approbation Tone documents muted expressions of concern that would later bloom into full blown controversy. In 1956 Berger had convened a national conference on tranquilizers under the auspices of the New York Academy of Sciences (Berger 1957). Perhaps mistakenly, he invited Aldous Huxley to give the opening speech. Author of "*Brave New World*," Huxley's novel had showcased "soma," a drug used by a totalitarian state to pacify its citizens "with all the advantages of Christianity and alcohol; none of their defects." Although Huxley subsequently insisted this was "only a literary fiction," he welcomed the arrival of new tranquilizing drugs that were less costly than agents previously used by humans in the search for "self-transcendence and relief from tension." Berger's paper, in contrast, was a scholarly review of the pharmacological differences between major tranquilizers like chlorpromazine and minor tranquilizers like meprobamate in animal and human studies. Throughout his life Frank insisted that his drug was only intended to treat biologically based anxiety disorders and had no capacity to endow "new insights, philosophic wisdom or creative power" (Berger 1970).

The need to distinguish between Huxley's enthusiastic endorsement of meprobamate and Berger's modest claims obviously struck home to some in the audience. Andrea Tone notes that The New York Academy of Medicine promptly established a Subcommittee on Tranquilizing Drugs whose final prescient report she quotes: "Anxiety and tension seem to abound in our modern culture and the current trend is to escape the unpleasantness of its input. But when has life ever been exempt from stress? In the long run is it desirable that a population be ever freed from this tension? Should there be a pill for every mood or occasion?"

This debate reminds us that human attempts to stifle anxiety and induce a state of tranquility (OED "...*Calm, free from disturbance*") are as old as recorded history including soma,

alcohol, marijuana, chloral, bromides, opiates and barbiturates. All of which share the common property of producing an immediate, sought after change in mental state but in many cases associated with dependence, tolerance, addiction and accidental or intended death by overdose. The widespread use and future controversy concerning minor tranquilizers would hinge to a large extent on this equation.

Back in Britain at Guy's Hospital neither the early evolution of psychopharmacology nor the concerns it engendered influenced my choice of psychiatry as a future profession. This decision was based entirely on a traumatic experience caring for a pregnant woman anxious and terrified of childbirth in the care of an obstetrician who declined to discuss my request for a psychiatric consultation or the possibility of a Caesarian section in favor of a Pitocin drip. I sat by her bedside as she screamed through labor and then wrote a letter, published in the *Lancet* on "*Human Relations in Obstetrics*" (Blackwell 2012).

After graduating I spent six months as a senior intern in Neurology at the Whittington Hospital in North London where I gained a closer relationship with the new drugs likely to impact my future career in psychiatry. The neurology service admitted two kinds of patients suffering from the side effects of psychotropic drugs. My chief resident and mentor had described, in a letter to the *Lancet*, a patient who suffered a subarachnoid hemorrhage while taking tranlycypromine (Parnate). He drilled into me the importance of taking a drug history in such cases, knowledge that formed the impetus for my future work as a first-year psychiatry resident on the MAO inhibitors and interactions with tyramine containing foods.

More common were many cases of barbiturate overdose admitted to a neurology bed from the emergency room. Despite the inroads being made by meprobamate and chlordiazepoxide, the barbiturates were still commonly prescribed in primary care to patients with anxiety, insomnia and, I suspect, others with early or covert depression and undetected suicidal thoughts. I chose this as a research project and sat by each patient's bedside injecting brain stem stimulants keeping them alive until recovery. This study won the hospital's annual research award and the results were published (Blackwell 1964). This experience colored my view that the newer benzodiazepines were safer and preferable to the barbiturates. Tone notes the massive amount of clinical research conducted on chlordiazepoxide (Librium) prior to its release in 1960, "involving 2000 physicians, more than a dozen leading institutions and upward of 20,000 patients." The studies covered a broad

spectrum of clinical conditions and outpatient populations backed up by sophisticated marketing strategies designed to “position Librium as the country’s newest ethical blockbuster.” Not everyone agreed with this body of information or my own conclusion that chlordiazepoxide represented a genuine step forward. One of the earliest textbooks in the field (Shepherd, Lader and Rodnight 1969) commented: “Although there are interesting differences between chlordiazepoxide and barbiturates, the clinical differences are minimal.” Malcolm Lader, my fellow resident and contemporary at the Maudsley who became one of the world leaders in benzodiazepine research, would later admit responsibility for this statement and repudiate it (Lader 1998). By the end of 1960 Librium had captured 20% of the market and doctors were “writing 1.5 million new prescriptions every month.”

While it was clear that chlordiazepoxide did not pose a serious overdose problem there was growing concern surrounding possible dependence due to withdrawal effects after rapid cessation. Leo Hollister’s work would demonstrate significant problems after high doses of chlordiazepoxide, later replicated with diazepam, raising concerns and controversy about abuse potential (Rickels 1966).

This was the status quo when I began my residency training in psychiatry. As a neophyte devoid of board certification in medicine, I began at the Bethlem Hospital in the country, but after six months, due to my early work on the MAOI-cheese interaction, was promoted to the Professorial Unit at the Maudsley where we wore white coats and worked under the eagle eye of Sir Aubrey Lewis. The Maudsley at this time was renowned for its descriptive and empirical approach to psychiatry in the European tradition, decidedly at odds with psychoanalysis. Descriptive implied a commitment to nosology and the natural history of disorders while the empirical approach demanded rigorous scientific evaluation of therapeutic claims. In this regard it is worth noting that while the FDA implementation of the Harris-Kefauver amendments in America had stimulated a large volume of relatively rigorous research on the safety and efficacy of new psychotropic drugs, including the benzodiazepines, anxiety as a medical disorder was an orphan compared to what had been studied and was known about in schizophrenia and melancholia. There was no Kraepelin, Bleuler, Jasper or Leonhard nor did the psychoanalysts’ interest in “neurosis” meet empirical standards. In many ways anxiety as a medical disorder was an invention of the drugs that had suddenly arrived to treat it. This created a scientific Catch 22 –

it was difficult, perhaps impossible, to study the nosology and natural history of a condition that was already being treated with drugs designed to stifle its symptoms and modify its course.

This is the moment to take a closer look at the semantics of anxiety in order to better understand what exactly might be being treated. Pichot (1999) provides an excellent historical account of the words used to convey anxiety in English, French and German including the differences, ambiguities and overlap in terms. He concludes his essay as follows, “The existing ambiguities, relics of the past histories of the words, are indications of the still incomplete clarity of the corresponding concepts.” What follows is a more detailed discussion of the current semantic situation in English. Bearing in mind these overlapping and ambiguous synonyms bring to mind Humpty Dumpty’s claim that, “When I use a word it means just what I choose it to mean, neither more nor less” (Lewis Carroll in “*Through the Looking Glass*”). All the definitions cited are from the OED.

