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Protecting mental health in the Age of Anxiety: The context of Valium's development, synthesis, and discovery in the United States, to 1963

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**Protecting mental health in the Age of Anxiety:
The context of Valium's development, synthesis, and discovery in the United
States, to 1963**

by

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A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

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ABSTRACT

This dissertation draws out various facets of the conditions preparing and situating Valium as a marketable substance and cultural entity. It offers one explanation for the widespread prescription and use of Valium in the 1960s.

The post-World War II conceptualization of mental health and illness as a spectrum, with the majority of Americans falling between the poles and therefore either neurotic or at risk, heightened interest in mental health. Increased availability of health insurance brought more Americans to their physicians. National programs – establishment of the National Institutes of Mental Health, the Hill-Burton Act, and formation of a Joint Commission on Mental Illness and Health through the 1955 Mental Health Study Act – recognized widespread support for programs to increase the number of mental health practitioners and facilities focused on neuroses, personality disorders, and outpatients in general. Popular theories, including Walter Cannon’s homeostasis and Hans Selye’s General-Adaptation-Syndrome, promoted the idea that stress, and response to it, were among the most important aspects of health. The American public increased its demands for mental health services. Interplay between these conditions promoted use of psychopharmaceuticals. They were quick to prescribe and therefore allowed doctors to see more patients each day. They somaticized mental illness, bringing it within the boundaries of traditional medical insurance coverage. They did not cure an illness; they reduced symptoms and therefore either allowed the body to

recover, or in an ongoing fashion prevented immature personalities from reaction to stresses in a manner leading to more serious medical problems.

In the 1950s, it became possible to screen chemicals for a tranquilizer. The expense of creating and treating experimental neuroses in animals to screen chemical compounds was prohibitive. Yet these experiments informed pharmacologists; they could identify antineurotic or tranquilizing drugs through physical manifestations. With availability of antibiotics, pharmaceutical industries could keep fairly healthy populations of mice, rats, cats, and monkeys for testing. Chlorpromazine's discovery and introduction into institutional psychiatry, around 1953, set out the basic features defining a tranquilizer. By 1958, pharmacologists had the ability and expectations required to inject a mouse with diazepam, check if it rolled off an inclined screen and, observing the tumbling rodent, recognize the ingested molecule was a potentially marketable tranquilizer.

Valium's development and discovery took place when tranquilizers were new and held out promise as mental health prophylactics, mild sedatives, and safe hypnotics. Mild mental illness needed rapid, effective, and fairly inexpensive treatment. Faced with patients undergoing severe or ongoing stress, doctors turned to anxiety-reducing drugs in order to prevent psychosomatic mechanisms resulting leading to any of a dozen physical illnesses. Compared with earlier alternatives – barbiturates, alcohol, major tranquilizers – Valium was safe, nonaddicting, and had few if any dangerous side effects.

CHAPTER 1. INTRODUCTION.

THE VALIUM STORY

Introduction

Valium is a cultural icon, ripe with meanings, rife with contradictions.¹ Viewed in hindsight, its place is remarkably like that of June Cleaver – mother in the iconic 1950s and 1960s television show ‘Leave it to Beaver’ – stuck forever in a perfect home, raising a perfect family, always perfectly calm. She is permanently associated with motherhood and subjugation of female independence to her own need and desire to nurture a family.² And like June Cleaver, Valium is a creation of history; widely associated with memories of a world that never existed.

In the United States, retrospect taints images of Valium. After the Women’s Movement, publicization of the gendered nature of psychiatry stuck to diazepam,³ the

¹ Valium is the brand name for diazepam, a benzodiazepine tranquilizer the Swiss pharmaceutical company Hoffman-LaRoche began marketing in the United States in 1963. Diazepam is no longer produced or sold by the company. Throughout this dissertation I use the terms Roche and Hoffmann-La Roche interchangeably. Company literature similarly uses the terms.

² The character June Cleaver is the mother in the 1950s television show ‘Leave it to Beaver.’

³ For examples of books from 1970s and early 1980s see: Barbara Gordon, *I’m Dancing as Fast as I Can* (New York: Harper & Row, 1979); Eve Barbmann and Sidney M Wolfe, *Stopping Valium, and Ativan, Centrax, Dalmane, Librium, Paxipam, Restoril, Serax, Tranxene, Xanax* (New York: Warner Books, 1983); for a differently gendered book see Anton Holden, *Prince Valium* (New York: Chelsea House, 1992); the theme is less prevalent in books intended to keep youth off drugs, such as Gail

drug marketed as Valium. It became the Rolling Stones ‘Mother’s Little Helper,’ a crutch used by women to cope with minor stresses.⁴ Beginning in the mid-1970s, authors write about Valium as an addictive mental sedative or taming agent, given mainly to women (particularly mothers) for long-term use, often for social reasons.⁵

Winger, *Valium: The Tranquil Trap* (New York: Chelsea House, 1986); the traditional themes appear in the more recent book Joan E. Gadsby, *Addiction by Prescription: One Woman’s Triumph and Fight for Change* (Toronto: Key Porter Books, 2000).

⁴ The song “Mother’s Little Helper” appears on the 1966 record *Aftermath*, by the Rolling Stones.

Kids are different today,
I hear every mother say.
Mother needs something to calm her down,
and though she’s not really ill, there’s a little yellow pill.
She goes running for the shelter of a mother’s little helper,
and gets helps her on her way, gets her through her busy day.

⁵ Decrying sexism in psychiatry played an important part in the women’s movement of the 1960s and 1970s. Although critiques focused mainly on psychoanalytic theory, somatic psychiatry was tarred with the same brush. Thematically the works focus on use of male behavior and socialization to define normal and healthy behavior, thereby define women and female socialization as unhealthy. An excellent example of feminist critiques of psychoanalysis is Juliet Mitchell’s *Psychoanalysis and Feminism: Freud, Reich, Laing, and Women* (New York: Vintage Books, 1974). One of the best known critiques is Phyllis Chesler’s *Women & Madness: When is a Woman Mad and Who is it Who Decides?* (Garden City, NY: Doubleday, 1972). Carol Gilligan’s landmark *In a Different Voice: Psychological Theory and Women’s Development* (Cambridge: Harvard University Press, 1982) challenges the concept that masculine socialization should be the norm for humanity in general, thereby pre-defining female difference as pathological. She argues for redefining models of human development based on interaction rather than dominance and power, incorporating female models of maturity. For an overview of the relationship between mental health and feminism see Stéphanie Austin, *The Influence of the Feminist Movement in/on the History of Psychology* (unpublished thesis, Wilfred Laurier University, 1999); for a more general critique of sexism in medicine see Gena Corea, *The Hidden Malpractice: How American Medicine Treats Women as Patients and Professionals* (New York: William Morrow and Company, Inc., 1977).

For a selection of recent books with focus on addiction to tranquilizers see:

Concerns rose and fell alongside the Women's Movement that prescribing Valium mainly to women indicated society's sexism; the Women's Movement raised awareness of Valium's dangers, the implication being that it thereafter declined in use. Yet sales of Valium, and benzodiazepines in general, did not decline until the late 1970s,⁶ by which point there was both a conservative and liberal backlash against the Women's Movement.⁷ By 1980, Americans conceptualized mental illness and health in new ways,⁸ emphasizing the individual's capacity to cope as boundary between mental

Stephen Fried, *Bitter Pills: Inside the Hazardous World of Legal Drugs* (New York: Bantam Books, 1998); Joan E. Gadsby, *Addiction by Prescription: One Woman's Triumph and Fight for Change* (Toronto: Key Porter Books Limited, 2000); recent books on the history of psychiatry or psychopharmacology, containing substantial sections on Valium include: David Healy, *The Creation of Psychopharmacology* (Cambridge, Harvard University Press, 2002); David Herzberg, *Happy Pills in America: From Miltown to Prozac* (Baltimore: The Johns Hopkins Press, 2009); Seymour Rosenblatt and Reynolds Dodson, *Beyond Valium: The Brave New World of Psychochemistry* (New York: G. P. Putnam's Sons, 1981); Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (Toronto: John Wiley & Sons, Inc., 1997); Mickey C. Smith, *A Social History of the Minor Tranquilizers: The Quest For Small Comfort in the Age of Anxiety* (New York: Pharmaceutical Products Press, 1991).

⁶ In 1975, doctors wrote fifty-three million prescriptions for Valium, in 1978 the number was down to 44.9 million. B. D. Colen, "America's Psychic Aspirin: Valium: Problems with America's 'Perfect Drug,'" *The Washington Post* January 21, 1980.

⁷ The concept of the conservative backlash is generally accepted. A liberal backlash, in this context, refers to increasing belief that the Women's Movement represented goals which denied the rights of the individual, as well as belief by some liberal groups that the women's movement's goals were far less important than that of the broader civil rights movements.

⁸ For a vivid example of the changes compare diagnostic categories in the first, second, and third editions of the Diagnostic and Statistical Manual of the American Psychiatric Association. Overall, the first edition attempts to merge interests of

health and illness. This reshaped Valium's appropriate uses.⁹

Valium as a social entity is a stand-in for discussing the general issue of medicalizing female problems, and the continuing tendency among psychiatrists to use statistically gendered diagnoses. For example, women are more often than men

institutional psychiatrists with the newer focus on neuroses seen after World War II. As a result neuroses are differentiated more than in any previous diagnostic manual. Valium prescribing fit well with the broad categories of 'psychoneurotic,' 'personality,' and 'psychophysiological autonomic and visceral disorders.' The second edition contains only ten types of neuroses, renamed as types of reactions; suggesting short term treatment associated with specific events rather than long-term treatment for personality disorders. It maintains the same categories for psychosomatic disorders aside from renaming 'neurasthenic neurosis' as 'psychophysiological nervous system reaction.' Drug dependence on tranquilizers becomes a recognized condition. The third edition introduces a 'menu' approach; disorders are defined through identification of core and secondary symptoms. This promotes treatment of symptoms as an appropriate path to treatment of mental disorders. American Psychiatric Association. Committee on Nomenclature and Statistics, *Diagnostic and Statistical Manual for Mental Disorders*, first edition (Washington, DC: American Psychiatric Association, Mental Hospital Service, 1952); American Psychiatric Association. Committee on Nomenclature and Statistics, *Diagnostic and Statistical Manual of Mental Disorders*, second edition (Washington, DC: American Psychiatric Association, 1968); American Psychiatric Association. Task Force on Nomenclature and Statistics, *Diagnostic and Statistical Manual of Mental Disorders*, third edition (Washington, DC: American Psychiatric Association, 1980); for an excellent description of the logic underlying creation of the third edition see Robert L. Spitzer, B. W. Janet, M. S. W. Williams and Andrew Skodol, "DSM-III: The Major Achievements and an Overview," *American Journal of Psychiatry* 137, no 2 (1980): 151-64.

⁹ In the 1960s, Valium was marketed for treatment of psychosomatic conditions. Today a psychosomatic condition, despite official medical definitions, is one which is not easily diagnosed or treated within a single doctor's specialty, which does not fit the disease path of any recognized condition, or appears a temporary condition associated with patient distress; it is a diagnosis associated with non-treatment; Authors such as Dr. James Le Fanu suggest another reason for minimal prescribing of Valium by 1990. He argued a widespread belief that Valium was highly addictive made patients wary of doctors prescribing the drug. James Le Fanu, "Health: Second Opinion," *The Independent (London)* January 28, 1990.

diagnosed as depressed or anxious. Understanding gendered diagnoses is a major issue to which a history of Valium can contribute, but it is not a widely recognized issue before 1967.

In this dissertation I attempt to understand how Americans, particularly mental health professionals, understood mental health and illness, the nature and purpose of tranquilizers, and how they conceptualized Valium before the period when it became a widely used drug. Although most clinical trials of Valium that used outpatient populations had at least a 60:40 ratio of female to male participants,¹⁰ few authors publishing in medical journals before 1966 discussed why this occurred or whether it was a problem. By the 1970s, sociologists and medical professionals recognized substantial discrepancies in medical diagnoses and treatments for men compared to women.¹¹ They questioned categories used and the factors shaping physicians'

¹⁰ See chapter 6.

¹¹ Aside from Edwin M. Schur's *Labeling Women Deviant: Gender, Stigma, and Social Control* (New York: Random House, 1984), two of the best sources for these arguments are articles by Ruth Cooperstock, and articles published in *Social Science and Medicine*. Ruth Cooperstock, "Sex Differences in the Use of Mood-Modifying Drugs: An Explanatory Model," *Journal of Health and Social Behavior* 12, no. 3 (1971): 238-244; Ruth Cooperstock, *Social Aspects of the Medical Use of Psychotropic Drugs* (Toronto: Alcoholism and Drug Addiction Research Foundation of Ontario, 1974); Edward W. McCrane, "Alleged Sex-Role Stereotyping in the Assessment of Women's Physical Complaints: A Study of General Practitioners," *Social Science and Medicine* 12 (1978): 111-116; Constance A. Nathanson, "Illness and the Feminine Role: A Theoretical Review," *Social Science and Medicine* 9 (1975): 57-62; Eva Lynn Thomson, "Sexual Bias in Drug Advertisements," *Social Science and Medicine* 13A (1979): 187-191; Mary T. Westerbrook and Reginald A. Mitchell, "Changes in Sex-Role Stereotypes from Health to Illness," *Social Science and Medicine* 13A (1979): 297-302.

treatment choices. That men and women were substantially the same was sometimes a tacit assumption.¹² Increased focus on addiction and dangerous controlled substances after 1970 promoted Americans looking back at Valium and seeing something obviously addictive;¹³ experts who failed to recognize the danger must have been negligent. Perhaps physicians knew the drug was addictive and prescribed it nevertheless, or the insidious drug companies bamboozled physicians, hiding knowledge of the drug's dangers as they squeezed all profit possible from unnecessary prescriptions.¹⁴ Looking back beyond the 1971 declaration of President Nixon's War on Drugs, it is easy to see danger in substances which prewar people, even medical experts, rarely noted.

Framing Roche's development and marketing of Valium without reference to the period after 1963, the widespread use of Valium within the context of contemporary 'knowledge' appears rational. After World War II, Americans were more aware of mental health; they knew stressful conditions wrought havoc on the body, caused neuroses and psychosomatic disorders in otherwise seemingly healthy individuals, and

¹² Examples of the assumption can be seen in literature focusing on feminization, the creation of female gender through socializing girls differently than boys. Laurie Davidson and Laura Kramer Gordon, *The Sociology of Gender* (Chicago: Rand McNally College Publishing Company, 1979);

¹³ For an excellent history of attempts to control illicit drugs in the United States see David F. Musto, *The American Disease: Origins of Narcotics Control*, expanded edition (New York: Oxford University Press, 1987).

¹⁴ From the 1940s to the early 1960s, the overwhelming proportion of physicians were men.

they were personally at risk. Openly taking tranquilizers during the day, not being in perfect mental health, no longer put them outside the boundaries of 'normal' members of society or into a dependent role. In the early 1960s, normal medical science explained anxiety as some dangerous or complicating factor underlying multifarious medical ailments. Physicians, and more so the popular press, highlighted interaction between psyche and soma, mind and body, in all illnesses. With better tranquilizers, physicians finally had the ability to treat not only neuroses, neurotic reactions to stress or personality disorders, but also psychosomatic disorders, and anxiety and tension with mainly somatic disorders. The nation's strength required creation of strong independent citizens, of men freed from the fetters of their own upbringing and history.

Tranquilizers reduced anxiety and apprehension, calmed emotional fear based on previous experience, and freed people to interact with the present in an informed and rational, not emotional, manner. There was a national push to prevent severe mental illness through preventive or early treatment of neuroses, addiction, social and personality disorders. Why wouldn't a doctor prescribe Valium as freely as Aspirin? Didn't he care for America? Preventive action wiped out polio, why not severe mental illness? Didn't he trust science?

It is easy to point flippantly to the time being ripe for Valium to sweep into use, painting a false picture of historic inevitability. This approach abdicates the historian's responsibility, using some black box causal agent entitled 'culture.' The idea of Valium as inevitable can foster a search for someone to blame for later-seen problems: a

gullible and frightened public wanting a medical cure for social problems, doctors beguiled by advertising, or a medical community refusing to accept evidence of Valium's addictiveness. Valium's rise and fall as inevitable can act as background for illustration of change in women's social position, to argue the dangers of unregulated marketing to doctors, or point out changes in how people related to physicians. Each of these interpretations is incomplete.

This dissertation proposes another possibility; widespread prescription and use of Valium made sense in the mid-1960s for a wide variety of reasons: how men and women interpreted physical and psychological problems, what physicians and psychiatrists thought they could and should do to help, and how Hoffmann-La Roche marketed a drug they had reason to believe beneficial as well as profitable. Examining broad patterns of contemporary medical knowledge, beyond specific changes in detail, suggests how Americans understood mental health, the roles of anxiety, stress, and tension, and the framework within which Valium was discovered and developed, and conditions around physicians' common decisions to prescribe Valium and similar minor tranquilizers.

Terminology and Assumptions

My choice of wording in this dissertation, overall, is intentional even where seemingly sloppy. Use of the terms 'pharmaceuticals,' 'prescription drugs,' 'ethical drugs,' and similar subgroupings constrain discussions of Valium. 'Pharmaceutical'

implies a substance has medicinal value, intentionally composed through chemical synthesis. This terminology omits some opiates and naturally occurring substances with psychotropic effects. ‘Prescription drug’ overtly classifies drugs based on method of acquisition, and implies the government, physicians, and pharmacists support its use. The alternative term ‘ethical drug,’ will not be used, because it is too historically specific, based on the way large-scale and self-regulating or industry-self-regulating manufacturers defined their separateness from new, small-scale, firms with little reputation to lose from unethical behavior.

I have chosen to use the term drug in many contexts. Referring to Valium (diazepam) as a drug removes preconceptions regarding the rationality of its use, whether it was addictive, and whether it should have become a controlled substance. What is more important, the term drug allows comparison of Valium with barbiturates and alcohol, drugs commonly used for similar purposes. As with Valium, most people obtained barbiturates by prescription, even though barbiturates faced restrictions on use earlier and more thoroughly than did Valium. Both were sleep aids, relieved stress and tension, used to treat alcoholism, and reduced tremors. Alcohol was a popular nonprescription alternative to Valium; a widely used drug, it served as an imperfect tranquilizer, reducing tension and stress, but with problematic side effects. Leo Sternbach, the chemist who first synthesized Valium, recognized the link; when talking to a reporter about Valium he said “My wife doesn’t let me take it,” and continued with

the quip “I like Scotch.”¹⁵

Construing Valium as a drug, rather than a pharmaceutical, implies a broader context. Widespread tranquilizer use was not new in the 1960s. Mother had little helpers before; dishwasher was not the only thing slobbered in the suburban kitchen. Looking at Valium as part of a second wave of tranquilizers, within the story of developing minor rather than major tranquilizers, is also over-confining. Roche developed Valium as part of a research program attempting to create an improved version of mephenesin, a muscle relaxant which predates the beginning of the psychopharmaceutical revolution (typically the starting bell is the 1953 introduction of chlorpromazine to psychiatry).¹⁶ Hoffman-La Roche’s benzodiazepines had roots in the 1940s, an age when physicians treated women complaining of insomnia, anxiety, worry, or nervousness with barbiturates, while they prescribed themselves an after work martini for similar complaints.

I toss the terms ‘anxiety,’ ‘stress,’ and ‘tension’ around in the following chapters with apparent abandon. In part this is intentional, reflecting similar conceptual slipperiness within writings of the time. To the extent I can tease out separate meanings from sources of the late 1940s through early 1960s, ‘anxiety’ refers to distressing heightened apprehension within the mind and body, and without currently reinforcing

¹⁵ Anon. “Chemist Gave World Valium,” *National Post (Canada)* October 3, 2005.