Anxiety: *A nervous disorder, marked by excessive uneasiness.*

Fear: (1) *An unpleasant emotion caused by threat of danger, pain or harm* or (2) *Feeling anxious on behalf of...*

Anguish: *Severe mental or physical pain or suffering.*

Apprehension: *Anxious or fearful anticipation.*

Dread: *Great fear or apprehension.*

Angst: *A strong feeling of anxiety or dread.*

Panic: *Sudden uncontrollable fear or anxiety*

With the exception of anxiety, panic and anguish the other four definitions combine anxiety and fear as alternate words. Even fear has anxiety as a second definition. Anxiety is qualified by calling it a “disorder” with (presumably) medical implications. Panic is qualified by “sudden” fear or anxiety. Anguish is the only word that combines mental and physical suffering. Pichot (1999) points out that the original Indo-European roots ‘ango’ or ‘anxio’ and their derivatives focused mainly on physical discomfort so it is surprising that none of the above, with the exception of anguish, include physical sensations. Even stress (OED: *mental or emotional strain*) omits any mention of bodily concerns. The word ‘Panic’ was re-introduced into the English speaking medical

lexicon in 1962 (Klein and Fink, 1962), but Pichot notes that the first application of the word to a psychiatric symptom was by Henry Maudsley (Maudsley 1879) when he described typical episodes of panic in patients suffering from melancholia.

The question of whether fear and anxiety are separate or synonymous terms is often debated by pharmacologists with the assertion that fear is a reaction to a “real” threat accompanied by a full blown “flight or fight” physiological response contrasted with a lesser form of arousal, anxiety, due to an implied or imagined threat. This dichotomy is not consistent with common usage where the terms “I am afraid of...” and “I am anxious about...” are used interchangeably. Nor is it consistent with the fact that a full-blown panic attack (as seen in emergency rooms) has all the psychic and physiological characteristics of fear absent a “real” threat. Conversely, PTSD arousal is evoked by only the memory of a real event.

Further semantic confusion is added by noting that “anxious” has an entirely contradictory, second OED meaning: “Very eager and concerned to do something or for something to happen.” This qualification is added to the verb but not to the noun. Tone notes that this second definition appeals to those who see anxiety as the driving force for ambition or “the seedbed of human and artistic talent.” We will see later how these opposing views of the role of anxiety play a part in lay and professional responses to an escalating use of minor tranquilizers in society. Interestingly, the alternate view of anxiety was apparent in the earliest stages of developing drugs to treat it when the psychoanalytic mainstream that dominated American society believed stifling anxiety would diminish motivation for therapy. Young psychiatrists in the USA, among them some future psychopharmacologists, were admonished that their eagerness to prescribe drugs was either a defense against verbal intimacy or a sadistic counter-transference towards a treatment refractory patient.

In the scholarly debates and discussions during teaching conferences at the Maudsley anxiety was seldom a topic worthy of consideration. My own interest about its ambiguous but pervasive influence arose out of an unusual study designed and carried out with my fellow resident and lifelong friend, David Taylor. In 1964 the gold standard, and perhaps the only standard for clinical evaluation of a therapeutic claim, was a meticulously designed, preferably double blind, controlled study with a well-crafted null hypothesis. My untidy mind thought this was slightly daft. How could one discover anything new or what was happening in the real world if you were already

single-minded or certain about the outcome? Immersed in animal experiments on rats injected with MAO inhibitors and administered cheese or tyramine via a duodenal tube, I was eager to discover why my mentors were using these drugs and with what results. Perhaps such a study would generate new hypotheses. So, David and I designed a study of all the patients prescribed these drugs by the five consultants working in the Maudsley outpatient clinic. We called it “An Operational Evaluation” but, in retrospect, it was a very early effectiveness study – a primitive, unfunded, CATIE study (Blackwell and Taylor 1967). Outcome was determined not by the usual diagnostic and demographic variables but by whom and how the drugs were prescribed. The enthusiasts prescribed the MAOI earlier, more often and got better results. A pertinent finding of this study was the way in which availability of antidepressant drugs influenced diagnosis in the interplay of anxiety and depression first noted by our namesake Henry Maudsley 85 years previously. In the triennial compilation of diagnostic statistics at the Maudsley Hospital (Hare 1963) a significant change occurred in diagnostic habits between 1955-1957, the meprobamate era, and 1961-1963, the MAOI antidepressant era. In the latter time frame the diagnosis of depression increased by 8.5% while the diagnosis of anxiety disorders (anxiety, hysterical and obsessional neuroses) declined by a corresponding 9%. Reviewing the chart notes of one enthusiastic and successful prescriber we came across the following case:

A 48-year married woman was diagnosed initially as suffering from an anxiety state. The clinician’s verbatim comment at that time was, *“The prognosis for such an anxiety state, unless there is an underlying treatable depression, is poor. It is possible however that treatment with an MAOI might benefit her.”* After three months treatment the clinician noted, *“Although she never looked depressed before, she looks less depressed now.”* (Blackwell and Taylor 1967; Blackwell 1975).

Further results are pertinent: Parstelin, (a combination of tranlylcypromine and low dose trifluoperazine), obtained statistically better outcomes than three other MAOI alone and overall the addition of a benzodiazepine improved outcomes from half to two thirds. Two thirds of patients treated with MAOI took them for only six months by which time 50% had achieved a good outcome.

At the completion of my psychiatric residency (1967) I had published more than 20 articles on a variety of topics, penned anonymous leading articles and annotations for the Lancet, acquired

a Master's degree in Philosophy and a Doctoral degree from Cambridge in pharmacology and medicine. But I was uncertain about a career in psychiatry. Clumsy from birth, I was not cut out for the fine finger work required for animal research: I shattered expensive glass pipettes and smudged endless smoked drums. Besides, I preferred humans to rodents and felt reluctant to relinquish the breadth of medicine for the narrower scope of psychiatry. The commanding officer of my reserve army Field Ambulance was a close friend and looking for a partner in his suburban London practice. So, I decided to try my hand at family medicine.

It was a fortuitous decision, though my time in the practice was brief it was productive and educational. Not only did it broaden my horizons by exposing me to the mild and early manifestations of affective disorders in primary care, but my contemporary and fellow resident, David Goldberg, was looking for a site to validate a new survey instrument (The General Health Questionnaire - GHQ) designed to study the prevalence of psychiatric disorders in a primary care setting. Wide disparities in this measure suggested it might be an "eye of the beholder" phenomenon. The fact we were identically trained in psychiatry but I now operated as a family doctor under time constraints and a medical focus created a unique design free of ideological or cognitive biases. The GHQ went on to become one of the first survey instruments for its designed purpose, translated into many different languages and used worldwide.

We published our findings in two articles in the British Medical Journal: the first on "*Psychiatric Interviews in Family Practice*" (Blackwell and Goldberg 1968) and the second on the psychometric properties of this "*New Method of Case Identification*" (Goldberg and Blackwell 1970). In a 200-patient sample, 20% had "conspicuous psychiatric morbidity" the majority were minor affective illnesses, two thirds of which had returned to normal in six months. My discussion noted that patients rarely presented with psychiatric symptoms but used medical metaphors; feeling "rundown," "fighting off flu," "low blood pressure," often coupled with requests for vitamins, iron tablets or a tonic. Closer enquiry revealed symptoms often present in both anxiety and depression. For example, a stereotypical patient would be a 30 odd year old mother of children who complained of lack of energy, sleeplessness, irritability with her kids, accompanied by guilt feelings and low sex drive. A study of symptoms in Anxiety States and Depressive Illness (Roth et al. 1972) found that they shared sadness, pessimism, irritability, guilt, agitation and suicidal thoughts.

Unused to seeing people in the earliest stages of affective illness, faced with diagnostic ambiguity and overlap, I chose to prescribe low dosages of a sedative tricyclic antidepressant (75 mgs of amitriptyline, Elavil) to be taken two hours before bedtime with advice that, as sleep improved, coping capacity, patience and sex drive would gradually return to normal. David Goldberg saw this pattern reflected so often in my chart notes he enquired if I believed the practice was Elavil deficient! In an interview by Tom Ban in 1999 for the Oral History of Neuropsychopharmacology (OHP) (Volume 9 ed. Blackwell 2011), Leo Hollister, asked about his classification of depression, replies: “Deniker’s group has classified a mixed anxiety depression syndrome. We called it anxious depression. We brought attention to that and it is beginning to be a popular idea. People are beginning to think there is a sort of co-morbidity or, maybe anxiety is part of depression. I remember raising this question with a psychiatrist and he said, ‘I can imagine somebody being anxious and not being depressed, but I have trouble imagining somebody being depressed and not being anxious. I thought that was not a bad summary statement.’” Elsewhere, Leo speculates whether the benefit and return to normal with antidepressants is due to improved sleep (“*sleep that knits up the raveled sleeve of care ... balm of hurt minds,*” Shakespeare: Macbeth), delayed antidepressant effect, a placebo response or some combination. In his 1998 OHP interview by David Healy, Karl Rickels (Volume 4 ed. Levine 2011) talks about his own work with Covi and Lipman in a series of studies on depressed and anxious patients that “clearly showed that benzodiazepines had only an anxiolytic and no antidepressant properties. In contrast antidepressants had both anti-depressant and anxiolytic properties.”

It took me only a year to realize that while I enjoyed some aspects of family medicine it was not the best career for someone with research interests and a need to know each person in depth. There was plenty of psychiatry in medicine and enough medicine in psychiatry.

In September 1968 I migrated to the United States, accepting the position as Director of Psychotropic Drug Research at the Wm. S Merrell pharmaceutical company in Cincinnati, Ohio. Like many others, the company was eager to explore the commercial opportunities in this new field; as Tone notes, by that time Valium had become the “first \$100 million brand in the industry.”

However, this was hardly the best time to become an industry physician. Merrell had recently marketed thalidomide as a safe drug to treat insomnia in pregnancy only to discover it produced fetal abnormalities of a particularly repugnant kind, phocomelia or deformed limbs. A

zealous FDA physician, Frances Kelsey, had detected flaws in Merrell's new drug application (NDA) to the FDA, leading to criminal indictments. In defense, Merrell "lawyered up" and everything we scientists wanted to do was legally adjudicated with a stifling effect on innovation.

But there were compensatory influences. Merrell had retained one of America's leading psychopharmacologists and a pioneer in the field, Frank Ayd, as a consultant. A devout Catholic and father of 12 children, Frank had lived in the Vatican and served as advisor to the Pope on ethical and psychiatric matters. He was also a founding member of both the CINP and the ACNP. Frank took me under his wing and introduced me to most of the leading psychopharmacologists in America. We made presentations to the ACNP and published together (Blackwell and Ayd 1971) on research in prison volunteers and Frank sponsored me as a member of the ACNP in 1970. Frank and I were both involved in teaching our new discipline to public and professional audiences; out of this we developed the idea of bringing together all the scientists in Europe and America who had made original discoveries in our field.

The conference took place in Baltimore and the proceedings were published in 1971 in a book we co-edited, *"Discoveries in Biological Psychiatry"* (Ayd and Blackwell 1971). Among the presenters were Frank Berger, on *"Anxiety and the Tranquilizers,"* and Irv Cohen, on *"The Benzodiazepines."* By this time the latter drugs were capturing the market, pushing meprobamate into the twilight. Less clear at the time, but viewed in retrospect, Berger's presentation was both humble and prescient. His opening statement is worth repeating:

"If anything distinguishes man from the animals it is that humans are anxious. Animals react only to real dangers and threat by showing fear. Humans also react to unreal danger, or anticipation of it, by showing anxiety."

Frank did not present minor tranquilizers as a panacea for all human anxiety; his discussion of anxiety as a potential motivating factor ranged from John Locke, the English philosopher (1689), to Rose's contemporary view (Rose 1958). He concedes that if this point of view is correct, *"It would be inappropriate to use drugs."* Frank then defines the emotional and behavioral characteristics of anxiety as a discrete disorder based on Cattell and associates development of a rating scale that defined a specific reaction pattern (Cattell and Scheier 1958), including, lack of confidence, a sense of guilt and worthlessness, an unwillingness to venture, a dependency, a readiness to become fatigued, irritable and discouraged, uncertainty about one's self, suspicion of

others and a general tenseness.” Finally, Frank cites electrophysiological evidence localizing anxiety to the thalamus, limbic structures and frontal lobes with the suggestion that electrical coagulation or stimulation can evoke or ablate this emotion (Delgado 1969) and concluding with the claim that meprobamate has a *“selective action on those specific areas of the brain that represent the biological substrate of anxiety.”*

Frank Berger’s conclusions are reflected in the following comments made at different points in his presentation:

Anxiety (by which he is alluding to the syndrome outlined above) is “usually one of the symptoms of a disease, such as a neurosis, depression or schizophrenia.”

“By showing it is a symptom of disease... anxiety is not present at all, or is only transiently and to a small extent, in normal healthy individuals.”

“Considerable evidence shows that anxiety is due to a dysfunction of a part of the brain and that it is a symptom of a disease state. Consequently, it should lend itself to medicinal treatment like many other symptoms of disease.”

“Tranquilizers, by attenuating the disruptive influence of anxiety on the mind, open the way to a better and more coordinated use of existing gifts. By doing this they are adding to the happiness, human achievement and the dignity of man.”

Berger did not consider phobias and obsessional states to be anxiety disorders. He notes that they respond to cognitive behavior therapy which is “of no value in the treatment of true anxiety states.”

In a final paragraph Frank states: “It would be wrong and naïve to expect drugs to endow the mind with new insights, philosophical wisdom or creative power.”

Frank Berger’s commentary was rendered in the context of DSM 1 and 2 (Pre-1980) diagnostic concepts; some of its conclusions hold water today and others not. Frank was a brilliant pharmacologist in the lab, but rusty clinically and certainly not a nosologist or a practicing physician at this stage in his career. He considers anxiety a symptom, but describes a syndrome of eight or more symptoms that are today scattered among post DSM 3 Axis 1 and Axis 2 disorders. Contemporary evidence for cerebral localization of this aggregation of symptoms is questionable

and some of the historical research dubious (Blackwell 2013). But Frank's insistence that minor tranquilizers were not a panacea and did not confer new skills or attitudes is prescient in view of the alarming increase in their use that was about to occur, blurring the boundary between focused and indiscriminate prescribing. Frank's opinion that the use of such drugs should be limited to attempts to stifle the troubling symptoms of defined disorders and not towards what became known as "problems of everyday living" remains valid and was a point of view to which he clung tenaciously for his entire life. Following Frank's death in 2005 at age 95, his wife Christine compiled and published a lifetime of his written philosophical reflections in the book "*A Man of Understanding: A noted Scientist's Guide to Happiness and Success*" (Blackwell 2014b). This remarkable book contains only a single comment about Frank Berger's famous discovery: "*There are misunderstandings about tranquilizers, about what they can and cannot do, who should use them and why use them. They may make you feel normal again, able to cope again, but they are no substitute for philosophy.*" This statement is on the book's back cover, but while the pages are divided alphabetically into 60 topics, including Frank's own ideas and those of others, "Anxiety" and "Tranquilizers" are not among them.