¹⁶ See chapter 5.

external causes. Physically, anxiety existed as an adrenal-feedback loop, wherein anxiety led to the heightened alertness which was anxiety; it could be cause or effect. ‘Tension’ more commonly refers to whole-body behavior; it was a state including psychological as well as physical (mainly muscle) effects. Tension was an effect of anxiety or stress. ‘Stress’ was the most general of the three terms, used to refer to a cause and effect, internal and external event, a thing and a state. Although all three terms tie into the theoretical framework of homeostasis and General-Adaptation-Syndrome, the nature of stress is most tightly bound to these concepts.

‘Homeostasis’ and ‘General-Adaptation-Syndrome’ refer to ideas pervading medical thought in the 1950s. I deal with these concepts more fully in chapter three. Walter Cannon, in the 1910s, argued the body responded to stresses in many ways, but with a goal of returning to the original, dynamically balanced state, homeostasis.¹⁷ Stressors were anything causing deviation from homeostasis. Stress in general harmed the body. Usual stressors caused minimal damage, but excessive stress could manifest in a wide variety of somatic conditions. Hans Selye’s General-Adaptation-Syndrome

¹⁷ Cannon’s more important writings can be found in books summarizing his research. Walter B. Cannon, *Bodily Changes in Pain, Hunger, Fear and Rage; An Account of Recent Researches into the Function of Emotional Excitement* (New York: D. Appleton and Company, 1920); Walter B. Cannon, *The Wisdom of the Body* (New York: W. W. Norton & Company, 1939); Walter B. Cannon, *The Way of An Investigator, A Scientist’s Experiences in Medical Research* (New York: W. W. Norton & Company, 1945); Russell Charles Maulitz, *Walter B. Cannon: Scientific Explanation in Regulatory Physiology* (Boston: Unpublished Thesis, Harvard University, 1966); Elin L. Wolfe, A. Clifford Barger, and Saul Benison, *Walter B. Cannon, Science and Society* (Boston: Harvard University Press, 2000).

was a slightly more dynamic version of homeostasis.¹⁸ Facing stressors, Selye argued, an individual tried to adapt. When adaptation failed or was impossible, physical problems developed. Selye argued these failures of adaptation took common forms; they were a syndrome. In both Cannon's homeostasis and Selye's General-Adaptation-Syndrome, focus is on the manifest physical ailments resulting from environmental stress.

Physicians prescribed Valium for a diverse group of psychiatric and somatic conditions. In general, the psychological ailments were neuroses rather than psychoses; functional problems of personality, manifestation of psychological problems physiologically, and behavior associated with stereotyped responses to internal or external stressful stimuli. Various terms were used: psychophysiological or psychosomatic disorders, neurotic reactions, neurotic personality, anxious personality, or anxiety reaction, one symptom underlay all... anxiety. Although boundaries between these groups were nebulous, and practitioners applied them in particular ways, the core ideas

¹⁸ Over the course of his career, Selye moved from physiological/medical research, to administration, theory, and proselytizing his theories. Hans Selye, *The General Adaptation Syndrome of the Diseases of Adaptation* (n.p.: Association for the Study of Internal Secretions, 1946); Hans Selye, *The Physiology and Pathology of Exposure to Stress; a Treatise Based on the Concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation* (Montreal: Acta, 1950); Hans Selye, *The Story of the Adaptation Syndrome: Told in the Form of Informal, Illustrated Lectures* (Montreal, Acta, 1952); David Le Vay, "Hans Selye and a Unitary Conception of Disease," *The British Journal for the Philosophy of Science* 3, no. 10 (1952); Nancy E. Gross, *Living With Stress*. Forward by Hans Selye (New York: McGraw-Hill, 1958); Russell Viner, "Putting Stress in Life: Hans Selye and the Making of Stress Theory," *Social Studies of Science* 29, no. 3 (1999).

differ. Neurotic reactions were considered responses of a fairly normal or mature personality to ongoing or extreme external stressors. Worry and hand-wringing after death of a parent might fit this prognosis, and warrant prescription of Valium to ensure the bereavement period was short and failed to cause more lasting physical or mental problems. Neurotic personalities required long-term treatment to prevent physical or behavioral problems. Neurotic people had immature personalities, often overreacted to minor stresses, and commonly developed self-sustaining, and fairly unfixable, neuroses. Valium prevented these over-reactions developing into neuroses. An anxious personality was similar to a neurotic personality, possibly manifesting fewer stereotyped responses. Compared with anxiety reactions, an anxious personality involved self-perpetuating anxiety, while anxiety reaction identified a person prone to overreact to external stresses. All these conditions included a component of anxiety, and therefore treatable with Valium. Each could lead to psychosomatic disorders, somatic illnesses caused and perpetuated by anxiety. When used to treat psychiatric illness, Valium treated symptoms, but in treating psychosomatic disorders it neutralized the underlying cause.

Synthesis of 7-chloro-1,3-dihydro-1-methyl-5-phenyl 2H-1,4-benzodiazepin-2-one, also known as Valium

Leo Henryk Sternbach, whose discovery of the benzodiazepines led to Roche's marketing of Librium and Valium, was part of the larger group of "organic medicinal

chemists¹⁹ who moved to the United States from the increasingly desperate situation in 1930s and 1940s Europe. Hoffmann-La Roche, a Swiss company, hired Sternbach and set him to work in Nutley, New Jersey, on synthesis of vitamins. Within a few years he established his reputation with a commercially viable method of synthesizing biotin, vitamin B₇.²⁰ This success led to promotion and recognition. In the 1950s, when Roche began putting significant resources into the search for tranquilizers, Sternbach joined this effort. Within a few years he would gain fame for his discovery, synthesis, of a new group of tranquilizers, the benzodiazepines.²¹ As one of his associates explained,

¹⁹ Milan Uskovic, preface comments to *Good Chemistry: The Life and Legacy of Valium Inventor Leo Sternbach*, by Alex Baenniger, Jorge Alberto Costa e Silva, Ian Hindmarch, Hans-Juergen Moeller, and Karl Rickels (New York: McGraw-Hill, 2004), iii.

²⁰ Milan Uskovic, in Baenniger et al, *Good Chemistry*, iii; Sternbach received patents for these processes and assigned rights to Hoffmann-La Roche. For example, see Leo H. Sternbach, assignor to Hoffmann-La Roche Inc. 1946. Process of Epimerizing Calcium δ -Arabonate. U.S. Patent 2,438,881, filed February 12, 1946, and issued March 30, 1948; Moses Wolf Goldberg and Leo Henryk Sternbach, assignors to Hoffmann-La Roche, Inc. 1949. Debenzylation of Benzylated Imidazolido-Thiophane Compounds. U.S. Patent 2,489,238, filed June 8, 1948, and issued November 22, 1949.

²¹ The related patents included Leo Henryk Sternbach, assignor to Hoffmann-La Roche, inc. 1959. 1,4-Benzodiazepines 4-Oxides. U.S. Patent 2,893,992, filed May 15, 1958, and issued July 7, 1959; Earl Reeder and Leo Henryk Sternbach, assignors to Hoffmann-La Roche, inc. 1962. Benzodiazepine Compounds. U. S. Patent 3,051,701, filed December 10, 1959, and issued August 28, 1962; Rodney Ian Fryer, Robert August Schmidt and Leo Henryk Sternbach, assignors to Hoffmann-La Roche, inc. 1963. 5-Prydiyl-1,4-Benzodiazepine Compounds. U.S. Patent 3,100,770, filed August 11, 1961, and issued August 13, 1963; Leo Henryk Sternbach and Gabriel Saucy, assignors to Hoffmann-La Roche. 1964. 2-Methyl-7-Trifluoromethyl-4H-3,1 Benzoxazine-4-one. U.S. Patent 3,120,521, filed March 23, 1962, and issued February 4, 1964; Oscar Keller, Norbert Steiger, and Leo Henryk Sternbach, assignors to Hoffmann-La Roche, inc. 1964. Aminobenzodiazepines. U.S. Patent 3,121,075, filed May 28, 1962, and issued February 11, 1964; Oscar Keller, Norbert Steiger and Leo

“He decided to reexamine the chemistry of his student period in Poland and resurrected the benzodiazepines into the most significant series of drugs to combat anxiety[.]”²²

Sternbach couched his account of the discovery in terms highlighting similarities to Paul Ehrlich’s discovery of Salvarsan (for syphilis), and Alexander Fleming’s discovery of Penicillin.²³ Based on solid scientific principles and insight, he decided on an approach; Sternbach turned to modification of certain azo dye intermediaries, known as 4,5-benzo[hept-1,2,6-oxidiazines] because of his previous experience modifying them.²⁴ Expecting a process with high yields, similar structures to existing tranquilizers, and ability to create a wide variety of side chain variants (assumed important in conferring bioactive characteristics), he found lack of useful resulting compounds a disappointment. It appeared his hard empirical work was all in

Henryk Sternbach, assignors to Hoffmann-La Roche, inc. 1964. Substituted-1,4-Benzodiazepine-5-one Compounds. U.S. Patent 3,121,077, filed May 28, 1962, and issued February 11, 1964; Earl Reeder and Leo Henryk Sternbach, assignors to Hoffmann-La Roche, inc. 1964. Amino Substituted Benzophenone Oximes and Derivatives Thereof. U.S. Patent 3,136,815, filed November 2, 1961, and issued June 9, 1964.

²² Milan Uskovic, in Baenniger et al, *Good Chemistry*, iii.

²³ For an example of the story as told by Sternbach see: Leo H. Sternbach, *The Benzodiazepine Story* (Basle, Switzerland: Editiones Roche, 1983), 8-12; to compare ‘stories’ for Ehrlich and Fleming see Paul de Kruif, *Microbe Hunters* (New York: Harcourt, Brace and Company, 1926); Gwyn MacFarlane, *Alexander Fleming: The Man and the Myth* (Cambridge: Oxford University Press, 1985).

²⁴ Lloyd Shearer, “The Man Who Invented Valium,” *Oakland Tribune* (Oakland, CA), June 27, 1976.

vain.²⁵ One of his superiors “demanded that he abandon his work”²⁶ and turn to other matters. But, as with Ehrlich and Fleming, hard work ended with near failure and serendipitous success. Needing to free up laboratory space, Sternbach focused his attention on compounds already synthesized, but hitherto untested.²⁷ He recalled how “Earl Reeder, my coworker, drew my attention to a few hundred milligrams of two products, a nicely crystallized base and its hydrochloride.”²⁸ Although synthesized in 1955, the compounds remained untested. According to Sternbach, other tasks in the lab pushed aside research on these compounds. Yet, when faced with cleaning up the lab, “instead of throwing them away, we submitted the water soluble salt for testing.”²⁹

My personal cynicism regarding myths of heroic inventors – because they fit tidily with both the expectations of American society and contingencies of the patent system – resulted in this dissertation looking at the ‘discovery’ of Valium more broadly. Roche set up a laboratory to search for certain types of substances; they risked capital for a long-term pay-off. For five years Roche allowed Leo Sternbach to experiment, to develop new compounds. It is improbable they gave him rein simply to substitute side

²⁵ Sternbach recalls his efforts as an empirical and planned approach. Sternbach, *The Benzodiazepine Story*, 7.

²⁶ Baenniger, et al., *Good Chemistry*

²⁷ Sternbach, *The Benzodiazepine Story*, 11.

²⁸ Baenniger et al, *Good Chemistry*, 51-52.

²⁹ Leo Sternbach from *The Benzodiazepine Story* as quoted in Baenniger, et al, *Good Chemistry*, 51-52.

chains on a new molecule chosen simply because he had experience with them as a dye-stuff,³⁰ even if prevailing theories in drug development argued substitution of side chains modified properties.³¹ Creating new pharmaceuticals wholesale, without choice of a central compound based on known activity, is what Sternbach recollects. Leaders at Roche invested in a financially promising field, presumably tranquilizers. But looking more closely at how physicians and scientists understood tranquilizers helps explain why the Roche pharmacology laboratory identified the usefulness of Sternbach's synthesized compounds. Understanding the relationship between Sternbach's discovery and Roche's development and marketing of Valium requires greater focus on the role of pharmacological testing. Sternbach submitted a substance; Lowell Randall recognized it had properties the company desired.

Overview

This dissertation draws out different facets of the conditions preparing and situating Valium as a marketable substance and cultural entity. It offers explanation for the widespread prescription and use of Valium in the 1960s. Due to constraints of time and space, it only sets up future discussions of why Valium became associated with women, questions of addictiveness, and why it declined in use.

³⁰ See the end of chapter five and beginning of chapter six for discussion of the types of compounds and tests used at Roche.

³¹ This trend was general for chemistry, not specific to pharmaceutical development.

Chapter two discusses the shift from mental health and mental illness as discrete entities to a continuum, with most Americans either neurotic or potentially neurotic; a view rising rapidly to prominence during and shortly after World War II. This change made it possible to see tranquilizers' usefulness for improving or protecting the mental health of a substantial portion of Americans.

Chapter three focuses on increasing interest in mental health as an integral part of treating psychological, psychosomatic, and somatic based illness. After World War II, Congress set up national programs and studies to protect Americans' mental health. In part, justification came from efforts to prevent debilitating long-term mental illness, something newly considered possible, and necessary for financial reasons. The new psychopharmaceuticals tumbling out of pharmaceutical companies, after 1953, offered the possibility of turning back the rising tide of the long-term institutionalized mentally ill, affordably.

Chapter four examines another side of the equation, how physicians, psychologists, and scientists understood the nature of stress, anxiety, and neuroses. Although traditionally discussed as relatively distinct, psyche and somatic based theories became increasingly intertwined by the 1950s. Combination of these theories is evident in the work of Jules Masserman and Horsley Gantt, two of the most influential figures establishing externally measurable characteristics associated with neuroses in laboratory animals. These theoretical underpinnings informed Roche's search for a marketable compound; events leading to the synthesis by Leo Sternbach of

a compound eventually marketed as Valium.

Chapter five focuses on how physicians, scientists, and allied health professionals conceptualized existing psychopharmaceuticals. They associated tranquilizers, sedatives, and hypnotics with specific actions within the body and with observable signs. The chapter includes discussion of how drugs affecting the psyche related to one another, their categorization and presumed modes of action. A substantial portion of the chapter examines the chain of events at Hoffmann-La Roche leading to Leo Sternbach's discovery of the chemical compounds later introduced into the American market as Valium.

Chapter six examines Valium's transition from chemical compound, to a drug worthy of further study and marketing. I focus first on the battery of pharmacological tests performed by Lowell Randall in company laboratories. Randall tested Sternbach's compound, and identified it as a tranquilizer worthy for Hoffmann-La Roche to put substantial resources towards clinical testing and marketing. The specific battery of tests Randall chose, reflects properties associated with potential market competitors; it suggests how medical and pharmaceutical scientists conceptualized tranquilizers, as well as the specific substances Roche saw as competition. Clinical trials further shaped and informed potential marketing approaches; shaping Valium as a treatment for psychiatric and psychosomatic conditions.

Chapter seven outlines Roche's early marketing efforts, tying together contemporary understandings of mental health and illness, in an effort to understand

why Valium became so widely used. Roche's compound entered a marketplace filled with popular, preexisting tranquilizers, sedatives, and hypnotics. Contrary to expectations of hindsight, which suggests marketing Valium as Mother's Little Helper, Roche's marketing program focused mainly on psychosomatic conditions and the anxiety component of somatic illnesses.

The chapter concludes with brief discussion of Valium's rapid rise in popularity, and reflections on how understandings of mental health and its relationship to minor tranquilizers might shed light on continuing debates about Valium's place in history. After its introduction in 1963, Valium rose in use, becoming the most prescribed brand-name drug by 1969. The chapter draws together earlier portions and suggests how Valium fit into contemporary ways of conceptualizing medicine, the mind, and the body.

**CHAPTER 2. ADAPTATION UNDER PRESSURE:
EFFECTS OF WORLD WAR II
ON DEVELOPING CONCEPTS OF NEUROSES**

World War II was a crucial turning point in the behavioral sciences.³²

Commonalities of experience among American medical and mental health professionals in World War II, specifically the interaction between the war experience and changes in conceptualization of mental health and illness, created new truisms. World War II established the concept of mental health and illness as a continuum, that prevention or early treatment was essential to ensure neurotic reactions did not develop into full-blown and strongly fixed neuroses, and that mental health – especially prevention of neuroses – was a broadly important social issue. The prewar concept of mind and self as inner- and inter-acting phenomena shifted towards greater focus on interaction of a fixed personality and a changing world. People adjusted to reality, to social role. Too

³² Military psychiatry in World War One is largely remembered for the concept of shell shock transforming from a physiological to psychological condition. It well represents that the focus during the Great War was on inner mental factors. One of the most clear contemporary statements of the theoretical approach can be found in a 1919 volume of *Science*. W. H. R. Rivers wrote “One, and perhaps the most important outcome of this combined activity has been the general recognition of the essential part taken in the production and maintenance of the psycho-neuroses by purely mental factors. In the early stages of the war especial stress was laid in the physical effects of shell explosion, an attitude which found expression in the term shell-shock. As the war has progressed the physical conception of war-neurosis has been gradually replaced by one according to which the vast majority of cases depend on a process of causation in which the factors are essentially mental.” W. H. R. Rivers, “Psychiatry and the War,” *Science* 49, no. 1268 (1919): 367.

harsh or sudden a change exceeded a threshold of stress, leading to stereotyped and less adaptive responses. To an extent people could modify environment or social role, but between 1945 and 1965 focus was on returning to the norm, to stability, to accepted role within mainstream, middle-class, American definitions of social place. The newly established need to promote mental health and treat mental illness increased focus on mental issues throughout American culture. When the war ended, the newly trained mental health professionals returned to the U.S. with more status and a far, far, larger potential clientele.

Changes solidifying during World War II provided fertile ground for development and marketing of tranquilizers, including Valium. The new understanding of mental illness as a continuum, with mental health as a goal rather than a state, increased the experts' tendency to focus on neuroses rather than psychoses or organic illness. Psychiatrists continued identifying severely mentally ill individuals, but after the war there was a newly identified massive population of neurotic, or seemingly normal preneurotic, Americans who needed protection lest stressors lead into relatively untreatable full-blown neuroses. Prevention of mental illness, and treatment at the earliest stages, became essential. Roche highlighted Valium's usefulness as a preventative in its advertising campaigns. The shift from conceptualizing neuroses mainly in terms of inner conflict, towards focus on interaction between an individual and its environment, placed focus on reactions to stress rather than resolution of conflicts. Roche marketed Valium, at least in part, as a substance mitigating

overreaction to stressful situations or conditions. Dissemination of knowledge within the military created a cadre of general physicians taught to consider mental health. Among soldiers, direct training or experience with mental health ideas, as well as routinization of concepts such as group morale, importance of leadership, and regularization of rest and relaxation, inadvertently taught them principles of the new mental health.

Preparing for War

In the early 1940s, practitioners dealing with mental illness fell into two main groups based on where they practiced, clinic or institution. Clinical psychiatrists and psychotherapists usually saw a small handful of financially well-off patients with neuroses.³³ To them, neuroses resulted from maladaptation, blocked development of internal drives, or conditioned responses. The problems resulted in inappropriate, inefficient, stereotyped, or primitive responses. Treatment focused on developing a patient's insight, the ability to understand underlying motivations and therefore respond to the environment effectively, unhindered by the past. Institutional psychiatrists worked mainly with physical treatment of institution-based patients, often those suffering from psychoses. They considered many of their patients chronic cases and untreatable. Most of the population in mental care institutions suffered from conditions

³³ At this time the majority of psychoanalysts, and other varieties of psychotherapists, held medical degrees.

such as extreme vitamin deficiencies, dementias resulting from syphilis, manic-depression, and schizophrenia. Most military psychiatrists at the beginning of World War II were institutional psychiatrists, accustomed to large caseloads, managing chronic cases, and focusing on care of the body with little hope of curing the mind.³⁴

The United States entered World War II relatively late. Internal debates over the utility, morality, and need to play an active role delayed national action. But, once engaged, the United States turned to a military footing quickly and dramatically. The Marine Corps and Navy expanded from 403 thousand in early December 1941 to number almost 3.9 million when Japan surrendered in 1945.³⁵ Because of rapid mobilization, flaws in existing systems rapidly became obvious.