Still, there remains an ambiguous line between Frank's 1970 assertion that drugs, by coordinating existing gifts, add to human kindness and achievement and the implied claim of his postmortem book that philosophy alone and not drugs are a guide to happiness and success. This may be a false dichotomy. Anxiety alone can impair performance and hamper restitution and recovery, while stress is often occasional or intermittent rather than unrelenting. It is possible, indeed likely, that a short, drug-induced respite from anxiety allows a person to recoup their equanimity, reassess their resources and successfully combat future episodes of anxiety. Frank's contention that anxiety is not, or only seldom, an attribute of "normal" people is tendentious and philosophically inaccurate. Anxiety is a ubiquitous companion of the human condition and life without it is an unattainable Utopian ideal.

By the time our book on Discoveries was complete, I realized that, while I had enjoyed and benefited from my time in industry, my self-image and esteem were tied to education and research rather than product development and commerce. Merrell had allowed me one day a week to teach psychopharmacology to medical students and psychiatric residents; this led to an offer to reverse

roles, to become a fulltime Professor of Psychiatry and Pharmacology at the University of Cincinnati with one day a week consulting to industry.

My turn to academic life included the opportunity to make piecemeal observations and contributions to the rapidly developing field of anxiety and its treatment. The decade, 1960-1970, gave birth not only to new medications but also to rating scales with which to measure their effects. Initially this mainly took place in the Veterans Administration (VA) collaborative study groups and the Early Clinical Drug Evaluation Units (ECDEU) linking State hospitals and developing Academic centers. The remarkable speed of development and widespread use of these instruments is epitomized by Doug McNair's survey on the use of the Psychiatric Outpatient Mood Scale (POMS). By 1991 there were 2,000 articles and it had been used in almost every branch of medicine (McNair 1997).

While indispensable to drug studies, rating scales are inevitably reductive (to a numerical score) and reveal little about the individual persona and pattern of response to interventions. Al Raskin notes Jonathon Cole's comment that rating scales are "quick and dirty" (Raskin, 1997). My own approach was obverse -- to attempt to understand each person's unique response to stress and what is generically called anxiety.

I developed and used the following approach with both patients and students, singly and in large groups. This was not a research project but was designed to understand and demonstrate the polymorphous and unique individual cognitive and somatic responses to stress for patients and doctors. It could be considered a "stress biopsy," perhaps especially useful to primary care physicians dealing with somatizing patients (Blackwell 1996). The individual(s) is/are told to choose and imagine a situation in which they typically feel anxious or stressed, such as public speaking, taking a test, arguing with a spouse, confronting the boss etc. Then they are asked to close their eyes and imagine the scene. After a brief pause, the subject is asked to choose one word that best describes the cognitive emotion - stress, tension, fear, worry, apprehension, doubt etc. Still with eyes closed, they are next asked to find a word that best describes any bodily sensation; palpitations, sweating, muscle tension, breathlessness, abdominal cramps, urge to urinate etc. Finally, they are to decide whether the cognitive or somatic response predominates. In classroom demonstrations the diversity of responses is illuminating while the predominance of emotion or bodily sensation tends to split evenly.

Once a person has identified their own pattern of response they are equipped to keep ratings that help to identify linkages between these feelings and everyday hassles as well as the benefit of any treatment.

Teaching psychopharmacology to medical students I also felt it was important they learn about the placebo response, especially as it related to sedative and stimulant drugs. Together with a pharmacology faculty member and a statistician, we designed a class experiment for first-year students explained as a “double-blind comparison of a stimulant and a sedative drug.” Students were randomly assigned to receive one or two blue or red capsules and completed a rating scale later in class to record their responses in mood and side effects. They also worked in pairs to measure pulse rate and blood pressure.

Both the red and blue capsules were placebos containing an inert powder. Based on the existing literature, faculty predicted the nature, size and frequency of the treatment responses and sealed them in an envelope to be opened at the following class after the results had been tabulated and analyzed. When the envelope was opened every prediction was confirmed. A third of the students reported changes in mood; red capsules produced more stimulant responses, including increases in pulse rate and blood pressure; blue capsules were more sedative. Two capsules of either color produced more effects than one. A few students also reported miscellaneous “side effects.”

Both faculty and students were surprised and delighted, but the Chair of the department expressed ethical concerns about the deceit involved. The students felt differently and awarded me their “Golden Apple” as the teacher of the year. The article was published in the *Lancet* (Blackwell, Bloomfield and Buncher 1972) with the title, “*Demonstration to Medical Students of Placebo responses and Non-Drug Factors.*” If it was ever replicated I never heard.

In the department of psychiatry, the psychoanalytic Chair, Maury Levine, who had written a book on psychiatry in family medicine, assigned me to run the Psychosomatic Unit (Two West) at Cincinnati General Hospital. This was hallowed ground, previously managed by George Engel, an internist and training analyst who became widely recognized for advocating the “biopsychosocial” model in practice and medical education. Much in vogue at the time was Hans Selye’s “Stress” model (a word he coined), modified by psychoanalysts in their customary manner by attempting to link specific personality disorders to particular medical diagnoses.

Although the views of Selye and the analysts were embedded and popular among faculty and residents, I was surprised to find a different viewpoint on the unit where the nursing staff, under my future wife Kathie Eilers, were dealing daily with difficult patient behaviors rather than with their subconscious origins. A creative and talented psychologist, Susan Wooley, whose father pioneered the heart-lung machine, was interested in cognitive behavioral approaches. This began a collaboration that lasted five years, spawning a new and different view of psychosomatic disorders and how to treat them (Wooley, Blackwell and Winget 1978). Selye's stress model and the prevailing dogma of psychoneurosis focused heavily on anxiety as an etiologic factor in neurotic and psychosomatic disorders; by the mid-1970s many such patients were also being treated, with little success, by minor tranquilizers.

The new treatment we developed evolved from David Mechanic's (1986) concept of "Illness Behavior" and Howard Leventhal's "Health Beliefs" model. We defined illness behavior as "disability disproportionate to detectable disease" and embarked on identifying why some people, unwittingly perhaps, adopted a sick role, what maintained that and how to reverse it. We identified both avoidance behaviors (primary gain) where patients were trapped in anxiety provoking existential predicaments from which the sick role offered relief and positive reinforcement (secondary gain) from the rewards of the sick role – solicitous caretakers, compensation, litigation and entitlement programs. We recognized that anxiety played a co-morbid role in this syndrome but did not accord it major significance nor did we employ minor tranquilizers for a population that used drugs as props for a sick role that encouraged dependency on health care providers and the drugs they dispensed.

The characteristics of our treatment approach are portrayed in the following vignette (Blackwell 1987):

"It Only Hurts When I Cry"

Lucinda did not look like a clown. She was short, skinny and sad. At her outpatient evaluation the staff was preoccupied with Lucinda's many pains, wheezy chest and ailing heart. Her hobbies hardly seemed relevant.

After she was admitted to the unit, Lucinda's cardiac condition was stable, her pain was chronic and she remained sad and anxious. Lucinda grudgingly agreed that

there was nothing fatal or malignant that caused her suffering, yet she was unable to give up her aches or their audience until she glimpsed solace elsewhere.

Lucinda's slow progress speeded up abruptly soon after she told us that four generations of her family were clowns, including men and women, from grandparents to grandchildren. Each clown created his/her own unique face; either White (the provocative French mime), Auguste (the boisterous German bully) or Tramp (a downtrodden American bum). Lucinda was too old to be Mime and too slender to be Tramp. She chose to be Auguste, a jovial extrovert who jostled the other clowns.

One day, Lucinda brought her clown regalia to the hospital and painted on her face to entertain the other patients. It was a metamorphosis as dramatic as caterpillar to butterfly. Lucinda's crescent lips curved upwards into a smile that spread as far as the crow's feet around her eyes. As she went into her routine Lucinda shed her limp, her shoulders lifted, and her voice lost its weary timbre.

Once clowns are attired they adopt an etiquette. Profanity, smoking and drinking are forbidden. If children rush up to tweak their bulbous nose or tread on their oversize feet, clowns are enjoined to banter back. Irritability and anger are outlawed. Lucinda played the part to such perfection that her aches and anxiety were no longer obvious. Talking about symptoms makes them worse, so in social situations staff and patients are instructed not to complain or enquire. But at morning rounds, when we wear our white coats, we are allowed to ask. Lucinda told us her symptoms were hardly present when she clowned. She sounded surprised, although it was something she had noticed years before but had ignored. Instead, the worse she felt the less she performed, so that even the clowns in her 'ally' left her alone.

When Linda learned she could control her bodily concerns everything else came quickly. She mastered biofeedback, reached her exercise quotas, and slept soundly. When we asked her later what helped the most, she talked about learning to be assertive with her family and no longer letting the kids take advantage. She learned

to set limits on their demands and to get her own needs met without needing to suffer or be sick.

Our time on the unit ran out together. My monthly stint as attending physician was over the day Lucinda was discharged. At morning rounds the patients sit in the day room waiting for us to see each of them in turn. As I looked up I saw Lucinda waiting in the wings, ready to walk on stage. She smiled and sat down. The rehearsal was over and the performance was about to begin. I asked how she would make it in the real world without grease paint. Lucinda laughed and said she thought she could; “now that I can be a clown without letting the kids walk all over me.”

Looking after patients on a psychosomatic unit taught me that many of these symptom sensitive worrywarts (aka ‘somatizers’ or ‘hypochondriacs’) had suffered abusive or emotionally deprived childhoods during which they failed to develop a rich emotional language – so called ‘alexithymia’ – no words for feelings. They communicated distress in body language. An extreme example was a man who volunteered for our study, published in the *Lancet*, on individual response patterns to Transcendental Meditation in patients with hypertension. (Blackwell et al. 1976). We used the “stress biopsy” to develop ratings for each person’s unique symptoms. One middle aged married man could only summon up the single word “irked” to describe the spousal tension from which he suffered.

It was during my time in Cincinnati (1970-1974) that a remarkable and exponential increase occurred in the use of diazepam. Thanks to my industry contacts I had access to national prescription data and was able to obtain and analyze the figures for psychotropic drug use in 1972, published in *JAMA*, “*Psychotropic Drugs in Use Today: the Role of Diazepam in Medical Practice*” (Blackwell 1973). The figures were derived from a monthly prescription audit of 400 drug stores throughout the USA.

The three most widely prescribed psychotropic drugs were all minor tranquilizers: diazepam (34%), chlordiazepoxide (15%) and meprobamate (9.3%), followed by phenobarbital (7%). Thus, only four sedative drugs accounted for 65% of all psychotropic prescribing. Diazepam alone amounted to 49 million prescriptions issued by 97% of general practitioners and internists. Trends for an eight-year period (1964-1972) revealed diazepam alone was responsible for this

increase. A graph showed its use increasing at a 45-degree angle while the use of antidepressants, major tranquilizers, combinations and the three other sedative drugs was almost flat.

Andrea Tone notes that in 1975 Roche Laboratories spent an estimated \$400 million promoting both diazepam and chlordiazepoxide. FDA tests in the 1960s had shown that diazepam was five times more potent as a tranquilizer and muscle relaxant than chlordiazepoxide.

Based on both market research and scientific results from other studies dissection of the prescription data revealed that less than a third of use of minor tranquilizers was for defined psychiatric disorders while the remainder was for a medley of medical disorders prescribed with other drugs. There was no single explanation for this upsurge in use of diazepam. I speculated on the semantic confusion and symptom overlap in categorizing minor affective disorders in primary care and data suggesting that, at least in the short term, early and mild affective disorders responded well to sedative drugs. In a primary care physician's mind anxiety seemed to be a ubiquitous accompaniment and possible contributing cause to a wide variety of putative psychosomatic disorders. In discussing the widespread popularity of diazepam, I noted it appeared to be more potent than chlordiazepoxide or meprobamate, far safer than barbiturates and perhaps equally effective and safer than tricyclic antidepressants with far fewer side effects. Tongue in cheek, I noted that continuation of the current rate of increase in use of diazepam might result in tranquilization of our entire population within the foreseeable future.

Not surprisingly, the data was already raising the question of whether such widespread usage was proper or the degree to which it concealed widespread overuse, misuse or abuse, (Blackwell 1975). A vigorous debate erupted that had both scientific and moral overtones. Later in life I published a vignette that combined my experience in family practice with these mid-career observations, (Blackwell 1986). Here it is:

Twice in a While

“The desire to take medicine is perhaps the greatest feature that distinguishes man from animals.”

William Osler, M.D.

“In every age there are medicines of the moment that divide doctors and patients down the middle. In the 18th century it was opium, in the 19th, bromides and in the early 20th century, barbiturates. The 1960s ushered in the benzodiazepines (like

Valium) in an era of John Kennedy's Camelot. By George Orwell's 1984 it was clear that some people were more equal than others and that these drugs were prescribed unequally and more often to women, the indigent, the elderly and the maimed.

"These new drugs were so safe that they could be used more often and for less reason, raising hackles on segments of the public. Were doctors dabbling in existential predicaments beyond their bailiwick? Were mind tampering drugs being used to correct a social or a chemical imbalance? Was there a medicine for mother-in-lawness or a pharmacologic lid to Pandora's Box?

"These are all appropriate questions to be asked in an age that has amplified 'anxiety' and invented safer 'tranquilizers' to stifle it. But the problem is broader and older than that. It has existed as long as there have been panaceas, physicians to prescribe them and a public eager to seek such comfort. Even if the correct agenda is caretaking and not chemicals, the drugs often help in uncertain ways.