Military leaders proved ill-prepared for neuropsychiatric problems among the troops.³⁶ Medical leaders held relatively little clout within the military, especially the Army. Assistant Surgeon General of the Navy, Captain Dallas G. Sutton, explained

³⁴ Howard McC. Snyder, "Observations of Psychiatry in World War II," *American Journal of Psychiatry* 104 (March 1947): 222; Francis J. Braceland, "Psychiatric Lessons from World War II," *American Journal of Psychiatry* 103 (March 1947): 587; David J. Flicker, "Army Psychiatric Literature, Factors in Interpretation," *American Journal of Psychiatry* 98 (May 1942): 796; Uno H. Helgesson, "Some Current Features of Psychiatry in the United States Navy," *American Journal of Psychiatry* 99 (March 1943): 633; William C. Menninger, "Psychiatric Experience in the War, 1941-1946," *American Journal of Psychiatry* 103 (March 1947): 580.

³⁵ Braceland, *Psychiatric Lessons*, 587; military planning before the war was extensive, allowing relatively quick recruitment, training, arming, and deployment of troops.

³⁶ The Navy situation differed substantially in terms of planning and expectations. The Navy and Marines developed a plan for identification and dispensation of potential neuropsychiatric cases toward the end of 1938.

recruitment screening plans to “weed out psychopaths and potential victims of mental disease[,]”³⁷ to the public in early 1939; Army medical leaders were in a poor position to bring similar plans to fruition.³⁸ The Army Surgeon General was not a member of the General Staff, so although charged with organizing medical services for the entire Army, he lacked access to the corridors of power. He reported to the Commanding General of Service Forces, who oversaw fields such as the Quartermasters and Military Police.³⁹ The Surgeon General did not directly command medical personnel, and the Army Air Force was outside his direct jurisdiction.⁴⁰ Marginalization of psychiatry, usually termed neuropsychiatry,⁴¹ was even greater than medicine in general. Between World Wars, Army physicians numbered around twelve-hundred, only thirty-seven of

³⁷ Anon, “Medical Officer Announces Plans for Psychiatry in War,” *The Science News-Letter* 35, no.11 (1939): 165.

³⁸ Lawrence S. Kubie claimed only one article was published in a U.S. military medical journal on the problems related to screening recruits between Armistice and Pearl Harbor days. “Technical and Organizational Problems in the Selection of Troops,” *Military Affairs* 9, no.1 (1945): 16; psychiatrists published articles relating to the issue in their own journals.

³⁹ Paul Wanke, “American Military Psychiatry and Its Role Among Ground Forces in World War II,” *The Journal of Military History* 63, no. 1 (1999): 137.

⁴⁰ Menninger, *Psychiatric Experience*, 579.

⁴¹ The term neuropsychiatry defined a field encompassing all disorders of the nervous system, including epilepsy, what were believed to be organic based dysfunctions—such as schizophrenia, dementias, and idiocy—as well as functional disorders—over or under stimulation, fatigue, poor transmission—of the nervous system and its integrating portions of the brain. Neuropsychiatry was therefore focused on physical aspects of the mind and behavior, but this was not deemed incompatible with a psychoanalytic outlook.

whom the military classified as psychiatrists.⁴² The 1939 Military Medical Manual exemplifies marginalization of mental illness. Only one of its 685 pages covered mental health.⁴³

The American Psychiatric Association created its own Military Mobilization Committee, to advise and promote the role of psychiatrists during the conflict. Citing the same problem of a staffing crisis they, and individual members, promoted ‘home service’ among older psychiatrists who, although too old for active service, could work at induction centers within the United States.⁴⁴ Recognition of need for screening recruits was more widespread than reflected in actual, well-formed, and practical plans ready for Army use.

Therefore, when the United States entered the war, military provisions for mental health were sparse where they even existed. There were no psychiatrists assigned to existing combat divisions. There were virtually no plans for treating mental casualties, by fiat or expectation.⁴⁵ Offices of the Surgeons General of the Army and Air Forces had few mechanisms to coordinate efforts.⁴⁶ Military headquarters lacked a

⁴² Wanke, *American Military Psychiatry*, 132

⁴³ Wanke, *American Military Psychiatry*, 130.

⁴⁴ Anon, “Men up for Army Training Will Have Psychiatric Examination,” *The Science News-Letter* 38, no. 21 (1940): 334-35.

⁴⁵ Menninger, *Psychiatric Experience*, 583.

⁴⁶ Snyder, *Observations of Psychiatry*, 221.

psychiatrist to plan improvements.⁴⁷ A 1939 American Psychiatric Association survey concluded the Army needed a minimum of one psychiatrist per five-thousand soldiers; rates existing in the Navy predicted need for one hundred fifty trained psychiatrists, minimum. Current staffing levels sat well below estimated need.⁴⁸

Screening Recruits

Military leaders involved in neuropsychiatry recognized mental illness as an economic and military manpower problem, but one they believed controllable by preventing the medically ill from becoming soldiers. Lieutenant Colonel William C. Porter, Chief of the Neuropsychiatric Section at Walter Reed General Hospital, reported that the Veterans Administration spent over 640 million dollars between 1923 and 1940 on veterans with neuropsychiatric disabilities. Veterans' facilities devoted almost one-third of their resources to neuropsychiatric casualties.⁴⁹ The interwar Army lost almost two percent of its total man hours due directly to these hospitalizations, and indirect "damage done to Army morale" was undoubtedly far greater.⁵⁰ Clearly military

⁴⁷ Menninger, *Psychiatric Experience*, 581, 583.

⁴⁸ Anon, "Men Who Break in Army Life Problem to Army Physicians," *The Science News* 40, no. 10 (1941): 148.

⁴⁹ William C. Porter, "The Military Psychiatrist at Work," *American Journal of Psychiatry* 98 (November 1941): 319; Robert Knight estimated the cost per patient for Veterans suffering from war neuroses at \$30,000, largely due to need for lifelong treatment. Robert P. Knight, "The Treatment of the Psychoneuroses of War," *Bulletin of the Menninger Clinic* 7 (1943): 148.

⁵⁰ Hugh E. Kiene and Major Arthur S. Hasell and Himon Miller, "Neuro-

efficiency required preventing these hospitalizations. Editors of the neuropsychiatry volume for *The History of the Medical Department of the United States in the World War* argued it would have been better practice to reject all draftees thought mentally unfit rather than burden the Army with the threat to morale and manpower required to deal with them. These editors' proposed measure reflected the dominant military solution.⁵¹ Rules set out by the Surgeon General's office dictated that after ninety days wartime service, the military assumed a soldier had been healthy when he first enlisted; after ninety days of service, Uncle Sam's dollar paid for treating medical problems. Early identification allowed the military to release soldiers while in training, or when potential recruits, before the military obligation to treat them for the full course of an illness kicked in.⁵²

Therefore, psychiatric preparation for World War II focused on identifying potential recruits who were mentally ill before they joined the Army, and quickly weeding out new soldiers unsuitable for service. Initial recruitment methods were slow

Psychiatric Examination at the R. I. Army Induction Station," *American Journal of Psychiatry* 98 (January 1942): 509.

⁵¹ Porter, *Military Psychiatrist at Work*, 319; Kiene noted this view when he wrote, "members of the army medical staff stated that mental misfits had no place in the Army as the personnel was too fully occupied...to allow time for proper diagnosis, placement and treatment of those showing neuro-psychiatric problems." Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 509.

⁵² Anon, *Men Who Break in Army Life*, 148; Flicker, *Army Psychiatric Literature*, 797; Kiene argued identifying and eliminating more 'mental cases' could have reduced the massive financial burden of caring for WWI veterans with war neuroses. Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 509.

and rejected a large proportion of candidates. In November 1940, the Selective Service began circulating Medical Circular No. 1, describing a double screening process intended to identify neurologic or psychological problems. Two doctors, not necessarily trained in the subject area, screened candidates for both organic and functional problems, including mental deficiency, alcoholism, and other psychopathologies. Classification of mental disorders into organic and functional was common at the time. Psychiatric typologies used the classification 'organic disorder,' for conditions they believed caused by physical ailments. These were problems of the brain. Functional disorders included all categories believed to have their root in dysfunction of the mind or integration of the nervous system. Candidates wrote 'intelligence' tests and filled in forms 149 and 200, which provided a brief school and work record.⁵³ Physical examinations of eyesight, ear-nose-throat, bone structure, and teeth preceded the neuropsychiatric examination; only once a recruit passed inspection for flatfeet was his mental structure considered.⁵⁴ Work and police records provided insight into behavioral problems. Perhaps history of hospitalization suggested mental illness or alcoholism. Gastrointestinal, circulatory, or cardiac problems might represent either organic diseases, or a psychoneurotic personality.⁵⁵ Written records allowed more easy identification of neuropsychiatric problems. Examiners referred suspected mental cases

⁵³ Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 511.

⁵⁴ H. H. Goldstein, "Neuropsychiatric Evaluation of the Potential Soldier," *American Journal of Psychiatry* 98 (July 1942): 29.

⁵⁵ Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 512-13.

to Medical Advisory Boards, which included at least one psychiatrist, for final dispensation.⁵⁶ Yet lack of trained manpower continued hindering the military's institutional capacity to screen recruits for neuropsychiatric problems.⁵⁷

While two percent of American recruits had been denied service in World War One due to neuropsychiatric problems, examiners in World War II turned away twelve percent of candidates for this reason.⁵⁸ Early optimists such as Colonel Stanley, First Corps Area Surgeon, believed this higher rejection rate to be a good sign. The “initial induction neuro-psychiatric examination should be able to keep out of service at least 75 percent of the potential neuro-psychiatric casualties[,]”⁵⁹ he enthused. Barring large numbers of recruits from service, optimists such as Stanley argued, proved that the military had arranged effective identification of most potential mental problems.

Initial screening procedures focused on diagnosis,⁶⁰ identifying organic and functional disorders.⁶¹ A history of organic disorders – severe problems such as chronic

⁵⁶ Wanke, *American Military Psychiatry*, 131-32.

⁵⁷ Anon, *Men up for Army Training*, 334-35.

⁵⁸ John W. Appel, “Incidence of Neuropsychiatric Disorders in the United States Army in World War II (Preliminary Report),” *American Journal of Psychiatry* (January 1946): 433.

⁵⁹ Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 509.

⁶⁰ Flicker, *Army Psychiatric Literature*, 796.

⁶¹ see Goldstein, *Neuropsychiatric Evaluation*, 29-32, for one description of the procedures used to identify neuropsychiatric problems, and what behaviors and/or histories were considered indicators of various diagnoses.

alcoholism, schizophrenia, mania, dementia, or severe mental retardation – excluded a man from service. After ruling out these major problems, the main concern of neuropsychiatric screening was assessment of personality as “determined not only by... constitutional endowment but also by... lifelong habits of attack or retreat, or motivation and of persistence[.]”⁶² Personality was a window on the future, how potential soldiers might respond to taking orders or recover from the trauma of combat.⁶³

When assessing the effect of military psychiatry on civilian psychiatry in the 1950s, it is important to recognize how American medical society understood personality as a pattern of interaction between individual and society. As the physician Abram Kardiner explained, “[t]he emphasis is placed upon the study of the “personality as a whole[.]” through observation focused on “functional and functioning units and drives.”⁶⁴ These were components of personality which were observable as behaviors. Personality was an issue of functionality, patterns of behavior in interaction with the social body and overall environment. It was a relationship between inherited and developed character, and the external world. The potential soldier of World War II was

⁶² Abram Kardiner, *The Traumatic Neuroses of War* (New York: Paul B. Hoeber, 1941), 502.

⁶³ Bromberg conceptualized the interaction of personality and neuroses similarly. He wrote “the neurotic reactions [depend]...on the psychological aspects of the personality.” Norbert Bromberg, “The Role of Conditioned Responses in Emotional Disturbances of War,” *American Journal of Psychiatry* 103 (July 1946): 26.

⁶⁴ Harry A. Steckel, review of Abram Kardiner *The Traumatic Neuroses of War*. New York: Paul B. Hoeber, 1941 in *American Journal of Psychiatry* (January 1942): 624.

a social being with predispositions “favorable for military service”⁶⁵ such as aggressiveness, respect for authority, love of competitive sports with personal physical risk, and “non-dependence on any one individual or group[.]”⁶⁶ He was a man with a personality allowing him to adjust to military life without succumbing to neuroses.⁶⁷

Thirty-three percent of those who were rejected appeared to be cases of mental insufficiency. Of the remainder, most rejections attributed to problems related to personality and neurosis. Major Appel, writing shortly after the war ended, calculated the proportion of neuropsychological rejections in certain categories. Examiners rejected only six percent due to neurological disease, but thirty-one percent of potential recruits for apparent psychoneuroses, and twenty-one percent for psychopathic personality.⁶⁸ The diagnosis ‘psychopathic personality’ identified someone who had “shown an inability to adapt himself in a adult, socially-acceptable manner to the demands of ordinary life[.]”⁶⁹ It was, like neurosis, a personality problem, an

⁶⁵ William C. Porter, “What Has Psychiatry Learned During the Present War?” *American Journal of Psychiatry* 99 (May 1943): 851.

⁶⁶ Porter, What Has Psychiatry Learned, 851.

⁶⁷ B. H. McNeel, “War Psychiatry in Retrospect,” *American Journal of Psychiatry* 102 (January 1946): 502; Bromberg, *The Role of Conditioned Responses*, 26.

⁶⁸ Appel, *Incidence of Neuropsychiatric Disorders*, 433.

⁶⁹ Porter, *The Military Psychiatrist at Work*, 317; Porter assumed this deviation from the social norm was caused by a biological problem, but it was not observable; Psychopathic personality was classified among disorders of psychogenic origin with no defined somatic cause – a category also including schizophrenia, manic-depressive psychosis, and paranoia – in one of the more widely used diagnostic manuals. Edwin P.

inappropriate or socially maladaptive pattern of behavior. The figures for diagnosis of organic (disease and insufficiency) versus functional disorders reflects a combination of how rare or common problems within these classifications were, as well as the ease of diagnosing organic disorders compared with the murky identification of psychoneuroses.⁷⁰

Important assumptions underlay the early focus on screening to keep the mentally ill out of the military. First and foremost is an assumption that mental illness is usually easily identifiable. Examiners easily screened out the obviously mentally ill; those making it past screening at recruitment stations were problematic because “many of them, are not ‘crazy.’”⁷¹ Although the “prevention of all future maladjustments is impossible,” screening could minimize mental casualties.⁷² Personal history and a short interview will keep seventy-five percent of these cases out, Colonel Stanley argues. Examination of school, work, and hospitalization history, combined with a few simple questions, would identify most recruits with a history or potential of mental illness.

Jordan, ed., *Standard Nomenclature of Disease and Standard Nomenclature of Operations*. Chicago: American Medical Association, 1942. Neuroses were separately classified. “Psychopathic personalities are characterized largely by emotional immaturity or childishness, with marked defects of judgement and without evidence of learning by experience.” Description from Clarence O. Cheney, *Statistical Manual for the Use of Hospitals for Mental Diseases* (Utica, NY: National Committee for Mental Hygiene, 1942), in Dom Thomas Verner Moore, *The Nature and Treatment of Mental Disorders* (New York: Grune & Stratton, 1944), 299.

⁷⁰ Goldstein, *Neuropsychiatric Evaluation*, 30-31.

⁷¹ Anon, *Men Who Break in Army Life*, 148.

⁷² Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 513.

Second is an assumption that mental illness affects only a subset of the population.

Turning away twelve percent of potential recruits suggested examiners did not expect the other eighty-eight percent to fall prey to mental illness. People were either mentally ill or they were not. These early assumptions, that mental illness was an easily identified ‘thing’ that some people had, and the majority did not have, were early casualties of war.⁷³

Military procedures gradually simplified inductee screening, but keeping the mentally ill out remained a focus. Even with streamlined medical examinations and placement of psychiatrists at all Army induction centers,⁷⁴ perceived neuropsychiatric conditions remained one of the most common reasons for rejecting recruits. Between 1 January 1942 and 30 December 1945, the military turned away approximately twelve percent of potential recruits for neuropsychiatric problems.⁷⁵ Despite changed procedures, induction centers continued to deny approximately one in eight recruits because of mental issues.

The optimistic belief that rigorous testing and screening at induction stations

⁷³ S. Kirston Weinberg, “The Combat Neuroses,” *The American Journal of Sociology* 51, no. 5 (1946): 468.

⁷⁴ Menninger, *Psychiatric Experience*, 577.

⁷⁵ Menninger, *Psychiatric Experience*, 578; Appel gives similar figures but for a slightly shorter time period. From 1 January 1942 to 30 June 1945 there were 1.75 million men rejected by the army, navy, or marines due to neuro-psychiatric concerns (NP). Appel, *Incidence of Neuropsychiatric Disorders*, 433. Proportionately this is the same as other estimates, 12% or 1 in 8 potential recruits turned away for NP disorders, and this NP disorders being the justification for 37% of all draftee/recruit rejections.

caught most potential problems and kept these men out of service was part and parcel of a belief in fixed and predictable personality types. The military promoted research to identify characteristics of the average soldier, but investigators found it far more problematic to figure out which characteristics predicted neuroses.⁷⁶ Even once staff at Walter Reed Hospital performed such studies, the results were impractical to implement. Porter and his colleagues looked at a group of men who had developed neuropsychiatric problems, then tallied the number whose life histories showed some of the fifteen characteristics contemporary psychology suggested would be good predictors:

- (1) Bed wetting beyond four years age.
- (2) Thumbsucking or nail biting beyond six years of age.
- (3) Failure to engage in competitive games involving risk of injury.
- (4) Tantrums in childhood.
- (5) Abnormal shyness or sensitiveness.
- (6) Preference of playing alone.
- (7) Repeated grades, difficulty with teachers, chronic truancy in school record.
- (8) Abnormal fears.
- (9) Shunning of girls after puberty.
- (10) Faints.
- (11) Excessive autonomic system reactions to emotion
- (12) Sulkiness under discipline.
- (13) Abnormal attachment to mother after puberty.
- (14) Stammering.
- (15) Obsessional traits.⁷⁷

The study found four or more traits were “not uncommon”⁷⁸ in hospitalized soldiers, but it required six or more before it was possible “to prognosticate a probable breakdown

⁷⁶ Porter, *What Has Psychiatry Learned*, 850.

⁷⁷ Porter, *What Has Psychiatry Learned*, 851; predictors number nine and thirteen presumably were associated with homosexuality, something mid-twentieth century psychiatry considered a mental illness in and of itself.