"Which drug it is doesn't really matter. But how it happens does. It could be (and has been) various tonics, liver extract, Vitamin B12 shots, iron tablets or thyroid pills. They are given to patients who visit primary care doctors when life events have loaded up on them. Often these are symptom-sensitive people with the amplifier turned up on their autonomic arousal. They voice distress in body language and invite doctors to collude with diagnoses and prescriptions.

"After they leave the office, life subsides or the drugs placate them. Next time a spouse leaves, a job ends or a child sickens they return expectantly for more. 'Those pills you gave me really helped,' they say.

"Doctors disagree about all this. Prescribers are 'chemophilic hedonists' say the withholders. Withholders are 'pharmacologic Calvinists' say the prescribers. My partner and I sit in friendly disagreement on opposite sides of this chemical fence. She is younger and knows where the benzodiazepine receptors are in the brain. When her patients see me, we talk briefly about their troubles. Some, in a minor

way, seem more tranquil. Others sense the skepticism with which I write their refills.

“‘There isn’t any harm,’ they ask, ‘if I just take them once in a while?’ ‘The only risk,’ I reply, ‘is twice in a while.’”

In the mid to late 1970s it was difficult to discern the extent to which differences of opinion about the benzodiazepines in general and diazepam in particular were driven by science or ideology. Malcolm Lader (1978) in Britain poured fuel on the fire in a *Lancet* article titled, “Benzodiazepines; Opium of the Masses?” His subsequent *mea culpa* (Lader 1998) more than 20 years later, voiced a more temperate opinion, closer to my own: “Short term they are excellent drugs ... the problem is preventing short term use from becoming long term.”

On the American side of the Atlantic, Karl Rickels, based on his own extensive research as related in his recent memoir (Rickels 2013), took a more nuanced, moderate and data driven stand. Some patients (about half) needed long term treatment, others took benzodiazepines only intermittently and some relinquished them entirely. Karl comments on the underlying “puritanical” beliefs among some primary care practitioners in both Britain and America who refuse to prescribe the drugs and, instead, prescribe high doses of anti-histamines. During the last four years of my career, working in the Wisconsin Correctional System, I commented in depth on this unwise practice (Blackwell 2012). The possibility of dependence on benzodiazepines is a poor excuse for substituting drugs with unpleasant or potentially harmful side effects and are, almost certainly, less effective.

Cultural as well as ideological views can color the extent and method of use of the benzodiazepines. While use fell in Britain and the United States it increased globally. Tone cites France and Japan as examples where use increased but for different reasons. In France physicians shunned the DSM 3 classifications preferring to see anxiety as a co-morbid spectrum disorder. “As benzodiazepine use dropped in the United States it increased in France. One study found that 75% of French users had taken pills regularly for over six months. Indeed, France seems to have realized the greatest fear of American journalists and policy-makers, millions of people for whom long term use was the norm.”

The situation in Japan was different: “While the United States and United Kingdom began to experience depression ‘epidemics’ in the late 1980’s Japan, for all appearances remained anxious. Japan did not have a cultural idiom for what in the West would be termed depression. Rather than being muted with medication, a person’s capacity to suffer loss was culturally accepted as essential... In Japan where the predominant culture sanctions cohesion, deference and calm, the pharmaceutical containment of anxiety continues to have political and social support.”

Concerns about overuse, misuse and abuse produced a social backlash with influences on public policy (Blackwell 1975). The state of South Carolina banned the use of minor tranquilizers from the Medicaid formulary (Keeler and McCurdy 1972). A comparison of prescribing in the six months before and after the ban showed 35% was replaced by increased use of a sedative phenothiazine (thioridazine), with known cardiac toxicity, a sedative tricyclic antidepressant (amitriptyline) with anti-cholinergic side effects and barbiturates, all three of which drugs are potentially fatal in overdose. No record was made of the outcome of discontinuing treatment in the remaining 65% of the population. In a public service Indian Hospital (Kaufman et al. 1972), vigorous propaganda directed at staff and patients reduced the use of sedative drugs and minor tranquilizers by a third, but the impact was on meprobamate and the barbiturates, not diazepam.

These unfolding events triggered my own curiosity leading to a focused effectiveness study of unusual design. It was accomplished without funding and by a resident under my supervision as senior author (Winstead et al. 1974). The study, “*Diazepam on Demand,*” was published in the Archives of General Psychiatry. The following is a summary of the results:

“For six months patients admitted to a psychiatric ward were allowed to seek diazepam on demand. Details of 689 requests by 83 patients were recorded. Drug seeking behavior was expressed as a drug seeking index (DSI) based on the ratio of requests to duration of stay. For the whole ward there was an increasing trend in drug use and nurses’ attitudes became more favorable.”

More than a quarter of the patients never sought drugs and requests were made on an average of only once every three days. The features correlated with DSI were anxiety, being female, white and having an elevated psychasthenia scale on the MMPI. The DSI was not correlated with either diagnosis or use of other psychiatric drugs.

Extensive use of anti-anxiety drugs might be reduced by prescribing them “when necessary” rather than on fixed schedules.”

Although not significant, the MMPI subscales that most distinguished high from low users were psychasthenia (bodily preoccupation), hypochondriasis, hysteria and depression.

As the 1970s came to a close a new influence was brought to bear on the term anxiety and its treatment. This was the radical transition to a multi-axial system of descriptive diagnosis. Tone describes this transition as follows: “In DSM 1 anxiety was considered the chief characteristic of psychoneurotic disorders, how a person handled anxiety denoted the type of reaction. DSM 2 (1968) written by the psychoanalytically dominated APA, expanded the number of listed diagnoses... but maintained the discipline’s etiologic emphasis. DSM 3 abandoned the etiologic orientation in favor of diagnostic criteria based on descriptive psychopathology.”

This replaced previous attempts to “understand the meaning of the symptoms and undo its psychogenic cause” (Klerman 1984). Anxiety now became ripe for dissection into contiguous disorders or syndromes. Tom Ban (2014) describes the onset of this process as follows: “Donald Klein in the early 1960’s identified a population within the anxiety disorders that was characterized by recurrent anxiety attacks. He used the term ‘panic disorder’ as a label for this population and the term was adopted in DSM 3 as an Axis 1 diagnosis.”

Other contiguous disorders followed: anticipatory anxiety, phobias, social anxiety disorder, generalized anxiety disorder and obsessive compulsive disorders, all based on the fact that anxiety was the commonest symptom, although not the defining one.

As Tone comments, the creation of a range of medical disorders was an invitation for industry to develop matching treatments. She quotes Leo Hollister’s sage comments” “Making individual brain chemistry rather than social conditions the target for intervention... the new classification of anxiety disorders has vastly broadened the scope of drugs used to treat them.”

Tone goes on to chart the way in which public opinion, shaped by pharmaceutical advertising, came to view anxiety as a medical condition for which psychotropic drugs were the most appropriate treatment: “patients increasingly expected and demanded them.” Karl Rickels (1998) noted how this “medicalization” was facilitated; although cognitive behavior was effective in some types of anxiety disorder this takes time, therapists are in short supply, and patients often

prefer medication. The modern system of health care insurance is reluctant to finance lengthy treatments. There is no doubt that a “quick fix” has appeal to patients crippled by panic; immediate onset of action is the quintessential attribute of all the drugs used historically to curb anxiety. Tone records how this propensity was manipulated by Upjohn’s astute marketing of alprazolam (Xanax) in 1981. Capitalizing on the drug’s rapid onset of action and short half-life, the impending end of diazepam’s patent and Don Klein’s groundbreaking research, the FDA approved alprazolam as “The First and Only Medication Indicated for Panic Disorder” (Upjohn’s promotional advertisement). Although this spurious claim for specificity was soon debunked, Xanax “became a top selling drug accounting for one fourth of Upjohn’s global sales.” Paradoxically, the drug’s metabolic properties contributed both to its early popularity and eventual demise. Its ultra-short half-life, compared to diazepam’s long one, made it difficult to wean and encouraged dependency. Xanax became known in parody as “The American Express Pill; don’t leave home without it.”

In contrast, the slower onset of action of the SSRI antidepressants hampered their popularity as anti-anxiety drugs. First introduced in 1987 for depression, they were later approved by the FDA for the treatment of anxiety disorders. Nonetheless, Tone describes how highly skilled and expensive advertising by GlaxoSmithKline (\$92 million in one year) succeeded in establishing a lucrative niche market for their drug paroxetine (Paxil) in social anxiety disorder.

In the ultimate chapter of her book, “Tranquilizers on Trial,” Andrea Tone notes that for all the misgivings about the commercialization of minor tranquilizers and their shortcomings, “the number of patients who seek medical advice for anxiety has risen from 13.4 million in 2002 to 16.2 million in 2006. Anxiety is currently the fifteenth most common reason for visiting a doctor, eclipsing consultations for back or joint pain and migraine headaches.”

How to summarize this roller coaster overview of anxiety, its manifestations and management? First, a brief historical reprise of the key events, followed by an analysis of their contribution to unravelling the enigma of anxiety.

Anxiety has been the sleeping giant of psychopathology, almost mute through most of history until it erupted on stage in the 20th century. Before then it was a term largely absent from the medical lexicon except for strange physical manifestations. Anxiety’s psychological presence was unveiled in Freud’s theories of psychoanalysis, on the cusp of the new millennium, and its

physical manifestations were explored in Selye's stress model (1930) with "psychosomatic" implications.

At the mid-point of the 20th century, at the beginning of the creative psychopharmacology era (1950-1970), minor tranquilizers entered the picture when meprobamate (1955) followed closely on the heels of chlorpromazine (1952). Following this, there was an astonishing increase in the use of minor tranquilizers to treat anxiety symptoms with a decline of interest in psychosocial theories of etiology or treatment and a shift towards a descriptive system of classification in DSM 3 (1980), with a biological emphasis on etiology. Anxiety moved from being viewed as a spectrum disorder, co-morbid with other forms of psychopathology to being a group of discrete "disorders."

While this chronology and sequence of events is clear, anxiety has remained an enigma, perhaps more so due to a false dichotomy between etiologic and psychosocial theories on the one hand with descriptive and biological explanations on the other. While there may be some scientific truth in either or both these formulations the fact that tranquilizers effectively stifle anxiety has markedly diminished public interest in psychological alternatives at the same time as increasing industry's zeal to market a new drug for every disorder. Contemporary economic trends have reinforced this ideology with concerns about the rising costs of health care coupled with constraints on psychosocial interventions imposed by managed care companies, government funding sources and private insurance companies.

This dichotomy might be resolved if, philosophically and existentially, anxiety was recognized as a protective warning system attached to the unique human attribute of "prescience," an ability to anticipate the future with both its opportunities or possibilities as well as its threats or pitfalls. This carries with it a person's self-awareness of their ability to achieve or fail these outcomes and with it an introspective accounting of their skills or shortcomings, available or not. To the extent there is a perceived gap between the capabilities and actions needed to meet these challenges and their availability, anxiety is aroused. In plain language: **anxiety is the watchdog of the human mind, monitoring its ability to meet life's challenges or match our ambitions; it warns psyche and soma of impending failure in either of these functions. Its manifestations can be stifled by drugs but not its underlying purpose.**

The only psychological defense against anxiety once it is aroused is to avoid the challenge or conflict that evokes it; Freud called this “primary gain.” Stifling anxiety is the pharmacological equivalent.

Anxiety, like pain and fever, is the harbinger of multiple etiologies. In medical school we learned how to interpret fever charts and to define 10 aspects of the pain experience that hinted at causes. The microscope, microbiology, X-rays and the surgeon’s knife revealed the rest. But the brain keeps its secrets better than the body, blurring cause and effect.

That anxiety arrived among the populace in a rush co-incident with minor tranquilizers stifled not only the symptom but also serious interest in pathogenesis and phenomenology. Yet, clearly, there are different manifestations of “anxiety.” In conversion disorders it is allegedly etiologic, but remains silent (*belle indifférence*), while in hysterical and borderline personality disorders it is vocal and robust. The bizarre and metaphorical manifestations of anxiety in schizophrenia differ from the unrelenting and more mundane “angst” of melancholia. The sudden onset of both psychic and somatic manifestations in panic disorder and PTSD differs from the pervasive but losing battle to free anxiety from itself by yielding to phobias, obsessions and compulsions.

Whether anxiety is part of a “disorder” *per se* or a co-morbid warning sign that something is wrong in the mind remains a riddle that brain imaging, neuroscience and generics have yet to solve.

This formulation can be applied to understanding a limitation of the DSM 3 classification of “Anxiety Disorders” that is based on combining syndromes characterized by the predominant and common symptom of anxiety. But this is not always the symptom that is unique to the particular syndrome. These are phobias, obsessions and hysterical conversion, all driven by failed pathological attempts to avoid anxiety. It is noteworthy, but hardly surprising, that minor tranquilizers are not effective or the treatment of choice for these disorders. Instead they respond to cognitive and behavioral strategies that directly confront the anxiety to eliminate it by flooding or desensitization rather than avoidance. Unlike drugs, this can lead to a permanent relief from symptoms. Similarly, conversion disorders are best treated by hypnosis, suggestion, psychotherapy or some combination.

It is in the remaining categories, where anxiety is the only or predominant symptom, that minor tranquilizers play the role of stifling anxiety, often without an attempt to explore its psychological origins or to remediate them. Short term therapy focused on identifying, removing or gaining control over these precipitating factors may remove the need for prolonged tranquilizer use. Pragmatically, this requires an enthusiastic referral and a willing, psychologically minded patient with the ability to pay by insurance or out-of-pocket.

The behavioral re-interpretation of many psychosomatic disorders as forms of “illness behavior” is supported by this formulation. Anxiety is not the cause of the physical condition, but avoidance of anxiety due to an existential predicament (primary gain) encourages the patient to seek relief in the sick role while also reaping its rewards, (secondary gain).