⁷⁸ Porter, *What Has Psychiatry Learned*, 851.

under stress.”⁷⁹ The main problem was, although it was possible to find characteristics common among soldiers who did break down, the same characteristics were also common among soldiers who did not. There appeared no clear divide between normal men and future neurotics.⁸⁰ Normal men might be latent neurotics.⁸¹

The military’s main concern was not mental health of prospective soldiers, it was their usefulness for the war effort.⁸² As Captain Francis J. Braceland explained, “[i]t was the functional capacity of a man which was to decide his future[.]”⁸³ Overall, testing for neuroses was less than intensive and focused on obvious signs of dysfunctional or maladaptive personalities. Apart from medical history reported by the recruit, which examiners scanned for “previous treatment or hospitalization for nervous and mental disorders,”⁸⁴ they asked the young man questions including whether he “had any worries”⁸⁵ or would admit to previous mental illness. Examiners forwarded suspected cases, in theory at least, for further study and dispensation. But in large part the focus of induction centers was to find and send on any and all men with military

⁷⁹ Porter, *What Has Psychiatry Learned*, 851.

⁸⁰ Bromberg, *The Role of Conditioned Responses*, 30.

⁸¹ Paul H. Hoch, “Psychopathology of the Traumatic War Neuroses,” *American Journal of Psychiatry* 100 (July 1943): 125.

⁸² Flicker, *Army Psychiatric Literature*, 795.

⁸³ Braceland, *Psychiatric Lessons*, 589.

⁸⁴ Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 513.

⁸⁵ Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 512.

potential.⁸⁶ They tried to exclude those men likely to “break down if they should be inducted[,]” but as military psychiatrists were quick to recognize, there was no clear test certain to predict who would adapt and who would break. “It is obvious[,]” Major McNeel wrote with benefit of hindsight in 1946 “that no single test or battery of tests whether of I.Q. or personality can give the answer; as to whether a man will make a satisfactory soldier.”⁸⁷

Prevention and Salvage

Gradually, mental health efforts expanded from exclusion through induction screening to include prevention and "salvage[.]"⁸⁸ Induction centers played an important role, but Army hospitals faced increasingly high admission rates for neuropsychiatric disorders. In 1942, slightly more than twenty-five of every thousand men had been in hospital for mental health reasons during the year. By August 1943 the number had risen to sixty-seven per thousand.⁸⁹ The rates of hospitalization were higher for those serving overseas, and even higher for those in active combat. Rates as high as two hundred and fifty per thousand, twenty-five percent, occurred among

⁸⁶ Kubie, *Technical and Organizational Problems*, 22.

⁸⁷ McNeel, *War Psychiatry in Retrospect*, 502.

⁸⁸ Wanke, *American Military Psychiatry*, 146; Lauren H. Smith, in “Treatment Activities in War Psychiatry,” *American Journal of Psychiatry* 101 (Nov 1944): 304, uses the term “salvage.”

⁸⁹ Wanke, *American Military Psychiatry*, 133, 139.

infantry involved in heavy combat.⁹⁰ One 1943 assessment placed war neurosis as “the most common mental casualty.”⁹¹ Robert Knight estimated neuropsychiatric casualties made up thirty percent of all war casualties. Faced with a massive problem, the military began an equally massive effort to prevent workforce loss, and return those who 'broke' to service or to the home front as quickly as possible.⁹²

Medical officers within the military began interpreting the problem as one of normal individuals or slightly damaged personalities facing overly rapid adaptation, extended, or excessive stress.⁹³ Psychoanalytic explanations before and during World War II generally assumed illness resulted from internal conflicts; in war, the conflict was usually between duty and danger.⁹⁴ Unconscious processes created neurotic illness

⁹⁰ Appel, *Incidence of Neuropsychiatric Disorders*, 434. The overall figures for the period from 1 January 1942 to 30 June 1945 were approximately 1 million admissions to hospitals for NP disorders. This was an average of 45/1000/year and 6% of all hospital admissions. Appel, *Incidence of Neuropsychiatric Disorders*, 433. Many of these (some estimates run as high as 40%) were found unsuitable for service during initial training; most shocking to ‘lay and military minds’ was the realization that “war neuroses formed such a large proportion of living casualties,…” Roy R. Grinker and John P. Spiegel, “Brief Psychotherapy in War Neuroses,” *Psychosomatic Medicine* (1944): 123.

⁹¹ Anon. “Sustained Strain Found to Cause War Neuroses,” *The Science News-Letter* 44, no. 25 (1943): 395.

⁹² Knight, *The Treatment of the Psychoneuroses of War*, 151.

⁹³ Grinker and Spiegel, *Brief Psychotherapy in War Neuroses*, 124-125; see also Anon, “War Neurosis Effects,” *The Science News-Letter* 42, no. 9 (1942): 134.

⁹⁴ Edward A. Streeker, “Neuropsychiatry,” *Proceedings of the American Philosophical Society* 88, no. 3 (1944): 204-07; Marjorie Van de Water, “Mental Combat Casualties,” *The Science News-Letter* 45, no. 25 (1944): 391, 394-96.

because of “a desire to be removed from danger[.]” which when left untreated, became fixed by “a progressive secondary goal of wishing to receive compensation or pension.”⁹⁵

Medical officers continued using this interpretation of neuroses caused by characteristics of the individual as an explanation for failures of psychiatric treatment.⁹⁶ For example, Major B. H. McNeel argued “[o]ne reason for the failure to return a large proportion of men to the front line was that even in their pre-casualty state many were vulnerable personalities.”⁹⁷ In his assessment, the developmental environment of an individual caused the original problem, a “vulnerability... due to the habit patterns and learned reactions”⁹⁸ which were fairly fixed by the time the man entered the Army.

It followed logically that although most soldiers did not break, anyone could. “No one is immune from a war neurosis[.]” warned Lieutenant Colonel Roy Grinker

⁹⁵ Hoch, *Psychopathology of the Traumatic War Neuroses*, 124; behavioral explanations were also used. For an example of psychoanalytic and behavioral explanations used in tandem see Hoch, *Psychopathology of the Traumatic War Neuroses*, 125.

⁹⁶ It also was used to argue WWI soldiers being treated for war neuroses (what had been called shell shock) in the Veterans Administration hospitals, had unconsciously chosen to become neurotic “to obtain Government compensation[.]” Kiene, Hasell and Miller, *Neuro-Psychiatric Examination*, 509. Kiene comes close to suggesting all longstanding war neuroses result from unconscious desire to obtain welfare.

⁹⁷ McNeel, *War Psychiatry in Retrospect*, 504.

⁹⁸ McNeel, *War Psychiatry in Retrospect*, 504.

and Major John Spiegel.⁹⁹ In the same vein, Major John Appel argued most people with identified neurotic or psychopathic personalities leading to hospitalization during the war were “no sicker than when they came into the Army[.]”¹⁰⁰ The sickness had simply manifested. Although the stresses of war rendered them unfit for service, the underlying flaws preexisted.

It is important to note the shift, from identification and exclusion to prevention and rapid treatment, suggests changing interpretation of neuroses. With the earlier understanding, physicians could identify a person who was neurotic because, although the problem was internal, it was also ongoing and likely to include noticeable external manifestations; it was a disorder existing within the individual. A neurotic personality was prone to stereotyped, inefficient, and maladapted responses. An individual either had this disorder or did not, they were either neurotic or not. Increasing interest in prevention and rapid treatment indicates a shift toward focus on neurotic reactions, rather than neurotic personalities, as the problem. Although some people were neurotic in most settings, others did not manifest these maladaptive reactions except under stressful conditions. Neuroses could exist within the individual without external signs before they became fixed and self-sustaining, a full-blown neurosis. Unfortunately,

⁹⁹ Grinker and Spiegel, *Brief Psychotherapy in War Neuroses*, 123; McNeel, reached a similar conclusion. McNeel, *War Psychiatry in Retrospect*, 505.

¹⁰⁰ Appel, *Incidence of Neuropsychiatric Disorders*, 434. Note that Appel considers these men as sick whether they require hospitalization or not; the men are sick even if it is not apparent in a civilian setting; Flicker similarly argues “Many soldiers were mildly psychoneurotic prior to induction, and having a restricted adaptability, fail in military life.” Flicker, *Army Psychiatric Literature*, 797.

physicians could not rapidly fix an internal disorder if it was a disorder of personality.

Prevention and rapid treatment made sense if neuroses were formed because of neurotic reactions to stress; lessening stressors could help an individual adapt. Samuel Futterman, working with the Veterans Administration, suggested in 1951 that the symptoms seen in war neuroses – startle reactions, nightmares, anxiety, depression, aggression – were active attempts by an individual to heal itself. “The symptoms[,]” he explained, “must be thought of in terms of abortive attempts at self-cure through a reliving of the original danger in small doses in an effort to master the threat[.]”¹⁰¹ The earlier idea of neuroses focused on an endogenous etiology, inner and interacting drives caused poor reactions to the environment. Neurotic reactions, the newer concept of neuroses, involved interaction of a person with the external environment. Neurotic reactions had endogenous and exogenous origins.¹⁰² The new concept included the earlier understanding of neurotic personalities, but acquired new breadth by including everyone who showed neurotic reactions under stress.¹⁰³ It placed greater emphasis on anxiety and stress.

Neurotic reactions manifested in affective behavior, breakdown of emotional control, as well as somatic symptoms. By late 1941, Allies were reporting that up to

¹⁰¹ Samuel Futterman and Eugene Pumpian-Mindlin, “Traumatic War Neuroses Five Years Later,” *American Journal of Psychiatry* 108 (December 1951): 401.

¹⁰² See Hoch, *Psychopathology of the Traumatic War Neuroses*, 125; see also Strecker, *Neuropsychiatry*, 204-07.

¹⁰³ For more extended analysis of internal and external factors in war neuroses see Weinberg, *The Combat Neuroses*, 463-78.

one-quarter of medical cases involved peptic ulcers, and believed them “due, partly at least, to nervous strain.”¹⁰⁴ Neuropsychiatrists could explain certain physical symptoms, such as peptic ulcer, as psychosomatic issues. New York psychiatrist Sandor Rado, a man with military experience in both World Wars, suggested “The spread of psychoanalytic knowledge is cited as a biggest reason for the changing symptoms of war neurosis, a change also reflected in civilian practice. Certain symptoms have lost their effectiveness since they are labeled ‘functional,’ ‘psychogenic,’ or ‘escape mechanisms.’ Others supposed to be more physical, are still useful because they have not been so labeled.”¹⁰⁵

An example of the overlap between earlier and later explanations is evident in Paul Hoch’s “Psychopathology of the Traumatic War Neuroses.” Endogenous events caused “emotional shock”¹⁰⁶ and conflict between drives. The primal (id) with a desire to escape danger conflicted with “the sense of duty”¹⁰⁷ (superego), leading to “total or partial collapse of the self-government of the individual” who turned to illness as a way to resolve the conflict. Whether or not the individual became neurotic depended on the ability of the ego/self to negotiate a socially acceptable solution. How neuropsychiatrists understood neuroses informed treatment choices. Treatment of

¹⁰⁴ Anon, *Men Who Break in Army*, 148.

¹⁰⁵ Anon, “This War’s Neurosis,” *The Science News-Letter* 42, no. 26 (1942): 404.

¹⁰⁶ Hoch, *Psychopathology of the Traumatic War Neuroses*, 125.

¹⁰⁷ Hoch, *Psychopathology of the Traumatic War Neuroses*, 124.

internal conflict focused on reintegrating inner drives. Instigation of problems by external events led Paul Hoch to also emphasize exogenous factors specific to a soldier's environment, including fatigue, sudden threats or catastrophic events, isolation, or changes in his group. Whether the individual became neurotic or not depended on his capacity to function or adapt and return to "the normal balance of excitation and inhibition[.]" Appropriate treatments included: reducing stressors (making events more predictable), maintaining strong group affiliation, preventing anxiety and somaticization from feeding back on each other (that is treating asthma or gastro-intestinal concerns), and providing soldiers with the time and tools to adapt through training and knowledge about mental health, or short-term medical treatment focused on reducing stress sufficient to allow adaptation.¹⁰⁸ Hoch's understanding of neuroses illustrates the shifting focus, increasing emphasis on the role of stress causing "previously unstable or psychologically vulnerable individuals"¹⁰⁹ to develop neurotic reactions.

The military medical leadership recognized the shift from civilian to soldier was stressful, and of course the hectic periods of battle interspersed with the monotonous boredom of military life added further stressors not seen in civilian life.¹¹⁰ Brigadier

¹⁰⁸ Hoch, *Psychopathology of the Traumatic War Neuroses*, 124-26.

¹⁰⁹ Bromberg, *The Role of Conditioned Responses*, 26.

¹¹⁰ Appel's assessment was that most NP patients would not require hospitalization if not for the war experience. They could have gone without treatment, been outpatients, or stayed in privately run sanatoria. In this category he placed psychoneuroses, psychopathic personality, and mental deficiency. Appel, *Incidence of*

Menninger declared that “[t]here are few, if any, life situations in civilian experience which are comparable in their demands to the amount of adjustment that is required regularly in the Army at War.”¹¹¹ One of the most important problems, according to contemporary assessments, was the requirement for soldiers to give up a cushy, self-oriented, civilian life; “as a free and independent American he feels the necessary curb of regimentation. Things are done to him over which he has no influence[,]”¹¹² explained Lieutenant Colonel Smith. A civilian’s life focused on “comfort and privilege,” and “to neglect personal responsibility.”¹¹³

Descriptions of the shift from a soft life of luxury to the virile masculine teamwork of military life abounded. Lieutenant Colonel Smith gives perhaps the most amusing description:

...simple observation points out certain problems and conflicts encountered by GI Joe which are obvious and common in his experience as he comes into the Army. He has been taught that this is the greatest nation in the world; that he is free, independent, and had the right to say and do anything he pleases. ...self-expression and individual self-determination have been encouraged. ...paternalism has...freed him of any great degree of responsibility and with little effort he makes a comfortable, near luxurious living. His social and religious life have emphasized good fellowship, passivism and absolute security. His political life tends to say, “Let George do it.” At home he has affection, the choice of what he wants to eat, a \$39.95 inner-spring mattress, some

Neuropsychiatric Disorders, 433-34.

¹¹¹ Menninger, *Psychiatric Experience*, 580.

¹¹² Smith, *Treatment Activities*, 309.

¹¹³ McNeel, *War Psychiatry in Retrospect*, 502; see also opinions of older relatives on their children and grandchildren.

kind of gadget to make the furnace go, and the bathroom has been moved inside the house. He gets to work by a five-cent ride or in a car on time payments. He has more entertainment than he knows what to do with by movie, radio, baseball, games, and vacation with pay. The girls are pretty and the friends are plentiful. He can take or leave them just about as he chooses. Then comes war.¹¹⁴

A soldier faced a regimented lifestyle; “he is told when he will get up, eat, work, go to bed; how he will talk, walk, and behave[.]”¹¹⁵ He could no longer focus on being an individual. “He has little or no feminine companionship. He is no longer an individual person such as he was before but is held strictly accountable to the standard of the group.”¹¹⁶ Strong and positive affiliation with the group was a sign of mental health, while feeling isolated, having poor interaction with superiors, and general “[u]nsatisfactory adjustment to the group in which he serves”¹¹⁷ suggested developing neuroses.

Increasingly, military medical professionals believed that in stressful situations even normal individuals sometimes returned to stereotyped responses as a defense. This was the essence of a neurotic reaction. As Samuel Futterman explained, a neurotic personality used “overridealization of the past” as a “defensive function” when the “ego’s ability to master the environment has been violently shattered by the traumatic

¹¹⁴ Smith, *Treatment Activities*, 308; a similar, although more dry, description can be found in August B. Hollingshead, “Adjustment to Military Life,” *The American Journal of Sociology* 51, no. 5 (1946): 439-47.

¹¹⁵ Smith, *Treatment Activities*, 309.

¹¹⁶ Smith, *Treatment Activities*, 309.

¹¹⁷ Hoch, *Psychopathology of the Traumatic War Neuroses*, 124.

event. Defensively, the ego overidealizes the pretraumatic period in an attempt to find for itself some stability, some security[.]”¹¹⁸

An initial neurotic reaction could be either passing, or develop into a continuing problem characterized by rumination and reliving the traumatic event, or generalizing anxiety and increased somatic symptoms.¹¹⁹ Adrenalin played an important role in neuroses becoming chronic, suggesting to Lieutenant Commander Bromberg that because “the patient cannot control his ruminations recapitulating traumatic events,...these are on a physiological level.”¹²⁰ The initial threat produced epinephrine (also known as adrenalin), which increased “irritability to external stimuli[.]”¹²¹ which in turn primed the system so “milder ordinary ineffective stimuli result in the liberation of still more epinephrine. Resultant physical symptoms further increase[d] fear so both external and internal stimuli continue[d] and increase[d] the reaction.”¹²²

In this new conceptualization of neuroses, stress was a major cause of mental

¹¹⁸ Futterman and Pumpian-Mindlin, *Traumatic War Neuroses Five Years Later*, 404.

¹¹⁹ This interpretation trickled down as far as newspaper reports. George E. McMillan, “Move Psychiatrists into Front Lines: Navy Begins What it Regards as Comprehensive Program for Treatment of War Neuroses,” *Joplin Globe* [Joplin, MO], April 2, 1944.

¹²⁰ Bromberg, *Role of Conditioned Responses*, 30.

¹²¹ Robert G. Heath and Stephen H. Sherman, “The Use of Drugs in the Treatment of Traumatic War Neuroses,” *American Journal of Psychiatry* 101 (November 1944): 355.

¹²² Heath and Sherman, *Use of Drugs*, 355.

illness, either because it tilted a precarious balance between drives or because it altered learning behavior and response to stimuli. If mental health was tenuous, if no personality was infinitely adaptable, if normal men could break under stress, there was a serious problem. War was stressful. Life was stressful. This reinterpretation of mental illness as a continuum, with vast numbers of Americans either neurotic or potentially neurotic, combined with focus on the role of stress, broadened the scope and importance of mental health professionals in the war effort.

Increased Roles for Neuropsychiatry

Psychiatrists recruited into the military could not meet the increased need for mental health professionals. Short and intensive programs trained physicians from other fields. Nurses, social workers, orderlies, and general officers became participants in mental health boot camps. In replacement training centers, psychiatrists worked in teams with a psychologist, a psychiatric social worker (usually from the Red Cross), and secretaries;¹²³ soon, these mental health professionals operated in induction centers, regional and station hospitals, evacuation centers, outpatient units, training camps, on transports, and in disciplinary barracks.¹²⁴ A Chief Consultant, then an entire Division of Neuropsychiatry were appended to the Army Surgeon General's staff.¹²⁵ From

¹²³ Smith, *Treatment Activities*, 303.

¹²⁴ Menninger, *Psychiatric Experience*, 577.

¹²⁵ Wanke, *American Military Psychiatry*, 137.

beginning beyond the pale of military planning – in an Army whose regiments included staff veterinarians, while psychiatrists disappeared from the order of battle above the corps level – mental health became an important locus of the war effort.¹²⁶

To meet assessed need, the military needed more trained professionals. Most Army and Navy physicians dealing with mental health matters gained training during military service. The number of naval officers with some degree of psychiatric training climbed from 25 before the war to 693. More than half received training while in service.¹²⁷ Of the 2400 physicians acting as neuropsychiatrists for the Army during the conflict, only 993 were members of the American Psychiatric Association (APA).¹²⁸ Although membership was less ubiquitous among clinical psychiatrists, many of the members joined the Association during the War. The swell in numbers illustrates the rising importance of psychiatry within the military, the status of the APA outside it, and the dramatic increase in self-identified neuropsychiatrists among physicians.

Increased numbers of auxiliary mental health personnel supported and amplified efforts at prevention and treatment. Prevention included promoting "mental hygiene" through education,¹²⁹ planning the induction and training process, promoting fixed tours of duty, and leadership training for officers. "From the day he is inducted the process

¹²⁶ Wanke, *American Military Psychiatry*, 130.

¹²⁷ Braceland, *Psychiatric Lessons*, 588.

¹²⁸ Menninger, *Psychiatric Experience*, 577, 580.

¹²⁹ Smith, *Treatment Activities*, 303.

of incorporating him, as a person, into the fighting forces must begin[.]" explained Major McNeel. Recruits learned to understand emotion and bodily function as linked.¹³⁰ They learned emotional turmoil was normal for men in their situation, but the military expected them to work through it quickly. Soldiers' indoctrination taught them that anxieties were normal, but they needed to return to the group quickly.

New Ideas, New Treatments, New Results

When prevention failed, mental health efforts throughout the military focused on triage, rapid treatment and return to duty, hospitalization, or discharge. Part of the reason mental health professionals returned from the war with a shiny new image was their proven effectiveness in treating traumatic neuroses during World War II. During the war, medical officials treated large numbers of men suffering from similar conditions. The military leadership demanded firm diagnoses and short periods of treatment leading to rapid return of soldiers to the war or home front. These requirements promoted use of shortcuts through traditional psychiatric practices. They promoted techniques such as group therapy, the use of drugs to lessen stress and allow the mind time to adapt. They justified short-term psychotherapy using narcotics to promote reliving of events (abreaction), breaking through defenses to speed psychoanalytic treatment, or force readjustment. To an extent these were "old

¹³⁰ Smith, Treatment Activities, 303.

treatments” combined with “new technologies[.]”¹³¹

Group therapy developed in the 1920s and 30s as an offshoot of earlier efforts to educate groups of patients with physical diseases such as tuberculosis. In the 1910s, J. H. Pratt extended his techniques of “instruction and encouragement”¹³² to patients thought to suffer from illnesses experienced in the body, but caused by the mind. A series of papers by Trigant Burrow pounded out the theoretical basis, beginning in 1924 with “Social Images Versus Reality.” A formal conference on ‘Group Method’ in 1932 led to William Allen White applying the technique at St. Elizabeth’s Hospital. By the late 1930s the technique had firm roots in the United States.¹³³

Noting the rapidly increasing need for psychiatric services after the United States entered World War II, leaders of the new group psychotherapy schools approached military leaders to offer their services. The technique became widely used, inside and outside formal hospitals and clinics, because it made more efficient use of a scarce resource, trained neuropsychiatrists. Group therapy offered the prospect of treating large numbers of patients, while allowing the psychiatrist more distance than psychoanalysis (this theoretically increased his objectivity). It could assist identifying the most easily cured cases who could then receive short-term psychotherapy, and might even give the patients in group treatment insight into their own social

¹³¹ Wanke, *American Military Psychiatry*, 140.

¹³² Joseph I. Meiers, “Origins and Development of Group Psychotherapy,” *Sociometry* 8 (August-November 1945): 503.

¹³³ Meier, *Origins and Development of Group Psychotherapy*, 504-05.

interactions.¹³⁴

That group psychotherapy focused on improved social adjustment, through social interaction, was part of its charm; it fit contemporary beliefs about healthy human behavior. People, persons, had personalities which were patterns of interaction within the group. Roy Grinker and L. A. Spiegel influentially argued, in *Men Under Stress*, that part of group therapy's benefits came from its approximation of humankind's natural situation, "as a gregarious animal seeking a satisfactory niche in his social setting."¹³⁵ Interacting within a group promoted becoming normal, fitting in to the norms of groups. "By working out his problems in a small way," Grinker and Spiegel wrote, "he should be theoretically able to face the larger group that is his world in an easier manner."¹³⁶ The War Department formally recognized, in its *Technical Bulletin 103*, superiority of group therapy over individual therapy when the soldiers involved were having interpersonal problems, for example, "in dealing with suspicious, hostile and guilty feelings" because it helped "minimize(s) personal feelings."¹³⁷

¹³⁴ Smith, *Treatment Activities*, 306; Wanke, *American Military Psychiatry*, 140.

¹³⁵ As quoted in Meiers, *Origins and Development of Group Psychotherapy*, 511.

¹³⁶ As quoted in Meiers, *Origins and Development of Group Psychotherapy*, 511.

¹³⁷ Meiers, *Origins and Development of Group Psychotherapy*, 510; the War Department promoted another type of group therapy during the war, dramatics. Amateur and impromptu dramatics were theoretically cathartic, as well as forcing individuals to interact in a manner suggesting the group effort was more important, but relied on, the effort of individuals. Meiers, *Origins and Development of Group*

Drugs such as bromides, amyals, and barbiturates provided a more medicalized approach to treatment of war neuroses. Whether used to enforce rest, promote reliving repressed events, or short-circuit the feedback of anxiety's psychosomatic effects,¹³⁸ the ultimate goal was the soldier curing himself sufficiently to return to work. Apart from alcohol, the most widely used drugs were sodium amytal and other barbiturates.¹³⁹ High doses rendered patients unconscious long enough to reduce fatigue, or work through problems in a dream-like state. But, while the soldier tidied his mind, nurses needed to care for his body, so the procedure drained manpower too much for widespread use. Moderate doses of barbiturates promoted sleep and therefore reduced the fatigue thought to play an important role in whittling down the soldier's mental defenses. Harry MacKinnon promoted use of narcotics to promote relaxation and sedation; most of the time patients became conscious before their mental defenses returned to full force, so "the natural curing process can get a start before the defenses return."¹⁴⁰ Dosages heavy enough to shut down conscious defenses provided the

Psychotherapy, 503-04, 508, 511, 514.

¹³⁸ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 355.

¹³⁹ Barbiturates acted faster than bromides, but were more effective and easier to administer. Sodium amytal and pentothal were less widely used but, because they were mainly associated with the abreaction therapy that gained public notice after the war, were more visible. Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 356.

¹⁴⁰ Harry L. MacKinnon, "Narcoanalysis and Allied Procedures," *American Journal of Psychiatry* 105 (September 1948): 224-25.

opportunity for neuropsychiatrists to distinguish, in theory at least, the difference between malingerers and those with true psychological problems.¹⁴¹

Increasingly, military physicians relied on drugs for a shortcut through psychotherapy, usually once rest alone failed to cure.¹⁴² Hypnotic and sedative effects lowered mental defenses, effectively putting the superego to sleep while the doctor talked to the ego and id. Grinker and Spiegel gained fame, within the American Psychiatric Association at least, by using sodium pentothal and suggestion to lead soldier into reliving their traumas.¹⁴³ The general techniques, called narcosynthesis and narcoanalysis, lacked clear boundaries between them.¹⁴⁴ In general, narcoanalysis used narcotics to lessen defenses, release repressed material, and thereby shorten the normal process of psychoanalysis from years to weeks.¹⁴⁵ Narcosynthesis was a shock-therapy version of narcoanalysis; using drugs not only to weaken defenses, but also to reduce

¹⁴¹ Jean Delay, "Pharmacological Exploration of the Personality: Narco-Analysis and Methedrine Shock," *Proceedings of the Royal Society of Medicine* 42 (July 1949): 491.

¹⁴² Menninger, *Psychiatric Experience*, 579; Robert L. Moody, "Bodily Changes During Abreaction," *The Lancet* 251, no. 2 (1946): 934-35; McNeel, *War Psychiatry in Retrospect*, 505; for an easy to read description of treatments see Marjorie Van de Water, *Mental Combat Casualties*, 391, 394-96.

¹⁴³ Roy R. Grinker and John P. Spiegel, *War Neuroses in North Africa: The Tunisian Campaign (Jan-May 1945)* (New York, NY: unpublished, distributed by Josiah Macy, jr. Foundation, September 1943).

¹⁴⁴ McNeel, *War Psychiatry in Retrospect*, 504.

¹⁴⁵ MacKinnon, *Narcoanalysis and Allied Procedures*, 224.

reality testing.¹⁴⁶ Neuropsychiatrists talked soldiers through their traumatic experiences and taught how to place the distressing events at an emotional distance. Some patients obtained a cathartic experience, termed abreaction.¹⁴⁷ Because soldiers experienced trauma in an emotional manner, narcosynthesis attempted to force readjustment between the individual and his experience of reality.¹⁴⁸ It removed the excessive emotional distance of repression so the soldier relived the traumatic experience and learned a more socially acceptable way to recall or deal with it. It was no longer emotionally crippling.¹⁴⁹ Use of barbiturates to hasten psychotherapy, through hypnosis, recall of traumatic events, or abreaction, was the most publicized technique.¹⁵⁰

Recognition of drugs' use beyond adjuncts to psychotherapy, although less dramatic than narcosynthesis, were in practical terms the most novel treatment shortcuts. Use of pharmaceuticals as treatments entailed interpreting neuroses as developing processes, continuation of emotional reactions through psychosomatic feedback, resulting in somatic generalization of symptoms.¹⁵¹ Neuroses developed from

¹⁴⁶ Strecker, *Neuropsychiatry*, 205.

¹⁴⁷ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 357; McNeel, *War Psychiatry in Retrospect*, 504; Moody, *Bodily Changes During Abreaction*, 934.

¹⁴⁸ McNeel, *War Psychiatry in Retrospect*, 504.

¹⁴⁹ Moody, *Bodily Changes During Abreaction*, 934.

¹⁵⁰ McMillan, *Move Psychiatrists Into Front Lines*, A11.

¹⁵¹ Bromberg, *Role of Conditioned Responses*, 29.

neurotic reaction to external stimuli, to the full-blown neuroses blithely continuing even with reduction or removal of the stressful stimuli.¹⁵² Robert Heath and Stephen Sherman provide a clear statement of the effects of this reinterpretation on drug treatment when they argued that the “subtle and intricate workings of the autonomic nervous system”¹⁵³ broadened logical uses of existing drugs. Psychopharmaceuticals acted on the nervous system.

During the war, physicians used barbiturates and amytals to break the psychosomatic cycle. Heath and Sherman treated soldiers afflicted by long-standing neuroses in a manner physically similar, but conceptually novel, compared to traditional methods. They assumed that traumatic events caused a physiologic reaction, release of adrenalin, which made body and mind prone to overreact to further events, which in turn resulted in production of more adrenalin. Therefore, physicians tried to break this cycle of adrenalin overreaction. Heath and Sherman saw insomnia, sweaty palms, “jitteriness, tremor, an empty feeling in the stomach, no appetite, pounding heart, thumping in the head,” as signs of adrenal overreaction.¹⁵⁴ Using ergotamine to neutralize the epinephrine (adrenalin) short-circuited “the chain of activity[.]”

¹⁵² Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 355-56.

¹⁵³ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 355.

¹⁵⁴ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 357; Heath himself uses the terms “autonomic imbalance” and “underlying cycle”, 355, 357.

Ergotamine was a therapeutic drug, which appeared to decondition the over-response.¹⁵⁵ Heath still saw this somatic treatment as an “adjunct to psychotherapy[,]”¹⁵⁶ but the key effect was neutralizing the emotional response physically, which in turn allowed objective analysis of traumatic memories.¹⁵⁷ This idea of psychosomatic feedback, from neurotic reaction to generalized and self-contained neuroses, played a key role in justifying use of Valium to treat neuroses and their somatic signs including: anxiety, fatigue, gastrointestinal, urinary, and sexual problems, muscle pains and headaches.¹⁵⁸

With new protocols and treatments, most neuropsychiatric casualties quickly returned to duty or their homes.¹⁵⁹ Treatment centers close to combat sent sixty percent of soldiers back to service within a week. Within a month ninety percent returned to service.¹⁶⁰ Convalescent hospitals in the U.S. returned between fifteen and twenty-five

¹⁵⁵ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 357.

¹⁵⁶ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 358.

¹⁵⁷ Anon, “Drug for War Neurosis,” *The Science News-Letter* 45, no. 22 (1944): 343.

¹⁵⁸ Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 355; Porter, *What Has Psychiatry Learned*, 854.

¹⁵⁹ For a description see Grinker and Spiegel, *War Neuroses in North Africa*, 28; also Grinker and Spiegel, *Brief Psychotherapy in War Neuroses*, 125.

¹⁶⁰ Menninger, *Psychiatric Experience*, 579, 581; Postwar articles in medical journals often suggest recognition that rapid treatment close to the front line was an important discovery or outcome of the war experience. While the World War II experience heightened awareness that quick and close treatment sped cure for the majority of neuropsychiatric casualties, one of the most important lessons psychiatrists

percent of the remainder to duty, and even the remaining cases had a relatively high discharge rate, suggesting the new methods provided sufficient cure to avoid expensive long-term custodial care.¹⁶¹ Comparison with medical treatment of physical injury only added to the luster of mental health professionals' prestige. Neuropsychiatry 'cured' or prevented problems to the extent that soldiers could continue as soldiers. Every active soldier was a psychiatric success story.

Conclusion

Before World War II, psychiatrists tacitly conceptualized most nonorganic, functional, mental illnesses as problems of adaptation. While this continued, the World War II experience was a locus of change in mental health theory. The new conceptualization placed greater emphasis on stress, prevention, early treatment,¹⁶² the individual as part of the group,¹⁶³ and a continuum from mental health to mental

drew from WWI was that treatment needed to be immediate. While those treated quickly, near the front lines, were likely to improve enough to return to the role of cannon fodder, those evacuated to the United States and Britain for treatment tended to prove chronic cases. More than half of the soldiers injured in WWI suffered from acute war neuroses. In the United States approximately 68,000 of these men were still in Veterans Hospitals during World War II. Knight, *The Treatment of the Psychoneuroses of War*, 148; see also Van de Water, *Mental Combat Casualties*, 391, 394-96.

¹⁶¹ Menninger, *Psychiatric Experience*, 579, 581; Neuropsychiatric discharges made up 41% of all medical discharges given between 1 January 1942 and 30 June 1945. 70% of the NP discharges classified the reason for discharge as psychoneurosis. Appel, *Incidence of Neuropsychiatric Disorders*, 435.

¹⁶² Menninger, *Psychiatric Experience*, 581, 585.

¹⁶³ McNeel, *War Psychiatry in Retrospect*, 503; Menninger, *Psychiatric*

illness.¹⁶⁴ Mental health professionals, overall, now considered neuroses far more prevalent and socially important than organic disorders and psychoses.¹⁶⁵ Some individuals adapted more easily than others, but almost none could adapt continuously under harsh and changing conditions. In other words, most personalities were neurotic to some extent, they lagged in extinguishing old stimulus response patterns and developing new ones.¹⁶⁶ Faced with uncertain conditions they fell back on old patterns. The problem was neurotic reactions to stress,¹⁶⁷ something preventable by reducing stress, giving people time to adjust, or training people to be more adaptable.

Rather than focus on mental illness, experts increasingly decided that the focus now needed to be on mental health, preventing vast numbers of fragile personalities from developing neurotic reactions. David Flicker describes true war-induced anxiety as “only exceptionally a reaction to gross external danger.”¹⁶⁸ Soldiers’ fears were real and temporary, while in the civilian population “[m]an lives more frequently in a

Experience, 582.

¹⁶⁴ McNeel, *War Psychiatry in Retrospect*, 501; Alan Gregg, “Lessons to Learn: Psychiatry in World War II,” *American Journal of Psychiatry* 104 (October 1947): 218.

¹⁶⁵ Menninger, *Psychiatric Experience*, 585; Braceland, *Psychiatric Lessons*, 593.

¹⁶⁶ Porter, *What Has Psychiatry Learned*, 851.

¹⁶⁷ McNeel, *War Psychiatry in Retrospect*, 501.

¹⁶⁸ Flicker, *Army Psychiatric Literature*, 799.

borderline, often quite unrealized, anxiety state.”¹⁶⁹

Change in prevalent treatments was part and parcel of the new conceptualization of mental health and illness. “The treatment obviously depends on one’s conception of the disorder[,]” wrote Major McNeel. Explanation of neurosis as “deep-seated conflicts[,]” with endogenous drives playing a central role, fit with “special, rather complex techniques” such as psychoanalysis. The goal had been to teach the patient to gain insight into his own mental processes so better to resolve conflicts between internal forces and desires. But focus on neurotic reactions to stress emphasized “a simple reaction of the individual to the immediate situation,”¹⁷⁰ which required rapid treatment to prevent “fixation and persistent disability.”¹⁷¹ This rapid treatment could now include more “[s]pecific therapy”¹⁷² with drugs to short-circuit the psychosomatic feedback loop of developed neuroses. Mental health practice needed to be preventative, part of “the field of psychosomatic medicine”¹⁷³ which, Captain Braceland prophetically suggested, might lead to “much more attention...to emotional overlay upon actual organic diseases.”¹⁷⁴

¹⁶⁹ Flicker, *Army Psychiatric Literature*, 799.

¹⁷⁰ McNeel, *War Psychiatry in Retrospect*, 504.

¹⁷¹ McNeel, *War Psychiatry in Retrospect*, 506.

¹⁷² Heath and Sherman, *Use of Drugs in the Treatment of Traumatic War Neuroses*, 356.

¹⁷³ Gregg, *Lessons to Learn*, 218.

¹⁷⁴ Braceland, *Psychiatric Lessons*, 593.

Although war neuroses, dealing with the World War II military, describe neurotic reactions in men, a gendered understanding is used. Neurotic, inappropriate, responses were emotional behaviors and therefore associated with the feminine. Lieutenant Commander Norbert Bromberg, writing on “The Role of Conditioned Responses in Emotional Disturbances of War,” declares it axiomatic that “a traumatic stimulus causes a disturbance in the organism which we call emotion[.]”¹⁷⁵ The emotional overreaction linked mental and physical/somatic responses, and therefore treatments dulling emotional responses to stress reduced psychosomatic complications.¹⁷⁶ While the primitive stereotyped response of neuroses isolated the mind from emotion, cure or symptomatic relief required relinking emotional response to events, then learning appropriate methods to tamp down emotional responses.¹⁷⁷ Implicitly, the ideas of mental health and illness developing in the mid-twentieth century defined emotional response as unhealthy, and cerebral ratiocination – objective, logical, and freed from the constraints of personal history – as the preferred way to interact with society.

The effects of World War II on the field of mental health were profound and long lasting. Large numbers of soldiers, nurses, and general physicians received crash courses in prevention, identification, and treatment of mental health problems. There

¹⁷⁵ Bromberg, *The Role of Conditioned Responses*, 28.

¹⁷⁶ Hoch, *Psychopathology of the Traumatic War Neuroses*, 126.

¹⁷⁷ Hoch, *Psychopathology of the Traumatic War Neuroses*, 126.

were also simply more trained psychiatrists; the Army trained over sixteen hundred physicians during World War II, thirteen hundred of these using a three-month course.¹⁷⁸ “Never before has there been so much interest among medical men in psychiatry as we have seen expressed in the Army[.]”¹⁷⁹ wrote Lieutenant Colonel Lloyd Grinker and Major John Spiegel. Physicians, psychologists, and auxiliary personnel returned to civilian life indoctrinated in the new ways of understanding mental health and illness.¹⁸⁰ When the 250 neuropsychiatry-trained physicians produced by the Navy returned to the U.S. the majority worked in private practice, usually focused on neuropsychiatry. Fifty-five percent worked primarily in neuropsychiatry, fifteen percent in general practice, thirteen percent in psychoanalysis.¹⁸¹ In Grinker and Spiegel’s assessment, military experience produced a shift from traditional psychoanalysis to more modern dynamic psychiatry. Military trained neuropsychiatrists were “interested in dynamic psychiatry[.]” Grinker and his colleague proclaimed, because “they have seen how little value there is in diagnostic labeling, persuasion, suggestion and authoritative forcing.”¹⁸² Innovative techniques,

¹⁷⁸ Menninger, *Psychiatric Experience*, 580.

¹⁷⁹ Grinker and Spiegel, *Brief Psychotherapy in War Neuroses*, 131.

¹⁸⁰ Braceland, *Psychiatric Lessons*, 592; Gregg, *Lessons to Learn*, 219; Menninger, *Psychiatric Experience*, 580; Smith, *Treatment Activities*, 303.