This understanding of the role social and psychosocial factors can play in anxiety and psychosomatic disorders is not a repudiation of contributory biochemical factors in etiology or treatment. The very fact that minor tranquilizers stifle anxiety is proof of that. This is compatible with Frank Berger’s lifelong assertion that while drugs can attend, short term, to the biology of anxiety, only philosophical or psychological understandings and interventions provide long lasting or permanent relief that ends the need for medication.

The contemporary hiatus due to a lack of psychopharmacologic innovation has re-awakened interest in psychosocial interventions including intensive short term dynamic psychotherapy (ISTDP). A recent review of 13 studies (Coughlin and Katzma 2013) and an editorial (Fawcett 2013) summarizes impressive clinical outcomes in populations relevant to this essay. Eighty per cent of patients were symptom free within six weeks at the relatively low cost of under \$1,500 for an average of 13 sessions. In seven studies, including anxiety disorders, chronic headache, treatment resistant depression and personality disorders, 60% of patients ceased taking medication with other significant “medical offsets,” including a reduction in hospitalizations, physician visits, emergency room attendance, drug costs and use of ECT. Since it is almost entirely primary care doctors who encounter anxiety disorders driven by “problems of living,” it is desirable that this form of therapy referral become accessible to them.

As the ideological pendulum swings, perhaps in the future anxiety and its treatment will seem less “mysterious or puzzling” with more productive outcomes if the short-term use of minor tranquilizers is judiciously used to stifle its immediate symptoms coupled, whenever possible, with

psychosocial interventions directed toward removing the precipitants and reducing the costs of long term treatment.

Perhaps the best way to end this essay is with a vignette (Blackwell 1986) that illustrates the intricate interaction of tranquilizer treatment, psychotherapy and social circumstances in the management of a particularly complex case.

Tranquility

“It was a balmy day with warm sand and calm waves lapping along the lakeside. When I teach people to relax, I use these images to graft over the anxious turmoil of their lives. I tucked the thought away. I was here for a respite. Leaving the beach for the swings, I took five-year-old Adam and his friend Christopher, with me. Together we ambled across a wide grassy meadow, its edges in shadow, where pine trees grew and picnic tables sat. In the corner a couple half faced each other. The man was playing a harmonica with expert zest; the woman was strumming a guitar and singing, not in perfect pitch but with a pleasing cadence. Some teen-agers strolling past stopped to applaud, but were ignored. The couple was doing this for themselves.

“Coming closer, I recognized Rosie and Robert. Shortly after I arrived in town Rosie sought me out, describing herself as a ‘schizophrenic who nobody would care for.’ The diagnosis was doubtful but her ostracism was not. Rosie functioned quite well between episodes of wild psychosis which were triggered by unwise intimacies. In over twenty years she had passed many times through the revolving doors that open unwilling hospitals to inhospitable communities. Now she was barred from inpatient units unable to cure her and shunned by psychiatrists unwilling to treat her for the pittance Medicaid sometimes paid. But Rosie was streetwise and a survivor. She found an agency social worker who understood the metaphor of psychosis and an academic psychiatrist who could afford to take a ‘good teaching case.’ Hillary interpreted Rosie’s struggle with an alien environment and I prescribed ‘pills’ to buffer her against it.

“Rosie never treated me as more than her medicine man; she came for tranquilizers, not advice. The major tranquilizer she took with a wise reluctance. The brain is a fine-tuned but well protected organ. The doses of drugs that penetrate its barriers often do damage when they mistake receptors that modify behavior for others that modulate movement. The rhythmic writhing of her lips and tongue testified to that. The minor tranquilizers she took with alacrity. Aimed at the limbic lobes, they brought a rapid respite from anxiety for which she would con me into giving her more with stories of lost scripts and stolen purses.

“We struck a bargain. In return for the drugs she liked, she took the ones I thought she needed. A balance was achieved, between us and within her brain. It was not total tranquility but it was not turmoil and her tongue was still.

“Over the past year Rosie had come to our offices with Robert. He was an older man and a professional musician who served as someone between a friend and a father. The money they made playing the sidewalks and smaller cafes supplemented Rosie’s earnings as an occasional organ tuner. Hillary saw them as a couple and helped them titrate their intimacy. She charged them two dollars and each paid half. On medication visits Robert waited patiently outside my office and the State paid.

“Nothing of this prepared me to recognize Robert and Rosie making music in the park. As the distance between us closed, I became aware of my swim shorts, unshaven face and the two noisy ragamuffins in tow. There was still time to turn away, so I did, unsure of whether I was protecting Rosie’s integrity or my dignity.

“A few days later I passed Rosie and Robert entertaining on the sidewalk outside the Summerfest grounds. I hid in the crowd and hurried past. Shortly after this second sighting Rosie missed her monthly appointment but called to make another. She sounded cheerful and calm but priorities had changed. She needed my medications less than the money she and Robert were making among the crowds. For Rosie it looked like this might be her first tranquil summer.

“Rosie was a real patient and at the time I was treating her Frank Berger was 73 and well into an active retirement as a consultant to many international drug

companies. But he was also a visiting Professor of Psychiatry at the University of Louisville where he, ‘Had the opportunity to learn some psychiatry and see psychiatric outpatients... My feeling was that most people we saw really had no psychiatric disorders. They had problems of living’ Berger 2014). I wish we could have shared Rosie’s story.”

After several weeks of creating and mulling over the anxiety enigma essay my subconscious decided it must have the last word. I dreamt I was the presenter at a celestial case conference presided over by Sir Aubrey Lewis. Seated next to one another, we faced an auditorium filled with leading psychopharmacologists from the creative era. Among them I recognized Jean Delay from France, Malcolm Lader and Michael Shepherd from Britain and Karl Rickels and Don Klein from America. Sir Aubrey told me to begin. So, I presented Rosie’s history ending with my formulation: that after the major tranquilizer had cut short her psychosis and the minor tranquilizer had stifled her existential anxiety, skillful therapy and a vibrant philosophy of living had ushered in her first summer of tranquility.

Questions and comments followed. First up was Michael Shepherd. He expressed wonder and disappointment that, given our work together on the myth of lithium prophylaxis, I could possibly be uncritical enough to think that a single summer of tranquility, following 20 years of relapsing and remitting psychosis, might be anything but a spontaneous remission.

During a vigorous debate Jean Delay, Karl Rickels and Malcom Lader shared their own career contributions and understandings which were closer to my own opinions. The final comment came from Don Klein, justly proud of his pioneer work on panic disorder, he felt my comments about the DSM nosology were too dismissive and he could not see how therapy and philosophy would lead to remission in an illness with such an unrelenting natural history.

As Don sat down I sensed time had run out and turned to face Sir Aubrey. His penetrating gaze met mine and behind his steel framed glasses I sensed the glimmer of a smile. Had I, he enquired, “seen the most recent Japanese literature on this topic?” Checkmated, anxious and crestfallen, I reluctantly admitted my ignorance.

It was not Sir Aubrey’s style to do a presenter’s work for him: “Stop by Miss Marshall’s office in the morning and pick up the journal.” I woke up drenched in sweat, relieved it was only

a dream. My anxiety abated, quicker than Xanax could stifle a panic attack. If only Frank could have been there. But I was dreaming and he was dead.

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