¹⁸¹ Elmer L. Caveny and Edward A. Strecker, “Subsequent Nation-Wide Effects of World War II Navy Psychiatric Training Program,” *American Journal of Psychiatry* 109 (January 1953): 482.

¹⁸² Grinker and Spiegel, *Brief Psychotherapy in War Neuroses*, 131; Navy

combined with belief in a widespread need for active prevention and treatment of neuroses, made mental illness an important and potentially solvable national problem. The new techniques, especially group therapy and drug therapy, introduced treatment options to those without the funds and time for long-term psychoanalysis.

Therefore, after the war, Americans had a different understanding of mental health. Mental health was a goal, not a thing. Mental health and mental illness were a continuum. Those institutionalized with chronic psychoses were still a problem, but it was easy to think of the institutionalized mentally ill as ‘them.’ Neuroses were the real danger, neuroses affected ‘us.’ Normal people, faced with stressful situations, could become neurotic. All of ‘us’ were at risk; the age of anxiety had begun.

neuropsychiatrists no longer associated with the military were employed in ways typical of broader changes in psychiatric practice. Only 10% worked in custodial mental hospitals, 13% practiced psychoanalysis, while 54% went into private practice which they did not consider psychoanalysis-based. Caveny and Strecker, *Subsequent Nation-Wide Effects*, 482.

CHAPTER 3. THE AGE OF ANXIETY: NATIONAL BATTLES AGAINST MENTAL ILLNESS

From the end of World War II, through to the early 1960s, average Americans consciously sought mental health. The mental health professions tried, and failed, to meet the growing demand for services. Americans increasingly looked at their personal, family, and national problems as problems related to personal mental health. At least as important was developing focus on promoting and maintaining mental health other than treatment of mental illness. Physician Thomas A. Gonda,¹⁸³ in an article for the *Annual Reviews of Medicine* summarized the change; “the trend[,]” he wrote, “has been to devote increasing attention and effort to the problems of life stress and to the treatment and prevention of neurotic disorders.”¹⁸⁴

How psychiatrists understood mental health shifted from focus on personality developed “as a reaction to the real social world in which an individual grew up[,]”¹⁸⁵ to interest primarily in an individual’s current situation. The latter emphasized interactions with the external environment, especially an organism’s social

¹⁸³ Thomas A. Gonda, M.D. worked in the Department of Psychiatry at Stanford’s School of Medicine.

¹⁸⁴ Thomas A. Gonda. “Psychiatry,” *Annual Reviews of Medicine* 10 (1959): 291.

¹⁸⁵ Daniel Katz, “Social Psychology and Group Processes,” *Annual Reviews of Psychology* 2 (1951): 138.

ecosystem.¹⁸⁶ Dr. Leon Saul, a Professor of Clinical Psychiatry at the University of Pennsylvania,¹⁸⁷ tied focus on neuroses to perceived growth in the field of psychiatry. “The emotional factors, which produce neurotic symptoms[,]” he wrote, were the same “emotional forces by which we all live.

As a result the scope of psychiatric ailments broadened.”¹⁸⁸ The conceptualization of mental health in terms of neuroses, personality defects, and psychoses promoted identification of diverse situations as problems of adaptation and inability to return to homeostasis, to balance of bodily functions. Dysfunction threatened the stability of America and its basic unit, the individual, which was both a person and a nuclear family unit.

National Efforts

When military officers assessed neuropsychiatric work in World War II, they often highlighted the future usefulness of war-gained knowledge, or took pains to explain the problems with extrapolating from war experience to civilian populations. This suggests there was a major debate over the ‘lessons’ of war. The debate, during and shortly after World War II, presumably focused on the extent to which the military

¹⁸⁶ Katz, *Social Psychology*, 137-72.

¹⁸⁷ Leon J. Saul, M.D. was also Chair of the Section of Preventative Psychiatry at the University of Pennsylvania School of Medicine.

¹⁸⁸ Leon J. Saul, “Preventive Psychiatry,” *Proceedings of the American Philosophical Society* 93, no.4 (1949): 330.

neuropsychiatric experience could or should apply to postwar America. Lieutenant Commander Norbert Bromberg took umbrage at the very idea that war neuroses were similar to neuroses seen in civilian life.¹⁸⁹ Terms such as “war neurosis” or “combat fatigue” were as inappropriate as the World War I term “shell shock[,]” he declared. Bromberg believed war neuroses differed fundamentally because the symptoms usually did not persist; true neuroses were long-term, fairly incurable, illnesses.¹⁹⁰ In this assessment he differentiated traditional concepts of neurosis as ongoing internal conflicts, often due to personality problems, from war neuroses, with an obvious environmental stressor as cause. Major John W. Appel warned readers of “Incidence of Neuropsychiatric Disorders in the United States Army in World War II,” that exigencies of diagnosis at recruitment stations shaped which classifications examiners used, probably influencing the high rates of neuroses and personality disorders in his own statistics.¹⁹¹ Yet, it was hard to ignore that extrapolating from recruitment statistics suggested at least one of every eight Americans was mentally unsuitable for military

¹⁸⁹ Norbert Bromberg, “The Role of Conditioned Responses in Emotional Disturbances of War,” *American Journal of Psychiatry* 103 (July 1946): 30.

¹⁹⁰ Bromberg, *Role of Conditioned Responses*, 26, 30-31.

¹⁹¹ John W. Appel, “Incidence of Neuropsychiatric Disorders in the United States Army in World War II (Preliminary Report),” *American Journal of Psychiatry* 102 (January 1946): 433; Flicker makes a similar argument. The military psychiatrist “does not have the necessary time to...seek the etiology of the aberration.... It makes no difference to the patient or the army if the soldier is discharged with the diagnosis of psychoneuroses, conversions hysteria, or psychoneurosis, anxiety tension state.” David J. Flicker, “Army Psychiatric Literature, Factors in Interpretation,” *American Journal of Psychiatry* 98 (May 1942): 796.

service. Kiene argued this high rate “does not indicate that our society is deteriorating[,]”¹⁹² it showed the military had higher standards than in the past. Based on hospitalization rates during the war, 2.5 percent of ‘normal’ Americans had little capacity to adapt, and between 6.7 and 25 percent of apparently healthy Americans were actually suffering from mental ill health. Even without including women in the estimate,¹⁹³ a pessimist could interpret the war experience as showing more than twenty percent of American men were sick of mind. And pessimists did. Doctor Alan Gregg, Head of the International Health Board at the Rockefeller Foundation, queried:

[T]he percentage of men between 18 and 35 being disqualified for military service because of some kind of disorder of personality—14% of all the men examined? Does a social structure which, in peacetime, shows one in seven so definitely deviant not deserve profound reflection and study?¹⁹⁴

Others warned that ignoring knowledge gained during the war could have dire results. There was far less debate over the role psychiatry should play in American society. The imminent postwar problem was the stress associated with demobilization. Helgesson warned of the dire results of unplanned demobilization on neurotic and preneurotic individuals, which involved millions of soldiers trying to adjust from

¹⁹² Hugh E. Kiene, Arthur Hassell and Himon Miller, “Neuro-psychiatric Examination at the R.I. Army Induction Station,” *American Journal of Psychiatry* 98 (January 1942): 510.

¹⁹³ Women were, and are, generally perceived as having a higher rate of functional, non-organic, mental health problems.

¹⁹⁴ Gregg, Alan, “Lessons to Learn: Psychiatry in World War II,” *American Journal of Psychiatry* 104 (October 1947): 219.

military back to civilian life. It was necessary to "plan for the solution of psychiatric problems incident to warfare before they become impossible to solve."¹⁹⁵ Helgesson was not alone in his concern; almost immediately after the war started, the National Research Council's Committee on Neuropsychiatry, War Neuroses and Neurosurgery began planning for eventual demobilization. As Grinker and Spiegel wrote, "Everyone-neophytes and psychiatrists have a great deal to learn from the study of war neuroses, much of which will be applicable to problems in civilian life."¹⁹⁶ Neuroses were far more widespread than the presumably organic psychoses,¹⁹⁷ and existing psychiatrists could not possibly deal with the millions in need of help after the war, especially using traditional methods.¹⁹⁸

Postwar mental health became a major public, political, and military concern. Helgesson prophesied that the potential social cost of "psychiatric mistakes" in World War II dwarfed the economic cost, "even if it amounts to over a billion dollars[.]"¹⁹⁹ There was a risk of disorganizing American society, the social aspect of the Republic. Victims of "psychiatric mistakes" and those unable to adjust to stressful conditions,

¹⁹⁵ Uno H. Helgesson, "Some Current Features of Psychiatry in the United States Navy," *American Journal of Psychiatry* 99 (March 1943): 638.

¹⁹⁶ Roy R. Grinker and John P. Spiegel, "Brief Psychotherapy in War Neuroses," *Psychosomatic Medicine* (1944): 131.

¹⁹⁷ William C. Menninger, "Psychiatric Experience in the War, 1941-1946," *American Journal of Psychiatry* 103 (March 1947): 580.

¹⁹⁸ Menninger, *Psychiatric Experience*, 580, 585.

¹⁹⁹ Helgesson, *Current Features*, 638.

such as the shift from military back to civilian life, threatened to form a large population drawing away from American society by living lives of "utter uselessness[.]" Military neuropsychiatric casualties, and potential casualties, he warned, might be "relatively content[,] but it is the contentment of asocial beings who contribute nothing to the community."²⁰⁰ They would never again be normal individuals, remaining isolated from the group. Saving American society required application of the psychiatric 'lessons of war.'

Increased focus on psychosomatics was another important outcome of the war. Leon Saul, explaining the need for "Preventative Psychiatry" in 1949, termed psychosomatic medicine "a whole new field devoted to exploring the role of emotions in physical disorders."²⁰¹ Psychosomatics, a medical approach focusing on interaction between mind and body, suggested mental health issues were physical issues.

The late 1940s also saw a burst of concern for those in mental hospitals. Mary Jane Ward's *The Snake Pit* moved from page to silver screen. Albert Deutsch's *The Shame of the States* went on book stands. Copious newspaper articles decried the horrific state of life in America's state mental institutions. In general, the media brought conditions within psychiatric institutions into the limelight, and the picture was ghastly. Although termed hospitals, many of these institutions served only as warehouses and appeared akin to overstuffed prisons. Treatment was slight to

²⁰⁰ Helgesson, Current Features, 638.

²⁰¹ Saul, Preventive Psychiatry, 330-34.

nonexistent in these overcrowded, underfunded, and understaffed State mental hospitals.²⁰²

Increasingly, a tacit consensus developed that Americans needed education for mental health. The people must be prepared, their psychological defenses shored up “[i]f we are to build a nation prepared to meet atomic warfare[,]” wrote Snyder.²⁰³ For the sake of Americans and America, it was necessary to promote mental health and prevent mental illness. The purview of psychiatry broadened and its status increased.²⁰⁴

National Defense- Federal Programs

Between 1945 and 1964, the Federal government passed a series of measures amply illustrating how Americans’ views on mental health differed from times before World War II. Americans increasingly questioned existing assumptions that treatment for severe mental illness should take place within institutions. Focus on environmental factors increased. Their presumed role in both producing and curing illness grew.

²⁰² Mary Jane Ward, *The Snake Pit* (New York: Random House, 1946); Albert Deutsch, *The Shame of the States* (New York, NY: Harcourt, Brace, 1948); Larry Hall, “Only 5 Per Cent of Mentally Ill Get Treatment in State Hospitals,” *Moberly Monitor Index and Democrat* (Moberly, MO), December 13, 1948; William C. Patrick, “State Hospital Must Get Help if It’s to Function as One,” *The Salt Lake Tribune* (Salt Lake City, UT) April 21, 1949; J. P. Porter, “Mental Hospitals in Texas Described as Penitentiaries,” *Amarillo News-Globe* (Amarillo, TX) March 20, 1949; Lionel Van Deerlia, “Mentally Ill Treated Like Criminals,” *Oxnard Press-Courier* (Oxnard, CA) April 21, 1949.

²⁰³ Snyder, Howard McC., “Observations of Psychiatry in World War II,” *American Journal of Psychiatry* 104 (October 1947): 225.

²⁰⁴ Gonda, *Psychiatry*, 291.

After 1945, the Federal government established a National Institute of Mental Health (NIMH), funded programs for research, established Federal commissions, and eventually passed the Community Mental Health Act. For a country previously delegating care of the mentally ill to the states, these were major changes. The United States even proclaimed a ‘Mental Health Week.’²⁰⁵

As discussed in the previous chapter, the shape of mental illness and mental health altered by the end of World War II. Emphasis on neuroses increased, alongside an assumption that neurotic reactions, and personalities prone to neurotic responses, created the greatest proportion of people not having good mental health. Focus shifted from mental illness to an area between the poles of complete mental health and severe mental illness.

National Institutes of Mental Health

Government actions reflected the new emphasis on mental health as one of the “problems which affect society as a whole.”²⁰⁶ In 1946, the Federal government passed the National Mental Health Act. This legislation provided funds to train mental health researchers, provide additional training for clinical practitioners, and to fund research

²⁰⁵ Anon, “National Mental Health Week,” *Joplin Globe* (Joplin, MO), April 24, 1949; Anon, “Mental Health Week Observed,” *Evening Capital* (Annapolis, MD), April 22, 1950.

²⁰⁶ Seymour D. Vestermark, “Training and Its Support Under the National Mental Health Act,” *American Journal of Psychiatry* 106 (December 1949): 416.

into the causes and potential cures of mental illness. It also created a system of grants to the states, intended to promote creation of new treatment programs.²⁰⁷ Out of the Act grew two new institutions, the National Mental Health Advisory Council and National Institute of Mental Health (NIMH). The Act focused federal action, for the first time, on promoting mental health more than decreasing the number of institutionalized mentally ill.²⁰⁸ At the State level, response to the Act was immediate; by 1947, every State had in place some form of agency to interact with NIMH and organize spending of Federal and State funds along the Act's parameters. Unfortunately most states began relying on Federal monies for training and professional education and dropped total spending from \$840,000 in 1948 to \$360,000 in 1955.²⁰⁹ The initial head of NIMH, Robert H. Felix, convinced the Surgeon General that the new institution belonged among medical research institutions, rather than the Bureau of State Services. NIMH became part of the National Institutes of Health,²¹⁰ although its approach differed from its cohort. For example, NIMH developed pilot community-based mental health programs, as well as fulfilling a research and education mandate.

²⁰⁷ Robert H. Felix, "The Relation of the National Mental Health Act to State Health Authorities," *Public Health Reports* 62, no.2 (1947): 41-49.

²⁰⁸ Gerald N. Grob and Howard H. Goldman, *The Dilemma of Federal Mental Health Policy: Radical Reform or Incremental Change?* (New Jersey: Rutgers University Press, 2006).

²⁰⁹ Robert H. Felix, "Training Mental Health Personnel," *Public Health Reports* 72, no.1 (1957): 25.

²¹⁰ Grob and Goldman, *The Dilemma of Federal Mental Health Policy*, 20-21.

Technically this was not the first foray Congress made into promoting mental health, but earlier efforts were unintentional (from the Federal Congress' viewpoint). In 1930, the Public Health Service added a Division of Mental Hygiene, tasked mainly with fighting and treating addiction. Heading the Division after 1944, Robert H. Felix tried realigning this division's focus toward developing knowledge of the extent and course of mental problems, broadly construed. He also began incorporating social science research into what his predecessor interpreted more exclusively as a medical problem.

Felix's work in the Department of Public Health informed the text of the 1946 Mental Health Act.²¹¹ Surgeon General Thomas Parran asked Robert Felix to write a

²¹¹ In his article "Research and Its Support Under the National Mental Health Act," *American Journal of Psychiatry* 106, no.6 (1949): 407-12, Lawrence Kolb, Director of Research Projects at NIMH argued plans leading to the NMHA developed from the 1938 Surgeon General of the United States Public Health Service report, which stated mental disorders were the most pressing public health issue. Thomas Parran, the Surgeon General in question, does not refer to mental health as a major public health problem in his addresses published in *Public Health Reports*. In his report to Congress his recommendations for the area of mental hygiene were as follows:

Because of the great economic and social importance of mental and nervous diseases, it is important for the Public Health Service to undertake more intensive investigations concerning their causes and prevention than is possible with the facilities now available. A neurological institute combining laboratory and clinical facilities for the study of the many and complicated phases of mental and nervous disease is needed. Consideration should therefore be given to the establishment of such an institute. House Document #2. 76th Congress, 1st session, *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1938* (Washington, D.C.: United States Government Printing Office, 1938).

It is unlikely this drowsy call to action was a turning point hearkening a crusade for massive changes in mental health institutions, research, or training. In contrast, Gerald Grob refers to efforts by Lawrence Kolb, Head of the Division of Mental Hygiene of

formal proposal outlining what the Division of Mental Hygiene should do. A modified form of the plan, introduced to Congress in 1945 and signed into law early in July 1946, promoted both research and the more radical approach of focusing less on institutional care and more on community care and services.²¹² Hospital-based treatments for the severely mentally ill continued and, through the Hill-Burton Act, expanded. The Veterans Administration and the United States Bureau of Prisons had their own extensive facilities for psychiatric patients, or prisoners with serious psychiatric problems. The Hill-Burton Act provided funding to expand the number of beds available for institutionalized mentally ill, in both mental and general hospitals. Overall, the Act focused on increased hospital construction and as a consequence, by 1965, added more than ten thousand beds in general hospitals, and nineteen thousand beds in mental hospitals, for institutional care of the mentally ill.²¹³ By reducing the number of beds in each existing and newly built hospital and ward, therefore having fewer patients per ward, the Hill-Burton Act promoted institutional mental health care as a therapeutic, rather than a custodial, affair.

the Public Health Service, to establish a version of the National Cancer Institute, focused on mental problems and called the National Neuropsychiatric Institute. Military concerns, Grob argues, pushed ahead of Kolb's efforts. Gerald Grob, "Creation of the National Institute of Mental Health," *Public Health Reports* 111, no.4 (1996): 378-81.

²¹² Grob and Goldman, *The Dilemma of Federal Mental Health Policy*, 18-22; for an example of public optimism regarding the Act's potential outcome see Anon, "A Commendable Step: Mental Health Bill is Good," *Morning Avalanche* (Lubbock, TX), March 29, 1946.

²¹³ Connery et al, *Politics of Mental Health*, 26-27.

The National Institute of Mental Health (NIMH), headquartered in Bethesda, Maryland, among other elements of the National Institutes of Health, served mainly as a center of research on prevention and treatment, if not complete elimination, of mental illness. The NIMH remained a bureau within the Public Health Service, in turn overseen by the Department of Health, Education, and Welfare. Beginning with a budget of four and a half million dollars, its programs and financing swelled quickly until, in fiscal year 1966, NIMH employed over twelve-hundred staff members and had a total budget greater than two hundred thirty million dollar per annum.²¹⁴ This allocation of funds to NIMH reflects Congress considering mental health an extremely important issue.²¹⁵ There were separate Associate Directors for activities within the institution and those outside. Within the Bethesda laboratories, staff came from a wide variety of disciplines, all with an interest in mental health and illness.²¹⁶ They applied a wide variety of techniques to better understand and treat mental illness. Encompassed topics included “community mental health problems, clinical techniques, and the pharmacological, neurophysiological, biochemical, psychological, and socioeconomic

²¹⁴ Connery et al, *Politics of Mental Health*, 21.

²¹⁵ Herbert H. Rosenberg, “Research Planning and Program Development in the National Institutes of Health: The Experiences of a Relatively New and Growing Agency,” *Annals of the American Academy of Political and Social Science* 327 (January 1960): 106.

²¹⁶ Lawrence Kolb, “Research and Its Support Under the National Mental Health Act,” *American Journal of Psychiatry* 106 (December 1949): 408.

aspects of drug addiction.”²¹⁷ The typically optimistic expectations of science held by the American public during the late 1940s and 1950s promoted “fundamental inquiry” on the nature of mental illness, on the assumption that because research “accelerates understanding of basic disease processes”²¹⁸ it would lead to treatments, if not cures.

From the first year of funding in 1948, through to 1966, finances associated with improving training and increasing the number of trained and available mental health professionals, accounted for a substantial portion of the NIMH budget. At first, the Institute used training grants to increase the number of clinical practitioners with specialties related to the medical aspects of mental health: psychiatry, psychiatric social work, psychiatric nursing, and psychology. Grants to the established eighty-four medical schools recognized by NIMH served “to improve or expand psychiatric instruction to the medical students.”²¹⁹ By 1956, annual funding subsidized and promoted increased psychiatric education for ninety-three percent of all medical students in the United States.²²⁰ Fellowships granted to individual researchers promoted increased knowledge for the field in general, helped shape the research paths of individuals, and increased experience for their future investigations. After passage of a 1956 amendment to the Public Health Service Act, the NIMH expanded grants to

²¹⁷ Connery et al, *Politics of Mental Health*, 21.

²¹⁸ Rosenberg, *Research Planning*, 107.

²¹⁹ Felix, *Training Mental Health Personnel*, 25.

²²⁰ Felix, *Training Mental Health Personnel*, 25.

States, nonprofit institutions, and metropolitan governments to promote a more geographically dispersed program of research, focused on improved diagnosis and treatment.

In 1959, NIMH initiated the “General Practitioner Program”²²¹ to grant physicians “awards to specialize in psychiatry”²²² or fund short courses in psychiatry for general practitioners, with the expectation they would return to general practice more aware of techniques for treatment and prevention of mental illness. Within six years, the short course program increased the number of physicians with at least basic psychiatric training by approximately 14,400.²²³ Gradual expansion of these programs increased the number of mental health professionals in auxiliary fields: epidemiology and public health, psychological and physiological studies of human behavior, and areas of the biological sciences related to study of mental illness.²²⁴ In 1949, thirty percent of training grant funds gave stipends to undergraduates to support “4 years training in psychiatry and psychology and 3 years training in psychiatric nursing and psychiatric social work.”²²⁵ Yet demand for mental health services continued to grow at rates far outstripping all efforts to increase the number of providers.

²²¹ Connery et al, *Politics of Mental Health*, 23.

²²² Connery et al, *Politics of Mental Health*, 23.

²²³ Connery et al, *Politics of Mental Health*, 23.

²²⁴ Connery et al, *Politics of Mental Health*, 23.

²²⁵ Vestermark, *Training and Its Support*, 417.

Studies of the nature and treatment of mental health, alongside efforts to increase access to mental health services, helped reshape the role of physicians in treatment of mental illness. NIMH set up outposts in cities such as Hagerstown, Maryland “to determine the relationship between physical and mental health, and social factors associated with mental disturbances.”²²⁶

The Joint Commission on Mental Illness and Health (JCMIH)

During a conference on mental health sponsored jointly by the American Medical Association (AMA) and the American Psychiatric Association (APA), Dr. Kenneth E. Appel, 1953 APA president, promoted creating a committee to report on current methods of caring for the mentally ill. He hoped the resulting report, highlighting serious deficiencies, would catalyze mental health professionals in the way Abraham Flexner’s famous *Medical Education in the United States* led to dramatic changes in the content and practice of medical education.²²⁷ Appel pointed out the lack of existing nationwide surveys dealing with the problem of mental illness in general.

²²⁶ Anon, “Office Opened Here to Conduct Mental Health Research in City,” *Morning Herald* (Hagerstown, MD), December 19, 1952; Anon, “Office Opened Here to conduct Mental Health Research in City,” *Daily Mail* (Hagerstown, MD), December 18, 1952.

²²⁷ Abraham Flexner, *Medical Education in the United States; A Report to the Carnegie Foundation for the Advancement of Teaching* (New York: n.p., 1910); Robert L. Robinson, “New Perspectives in Mental Patient Care: History, Significance and Potential Impact of the Report of the Joint Commission on Mental Illness and Health,” *Psychiatric Services* 12, no.4 (1961): 11.

Pulling together members of the APA and the Council on Mental Health, a group within the AMA, Appel championed efforts to begin nationwide studies. He promoted an inquiry, or study, to State Governors during one of their conferences, held at the Mental Hospital Institute.

Existing studies, the best known of which were the 1936 Baltimore Eastern Health District Survey, and the 1938 Williamson County Survey (Tennessee), gave snapshots of the incidence of mental illness. They were not in agreement and studied disparate populations. The Baltimore survey covered a residential area in the eastern part of the city, where the average income was lower than the citywide figure. One-quarter of the population were African-Americans, with the remainder including many Czech and Jewish peoples. Researchers identified cases of mental illness through written evidence in public institutions, including public schools and, where necessary, gave a provisional diagnosis based on this secondhand evidence. They divided forms of mental disorder into groups reflecting a schema of organic psychoses, neuroses and personality disorders, and problems in children. Typical of the pre-World War II period, most cases fell within the psychoses group. In a population of 55,000 they identified 3,337 cases of mental illness (6.05 percent of the population). A partial breakdown of their findings is listed below.

Classification	Sub-classification	Number of cases	Percentage of population
Psychoses		367	.67
	Schizophrenia	158	.29
	Manic-depressive	41	.07
	Senile and arteriosclerotic	38	.07
	Alcoholic	15	.03
	Syphilitic	29	.05
	with Mental Deficiency	28	.05
	Other and undiagnosed	58	1.1
Psychoneuroses		171	.31
Psychopathic personality		30	.05
Personality disorder in adults		218	.4
Behavior disorder in children		449	.81
Minor and possible disorder		651	.118
Epilepsy		75	.14

Table 1. 1938 Baltimore Study

The second major study took place in Williamson County, Tennessee. Unlike Baltimore the population was rural, with most families involved in agriculture. Again one-quarter of the population consisted of African-Americans, but the remainder was more homogenous, mainly people of British ancestry. In this survey, the researchers

developed relationships within the community over a longer period of time, living within the community beginning in 1935. Identified cases came from referrals “by physicians, nurses, teachers, clergymen, judges, and others who were in contact with large numbers of residents.”²²⁸ The researchers also conducted a house-to-house survey of three districts within the area, during which they found incidence of mental illness double the proportion reported by referral. Although convinced the actual incidence rates were twice as high, their results reflected similar proportions of mentally ill found among the general population in the Baltimore study. Overall rates of mental illness were approximately 6.9 percent, although intensive case finding suggested the actual rate might be closer to 14 percent. Within the psychoses, the reported findings were remarkably similar for both studies; for the neuroses they varied more (0.31 percent in Baltimore, 0.4 in Williamson County). Construing neuroses more broadly, under post-World War II definitions, the results varied from 0.4 percent to 4.17 percent incidence depending on the study used and groups included. The estimate of 4.17 percent comes from the Williamson County Study, in which the authors concluded actual rates were probably twice those reported, which would place the actual rate of neuroses at 8.34 percent of the population.²²⁹ Although studies with more defined approaches, intended to identify all cases, were in the works in 1952, there were no completed studies.

²²⁸ Robert H. Felix and Morton Kramer, “Research in Epidemiology of Mental Illness,” *Public Health Reports* 67, no.2 (1952): 154.

²²⁹ Felix and Kramer, *Research in Epidemiology*, passim.

Classification	Sub-classification	Number of cases (Note population of survey area is approximately 1/2 that in	Percentage of population
Psychoses		156	.63
	Schizophrenia	43	.17
	Affective (would include manic-depressive and depressive)	41	.17
	Senile	23	.09
	Other	51	.2
Psychoneuroses		99	.4
Psychopathic traits		186	.75
Conduct and behavior disorders		414	1.67
Organic and miscellaneous		328	1.32

Table 2. 1938 Williamson County Study

The important shift from recognizing need for a national study, to the actual studying itself, began in 1954 when the Field Foundation donated five thousand dollars to help set up a commission.²³⁰ In Congress, Senator Lester Hill introduced a resolution for the study of mental illness in February 1955; Congressman J. Percy Priest introduced a similar legislative proposal to the House of Representatives. The medical

²³⁰ Leo H. Bartemeier, Kenneth E. Appel, Jack R. Ewalt, and Walter E. Barton, “The Future of Psychiatry: The Report of the Joint Commission on Mental Illness and Health,” *American Journal of Psychiatry* 118 (May 1962): 975.

director of the APA, Dr. Daniel Blain, helped draft the resolutions, which eventually congealed to form the Mental Health Study Act of 1955. This Act passed “without a dissenting vote[.]”²³¹

The Act gave Federal funding to the Surgeon General of the United States Public Health Service, who would distribute funds to one of more nongovernmental organizations to conduct the study. The existing Joint Commission on Mental Illness and Health (JCMIH) applied for and received the funds.²³² An organizational meeting for the Commission, in April 1955, involved representatives of thirty-six national organizations.²³³ Smith, Kline & French provided funds to continue planning before Federal monies began to flow, suggesting major pharmaceutical manufacturers saw no threat in a Commission expected to illustrate need for increased mental health services. The Joint Commission was in a potentially awkward position as a nongovernmental entity endorsed, and partially funded, by the Federal government.²³⁴ Those in mental health related fields generally viewed the arrangement optimistically; the Commission’s effectiveness would be greater, all parties agreed, if led by professional organizations such as the American Psychiatric Association, the American Medical Association, the

²³¹ Robinson, *New Perspectives*, 12.

²³² M. A. Tarumianz and Daniel Blain, “A Report on the Joint Commission on Mental Illness and Health,” *Psychiatric Services* 7, no.2 (1956): 52-53.

²³³ Bartemeier et al, *Future of Psychiatry*, 975.

²³⁴ Grob and Goldman, *Dilemma of Federal Mental Health Policy*, 26.

Veterans Administration, and the American Hospital Association.²³⁵ Between funding authorized by the Mental Health Study Act in 1955 and later Federal funds, the Commission's reports represented more than a 1.4 million dollar investment into investigating existing mental health and mental illness provision, and developing proposals for improvement. Obviously, at this time, there was broad support within Congress, which also suggests public support, for improved and possibly expanded efforts to understand barriers and promote mental health.

Based on the mandate set out in 1955, (Public Law 1982, also known as the Mental Health Study Act) the JCMIH studies looked at mental illness with a very broad lens.²³⁶ The Act's preamble set out general principles for conducting the research. Among the axioms was that new treatment techniques made it possible for a greater portion of the mentally ill to live their lives outside hospitals where care focused on custody, and which had inadequate facilities, funding, and personnel. Research should focus on cost of existing mental health facilities, as well as effects on families. The Act associated mental illness with broader social problems, and implicitly with nonorganic (functional) neuroses, neurotic reactions, and personality disorders, as well as situational problems affecting the large proportion of Americans falling between the poles of mental health and mental illness. The preamble placed drug addiction, crime,

²³⁵ Connery et al, *Politics of Mental Health*, 38-41.

²³⁶ The JCMIH excluded study of psychoanalysis as well as mental retardation because other organizations were already planning or conducting similar studies. Bartemeier et al., *Future of Psychiatry*, 976.

and divorce or family breakdown within the boundaries of mental illness for study.

The Joint Commission on Mental Illness and Health planned a series of ten monographs. Each studied one aspect of the overall problem and suggested possible solutions, intended for providing information feeding into a final report of the Commission as a whole. The monographs leading to the final report by the Joint Commission on Mental Health and Illness illustrate the broad concerns associated with mental illness and health in the 1950s and early 1960s. In *Current Concepts of Positive Mental Health* Dr. Marie Jahoda, a Professor of Social Psychology and Director of the Research Center for Human Relations at New York University, surveyed various interpretations of the ideas ‘mental illness’ and ‘mental health.’ “There is hardly a term in current psychological thought as vague, elusive, and ambiguous as the term ‘mental health,’ she began.²³⁷ Throughout the monograph Doctor Jahoda teased out the interactions between definitions of mental health and philosophies or value sets associated with them. Typical of the post-World War II period, the majority of her work focused on the area between mental health and mental illness. “Knowledge about deviations, illness, and malfunctioning far exceeds knowledge of healthy functioning[.]” she noted.²³⁸ Consequently, she endorsed increased emphasis on the causes and nature of mental health.

²³⁷ Marie Jahoda, *Current Concepts of Positive Mental Health*, Joint Commission on Mental Illness and Health Monograph Series No. 1 (New York: Basic Books, 1958), 3.

²³⁸ Jahoda, *Current Concepts*, 6.

Jahoda's survey took place within the existing and popular concepts of homeostasis and General-Adaptation-Syndrome. Homeostasis, a concept usually associated with the works of Walter Cannon, essentially argued there was an equilibrium within the human body, and stresses interfere with that equilibrium.²³⁹ In mental health terms, the rapid reestablishment of equilibrium, whether the previously existing one or (preferably) something new, was healthy behavior. Ability to adapt to changing situations signified mental health. Cannon's theory translated easily within the precepts of Freudian psychology; mental stresses created a tension between the Id, Ego, and Superego, which needed resolution to restore homeostasis. Psychoanalysis freed individuals from constraints of the past, which allowed personal growth, interaction with the environment, and redevelopment of homeostasis in an ongoing, dynamic, manner. The General-Adaptation-Syndrome (G-A-S) concept was associated with the works of Hans Selye.²⁴⁰ His physiologic research convinced him there were

²³⁹ For more information on Cannon's approach and examples of his work see: Walter B. Cannon, *Bodily Changes in Pain, Hunger, Fear and Rage; An Account of Recent Researches into the Function of Emotional Excitement* (New York: D. Appleton and Company, 1920); Walter B. Cannon, *The Wisdom of the Body* (New York: W. W. Norton & Company, 1939); Walter B. Cannon, *The Way of An Investigator, A Scientist's Experiences in Medical Research* (New York: W. W. Norton & Company, 1945); Russell Charles Maulitz, *Walter B. Cannon: Scientific Explanation in Regulatory Physiology* (Boston: Unpublished Thesis, Harvard University, 1966); Elin L. Wolfe, A. Clifford Barger, and Saul Benison, *Walter B. Cannon, Science and Society* (Boston: Harvard University Press, 2000).

²⁴⁰ For information on Selye and examples of his work in the General-Adaptation-Syndrome see: Hans Selye, *The General Adaptation Syndrome of the Diseases of Adaptation* (n.p.: Association for the Study of Internal Secretions, 1946); Hans Selye, *The Physiology and Pathology of Exposure to Stress; a Treatise Based on the Concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation*

certain commonalities in illness response, existing regardless of the disease, stressor, or illness. Stress on the body, no matter whether primarily psychological or somatic, caused a series of responses designed to mitigate stress. Quick response to stress reduced, but did not prevent, somatic damage.

These theories of homeostasis and the G-A-S played important roles later in justifying widespread prescription of Valium, because they suggested poor response to stress played an important role in neuroses, psychosomatic disorders, and even somatic illnesses. Valium, as a tranquilizer, effectively short-circuited an adrenaline feedback loop which occurred under prolonged stress, especially in those with neurotic personalities. Faced with stressful conditions, the body's fight-or-flight reflex kicked in. Bursts of adrenaline helped an individual remain on alert, but could also result in reaction to lesser stimuli. In those predisposed by genetics or experience, or apparently 'normal' people facing long-term stresses, a feedback loop could result; stress produced adrenal response which heightened awareness of stressful stimuli, which produced more adrenalin and so on, ad infinitum.

Jahoda's wrote with implicit assumption of a link between physiology and psychology, and her findings therefore fit the broader definitions of mental illness and health typical of the 1950s and 1960s. In an introduction to the book, physician Jack

(Montreal: Acta, 1950); Hans Selye, *The Story of the Adaptation Syndrome: Told in the Form of Informal, Illustrated Lectures* (Montreal, Acta, 1952); David Le Vay, "Hans Selye and a Unitary Conception of Disease," *The British Journal for the Philosophy of Science* 3, no. 10 (1952); Nancy E. Gross, *Living With Stress*. Forward by Hans Selye (New York: McGraw-Hill, 1958); Russell Viner, "Putting Stress in Life: Hans Selye and the Making of Stress Theory," *Social Studies of Science* 29, no. 3 (1999).

R. Ewalt, Director of JCMIH, explained that laboratory research “showed us long ago that severe emotional stress can profoundly alter the physiology of the body.” Up-to-date research, he emphasized, only further confirms that “chemical-physiologic disturbances can affect behavior and perception.”²⁴¹ Jahoda worked within this understanding; she placed alcoholism within the boundaries of mental illness, in part because it was an inappropriate mental reaction to stress, and because it resulted in “deterioration of the brain” because of alcohol’s toxic properties.²⁴²

Jahoda’s book focused on positive mental health, maintaining mental health for prevention and treatment of mild mental illness before it progressed toward chronic mental and physiologic conditions. Insightfully, she noted two major ways of defining mental health, either in terms of current behavior, “a *momentary function of personality and situation*[,]”²⁴³ or as a more continuing dysfunction of personality, what she described as “differences in behavior and feelings dependent on the stresses and strains of the situations in which a person finds himself[.]”²⁴⁴

Dr. Jahoda emphasized that initial assumptions informed ways to examine an individual’s mental health. In the first case, mental health studies focused on current behavior patterns, which could be more healthy or less. The second approach lead to

²⁴¹ Jahoda, *Current Concepts*, xii.

²⁴² Jahoda, *Current Concepts*, xii.

²⁴³ Jahoda, *Current Concepts*, 8.

²⁴⁴ Jahoda, *Current Concepts*, 8.

focus on “individuals as more or less healthy[.]”²⁴⁵ Either approach could underlie acceptable or unacceptable definitions of mental health. The popularity of both perspectives led to lack of consensus on definitions and proper approaches to achieve positive mental health.

The widespread exclusionary definition of mental health as “the opposite of mental disease”²⁴⁶ is unworkable, Jahoda argued. Physiologic identification of mental disease was impossible, and therefore identification must be based on behavior linked to organic problems. But, she pointed out, people widely accepted as mentally ill did not always show these extremes of behavior. “[S]imilarities and symptoms[.]” she wrote, “must not be mistaken for identical disturbances of functions.”²⁴⁷ A wide variety of symptoms could result from similar functional problems. Jahoda concluded that the tendency within psychiatry, to base diagnoses on types of personalities or patterns of interaction with the external world, was untenable if there was no one-to-one link between symptoms and functional categories of illness.

Defining socially unacceptable behaviors as indicators of mental illness is equally unacceptable, Jahoda continues, this approach usually fails to take into account cultural differences between acceptable and unacceptable behavior. Contemporary work of anthropologists and sociologists illustrated normality, whether based on

²⁴⁵ Jahoda, *Current Concepts*, 8.

²⁴⁶ Jahoda, *Current Concepts*, 10.

²⁴⁷ Jahoda, *Current Concepts*, 12.

statistical frequency or ideals, remained rooted in culture.²⁴⁸ An underlying theme of work in these fields was “the plasticity of human nature and... the vast range of what can be regarded as normal.”²⁴⁹ This means the JCMIH recognized deviations from behavioral norms in a culture was not an acceptable basis for defining mental illness. It did not fit with contemporary ways of defining positive mental health. Daniel Katz, in the 1951 edition of *Annual Reviews of Psychology*, neatly summarized the changes in psychological theory; “social norms are not statistical averages or modes but consciously shared beliefs and values[,]” he explained.²⁵⁰ Normal people were ideals, not commonly found people.

Cutting a broad swath through publications in sociology, psychology, anthropology, and psychiatry from the mid-1930s to the late 1950s, Jahoda boiled down the multifarious, nuanced, and implied definitions of mental health into six categories, two defined by the individual involved, two by socially acceptable behavior, one identifiable by mental-health practitioners, and the final one identifiable by anyone possessing mental-health and familiar with the individual involved.²⁵¹ Personally

²⁴⁸ For example see Margaret Mead, *From the South Seas: Studies of Adolescence and Sex in Primitive Societies* (New York: W. Morrow & Company, 1939); Margaret Mead, *Male and Female: A Study of the Sexes in a Changing World* (London: Gollancz, 1950); Margaret Mead, *Coming of Age in Samoa: A Psychological Study of Primitive Youth for Western Civilization* (New York: Modern Library, 1953).

²⁴⁹ Jahoda, *Current Concepts*, 15.

²⁵⁰ Daniel Katz, “Social Psychology and Group Processes,” *Annual Reviews of Psychology* 2 (1951): 137.

²⁵¹ Parsing the six categories is my own. Jahoda identifies autonomy,

defined measures of mental health included “*attitudes of an individual towards his own self[,]*”²⁵² and the extent of “*growth, development, or self-actualization[.]*”²⁵³

Definitions based on deviation from social norms relied on mid-twentieth century ideals of American middle-class society; environmental mastery, and autonomy served effectively as measures of individuality and independence. Another definition of mental health, degree of psychological integration – presumably referring to a successful functional balance between portions of the psyche – informed identification by a trained psychotherapist. The remaining approach Jahoda identified is “that mental health is manifested in the adequacy of an individual’s *perception of reality*.”²⁵⁴

Application of this idea required another person to assess mental health or mental illness, although it suggested trained psychiatrists, neuropsychiatrists, psychotherapists, or political psychologists held no monopoly on diagnosis and treatment. Anyone could tell if a person was facing up to reality, they might be wrong, but in theory any healthy individual could identify people who could not accurately perceive reality.

perception of reality, and environmental mastery all measures of “the individuals relation to reality.” Jahoda, 1958, 23. Integration is singled out as an approach which places “the emphasis on a central synthesizing psychological function,” usually assessed in ways including the remaining two approaches, attitude toward self, and degree of self-actualization; Jahoda lists the six approaches on page 23 of *Current Concepts of Positive Mental Health*. Discussing each she focuses more on the variety of expressions for each theory.

²⁵² Jahoda, *Current Concepts*, 23.

²⁵³ Jahoda, *Current Concepts*, 23.

²⁵⁴ Jahoda, *Current Concepts*, 23.

The breadth of approaches accepted by members of the Joint Committee on Mental Illness and Health influenced how they proposed to solve staffing problems in the face of increased public demand for mental health services. The monograph on *Epidemiology and Mental Illness* amply illustrates how hard it was to estimate the proportion of Americans who, although not institutionalized, were mentally ill; it depended on methodology and definitions. Physicians Richard Plunket and John Gordon suggested existing estimates range from five percent to twenty-three percent of the entire population did not possess mental health. This and other JCMIH monographs implicitly accepted that need for services far outstripped availability; in *Community Resources in Mental Health* and *Mental Health and Manpower Trends*, Commission members argued strongly that current numbers of mental health professionals were insufficient. The greatest difference between need and supply existed in state-run institutional care facilities, but the authors' concerns focused on a perceived overall shortage of mental health professionals. As they stood, institutes of higher education appeared unable to create a large enough pool to meet staffing demands in the near future. The Commission members' observation that more physicians and allied mental-health professionals preferred working in clinics or private practice, and therefore with the less mentally ill, fit the post-World War II trend of interest in neuroses rather than psychoses.

Focus on poor mental health, rather than treating those defined in earlier times as mentally ill, also influenced estimates of the economic need for action. In

Economics of Mental Illness Rashi Fein, Professor at Harvard's School of Medicine, discussed psychosomatic illness as well as the neuroses and psychoses.²⁵⁵ Although the cost of mental illness to individuals, states, and the Federal government was staggering, including potentially psychosomatic disorders (circulation, digestion, gastric, or respiratory problems) in estimates resulted in mind-boggling drains on the country's purse.²⁵⁶

Using a national survey, the authors of *Americans View Their Mental Health*, established widespread need for personnel and facilities, if Americans were to achieve positive mental health. As well as assessing help-seeking behavior and current sources of assistance, their survey used an extremely broad concept of what prevented Americans from achieving mental health. They looked at achievement and personal satisfaction with life, but also attempted to understand extent of adjustment problems, family dysfunction, and other hindrances to happiness.

Personnel, an important factor in supply of mental health services, was a widely accepted existing problem. It was axiomatic at the time that promoting mental health

²⁵⁵ George W. Albee, *Mental Health Manpower Trends* (New York, NY: Basic Books, 1959); Rashi Fein, *Economics of Mental Illness* (New York, NY: Basic Books, 1958); Gerald Gurin, Joseph Veroff, and Sheila Feld, *Americans View Their Mental Health* (New York, NY: Basic Books, 1960); Marie Jahoda, *Current Concepts of Positive Mental Health* (New York, NY: Basic Books, 1958); Richard J. Plunkett and John E. Gordon, *Epidemiology and Mental Illness* (New York, NY: Basic Books, 1960); Reginald Robinson, David F. DeMarche and Mildred K. Wagle, *Community Resources in Mental Health* (New York, NY: Basic Books, 1960).

²⁵⁶ Elaine Cumming, "Review: A Review Article— The Reports of the Joint Commission of Mental Illness and Health," *Social Problems* 9, no.4 (1962): 394; Fein, *Economics of Mental Illness*, passim.

and preventing or treating mental illness was a pressing national need.²⁵⁷ Apart from aiding those already sick, early identification and treatment of incipient mental illness required more professionals,²⁵⁸ “[i]f we are ever to prevent the inexorable flood of mental illness from rising year in and year out[.]”²⁵⁹ Some, especially politicians and those whose concern with the problem was primarily fiscal, associated early identification and treatment with preventing degeneration from neuroses into psychoses, and therefore reducing the number of institutionalized mentally ill people. A massive prevention program focused on identification and early treatment, they believed, could reduce the overall cost of institutional care. The pent up demand for goods, often described as an important reason the economy boomed after demobilization, also applied to demand for mental health care.

In general, Americans cared about maintaining the mental health of those closest to them, and reducing the financial burden for long-term institutional care of others. The demand for mental-health professionals was, and continued through to the 1960s, to be greater than the supply of available providers, especially physicians with substantial mental health training. In 1957 Robert Felix who, as head of the NIMH,

²⁵⁷ Kennedy, Special Message, passim.

²⁵⁸ Gerald N. Grob refers to this belief that “early identification of symptoms and treatment in community settings could prevent the onset of more serious mental disorders and thus reduce the need for prolonged institutionalization[.]” Grob argues this belief in early identification and prevention is rooted in physicians World War II experiences. Gerald N. Grob, “Creation of the National Institute of Mental Health,” *Public Health Reports* 111, no.4 (July/August 1996): 378.

²⁵⁹ Vestermark, Training and Its Support, 416.

established programs in 1947 to increase dramatically the number of mental health workers, still bemoaned existing strains on the workforce. “There are limits to how far workers can be stretched to cope with mental health needs[,]” he warned.²⁶⁰ This is surprising when the number of physicians with mental health training was rising. Most of these physicians were general practitioners who, by the time Valium entered the market (December 1963), saw the vast majority of outpatients with mental health issues.²⁶¹

Mental Health Professionals

As relative peace allowed massive demobilization of military personnel, the demographics of psychiatric practice in the United States shifted. Thousands of newly trained neuropsychiatrists returned in search of employment. General practitioners, previously “unacquainted or resistant to psychiatric concepts were confronted in their combat experience with undeniable evidence of the influence of emotional disturbance upon bodily function.”²⁶² They reclaimed their practices with an increased sense that mental health was not only an important issue, but something they could identify and potentially treat. To practice psychiatry, they required a state medical license. Other qualifications included membership in professional organizations or certification by the

²⁶⁰ Felix, *Training Mental Health Personnel*, 25.

²⁶¹ Bartemeier, *Future of Mental Health*, 194.

²⁶² Felix, *Relation of National Mental Health Act*, 45.

American Board of Psychiatry and Neurology, but only the state medical license was technically required.²⁶³

In 1954, for the first time in history, the number of psychiatrists in private practice exceeded the number associated with institutions, hospitals, and agencies.²⁶⁴ Approximately one-quarter of those in private practice were effectively psychoanalysts, seeing a small number of patients for one hour, three or more times a week. Considering the small number of patients seen in a week (physicians, unlike lawyers, have only 12 maximum billable hours per day and saw on average one patient per fifty-minute hour), it is unsurprising psychiatry ranked among the lowest paid medical specialities.²⁶⁵ The average fee was between ten and fifteen dollars per hour²⁶⁶ which, at three to five sessions of psychotherapy a week, placed the cost of treatment above the income of an average American family (average family income was approximately seventy dollars per week). The other seventy-five percent of private practice psychiatrists were more somatically and behaviorally oriented. They saw up to eighteen patients per day, compared with a usual maximum of nine for an analyst. General practitioners treated a wider variety of patients, from a broader economic spectrum, and tended to attend each patient for an even shorter period of time. On

²⁶³ Daniel Blain, "Private Practice of Psychiatry," *Annals of the American Academy of Political and Social Science* 286 (March 1953): 136-49.

²⁶⁴ Davidson, 1956, 41.

²⁶⁵ Davidson, 1956, 41.

²⁶⁶ Blain, *Private Practice of Psychiatry*, 148.

average, they saw thirty-one patients per day. The number of patients seen by psychiatrists in private practice in the United States annually was approximately equal to the number of patients in public mental institutions, roughly eight hundred thousand.²⁶⁷

At least some psychiatrists in the mid-1950s were consciously aware that somatic treatments, such as electroconvulsive therapy or pharmaceuticals, could improve their own economic and social situation. Henry Davidson, in a paper presented at the 1955 American Psychiatric Association meeting and later published in the association's journal, suggested a somatic orientation could increase the number of clients seen, allow lower fees, and by allying their practice to other areas of medicine (physical) offer the prospect of medical insurance covering mental health services.²⁶⁸ Joseph Eaton, a sociologist/anthropologist, explained to readers of the *American Journal of Psychiatry* that Americans wanted certainty from professionals, and highlighted ties between the psychiatrists' position and public "confidence in the remarkable curative powers of drugs[.]"²⁶⁹

One of the most pressing problems identified by the Joint Commission on Mental Illness and Health was the personnel shortage, a consequence of changing expectations. The problems psychiatry could assist with were broader than previously

²⁶⁷ Blain, *Private Practice of Psychiatry*, 136.

²⁶⁸ Davidson, 1956, 43.

²⁶⁹ Joseph W. Eaton, "The Assessment of Mental Health," *American Journal of Psychiatry* 108 (August 1951): 81.

thought, including “the enormous mental hospital load, alcoholism, crime, ‘psychosomatic’ disease, and plain unhappiness[,]” all of which were becoming part of psychiatry’s “operational field[.]”²⁷⁰ Over the course of the late 1940s and 1950s, medical students increased the amount of time spent taking “in the psychological aspects of medicine.”²⁷¹ This produced increasing numbers of non-psychiatrists with interest in, or at least knowledge of mental health issues and treatments. General practitioners increasingly called on psychiatrists for consultations.²⁷² Physicians with the most extensive training in psychiatry or psychotherapy preferred not to work with inpatients; they went into private practice, increasing demand for institutional psychiatrists as well.²⁷³

The allied mental health fields – psychiatric nursing, social work, psychology – began filling the manpower gap during World War II, and the trend increased postwar as government efforts established community mental health programs. These programs, in intent at least, promoted positive mental health by framing barriers to mental health in extremely broad terms, then trying to surmount these barriers. The number of trained

²⁷⁰ Gonda, *Psychiatry*, 292.

²⁷¹ Blain, *Private Practice of Psychiatry*, 146.

²⁷² Franklin N. Arnhoff, Eli A. Rubenstein, Beatrice M. Shriver, and Donald R. Jones, “The Mental Health Fields: An Overview of Manpower Growth and Development.” In *Manpower for Mental Health*, eds. Franklyn N Arnhoff, Eli A. Rubenstein, and Joseph C. Speisman, chapter 1. (Chicago: Aldine Publishing Co., 1969), 7.

²⁷³ Cumming, *Review Article*, 398.

clinical psychologists went up sixty-six percent between 1952 and 1962; during the same period the number of psychiatrists and nurses both increased by approximately thirty-eight percent.²⁷⁴ Social workers and clinical psychologists played an important role in these new government programs.²⁷⁵

Final Report of JCMIH and Creation of Community Mental Health Facilities

The Joint Commission on Mental Illness and Health combined with the Community Mental Health Centers Act, altered the face of mental health treatment. Allied professions increasingly took over short-term psychotherapies. Counselors helped families cope with social problems, such as alcoholism and marital dysfunction. Medical doctors' roles within the mental health professions increasingly focused on somatic treatments, particularly use of pharmaceuticals. In this way, physicians treating incipient or mild mental illness became increasingly associated with prescribing drugs. Valium and the minor tranquilizers were ideal for the physicians' new roles in mental health care; they were safer than previous tranquilizers and sedatives, had a wide spectrum of uses, and were only available from medical doctors because their 'specialized knowledge' was necessary in use of such 'powerful' treatments.

In 1961 the Joint Commission on Mental Illness and Health (JCMIH) published

²⁷⁴ Bartemeier et al, *Future of Psychiatry*, 980.

²⁷⁵ Davidson, 1956, 44.

its final report, titled *Action for Mental Health*. To improve the mental health of the nation, the group concluded, three major problems needed resolution: insufficient personnel, inadequate facilities, and ridiculously low funding levels given America's psychic woes.²⁷⁶ They suggested increased funding for long-term fundamental, rather than applied, research on cures for mental illness. Treatment oriented to restoring mental health was desirable. They advised attempting to increase numbers of scientists and researchers, and funding a greater number of physical facilities for research.

The report defined mental health and mental illness in a manner privileging focus on obtaining a positive state of mental health, and treatment of less severe mental health problems. Elaine Cumming of the New York State Department of Mental Hygiene wrote of her shock that although the report "explicitly states that the treatment of the seriously ill is our most important task," the Committee's recommendations mentioned cost and high numbers, but otherwise did not "relate directly to the seriously ill[.]"²⁷⁷ The primary approach involved preventing mental illness, or heading off problems before they became more severe.

Persons who are emotionally disturbed – that is to say, under psychological stress that they cannot tolerate – should have skilled attention and helpful counseling available to them in their community if the development of more serious mental breakdowns is to be prevented. This is known as secondary prevention, and is concerned with the detection of beginning signs and symptoms of mental illness and their

²⁷⁶ These three problems are identified at the beginning of the report. Joint Commission for Mental Illness and Health, *Action for Mental Health: Final Report, 1961* (New York: Basic Books, 1961), vii.

²⁷⁷ Cumming, Review Article, 393.

relief; in other words, the earliest possible treatment. In the absence of fully trained psychiatrists, clinical psychologists, psychiatric social workers, and psychiatric nurses, such counseling should be done by persons with some psychological orientation and mental health training and access to expert consultation as needed.²⁷⁸

Framing the issue in these terms resulted in the committee suggesting “psychiatry and the allied mental health professions should adopt and practice a broad, liberal philosophy of what constitutes and who can do treatment[.]”²⁷⁹ This idea, as embodied within the 1963 Community Mental Health Centers Act, reshaped the roles of mental health practitioners in a manner promoting greater use of psychopharmaceuticals, such as Valium. The most effective use of physicians’ time was to practice approaches the allied professions could not handle. Only physicians could prescribe drugs, and therefore short or long-term treatment with pharmaceuticals became associated with treatment by medical doctors.

The report also minimized differences between physical and presumably mental illnesses. Within the summary of recommendations, the Committee declaimed, “*Mental illness is different from physical illness in the one fundamental aspect that it tends to disturb and repel others rather than evoke their sympathy and desire to help.*”²⁸⁰ This concept of essential similarity between mental and physical illness was not novel; Robert Robinson, the APA’s Public Information Officer, referred to it as a

²⁷⁸ JCMIH, *Action for Mental Health*, xii.

²⁷⁹ JCMIH, *Action for Mental Health*, ix.

²⁸⁰ JCMIH, *Action for Mental Health*, xviii.

“common platitude”²⁸¹ of the time. The JCMIH report, however, took pains to show how treating mental illness as different from physical illness helped create the apathetic state of mental hospitals in 1920s; without prospect of medical treatment, physical treatment, many superintendents saw their job as “to take custody of any and all persons committed to their institutions by the courts and thenceforth guard the public and patients against the latter’s irrational act, if any.”²⁸² The resulting pre-war approach focused on custodial care rather than medical treatment, “keeping the mentally ill alive,”²⁸³ with little expectation or effort to mitigate the illness. Although the Commission did not explicitly promote physical treatment through pharmaceuticals or surgery, they promoted the idea that caretakers and the public were likely to ignore therapeutic possibilities as long as they considered mental illness as fundamentally different from physical illness.

In *Action for Mental Health*, the Committee put physicians in a privileged, though limited, position. The report asserted that “certain kinds of medical, psychiatric, and neurological examinations or treatments must be carried out by or under the immediate direction of psychiatrists, neurologists, or other physicians specially trained

²⁸¹ Robert L. Robinson, “New Perspective on Mental Health Care: I. History, Significance, and Potential Impact of the Report of the Joint Commission on Mental Illness and Health,” *Psychiatric Services* 12, no.4 (1961): 13.

²⁸² JCMIH, *Action for Mental Health*, 65.

²⁸³ JCMIH, *Action for Mental Health*, 65.

for these procedures.”²⁸⁴ They did not discuss the role of physicians in expansive terms. In fact, the committee effectively recommended “nonmedical mental health workers”²⁸⁵ take charge of short-term psychotherapies, including direct interaction with patients using “objective, permissive, nondirective techniques of listening to their troubles and helping them resolve these troubles in individually insightful and socially useful way[s].”²⁸⁶ The Committee even placed longer-term psychotherapeutic techniques within the purview of psychoanalysts or psychotherapists without a medical degree. Unlike short-term therapy, “psychoanalysis and allied forms of deeply searching and probing”²⁸⁷ held the risk of harming patients, the Committee argued, therefore practitioners required special training. *Action For Mental Health* did not suggest psychoanalysts and psychotherapists trained initially as physicians, should not practice these techniques; it did, however, explicitly suggest allowing “psychologists or other professional persons who lack a medical education but have an aptitude for, training in, and demonstrable competence in such techniques of psychotherapy”²⁸⁸ into this realm of mental health practice. With wary optimism, the Committee suggested that recruitment drives, scholarship programs, increased educational facilities, expansion of

²⁸⁴ JCMIH, *Action for Mental Health*, x.

²⁸⁵ JCMIH, *Action for Mental Health*, x.

²⁸⁶ JCMIH, *Action for Mental Health*, x.

²⁸⁷ JCMIH, *Action for Mental Health*, x.

²⁸⁸ JCMIH, *Action for Mental Health*, x.

medical schools, and “short courses and on-the-job training in some professions and upgrading for partially trained persons”²⁸⁹ together might make it possible to overcome the manpower shortage. In other words, to meet demand for psychiatric services, the country needed to use a broader array of mental health professionals and semi-professionals, with public needs served by those with the least training necessary for the task.

Strangely, the JCMIH in *Action for Mental Health* did not promote using psychopharmaceuticals.²⁹⁰ Although most psychiatrists recognized major tranquilizers had changed the face of institutional psychiatry, making it possible to focus on treatment and offering the realistic possibility of releasing patients who earlier would have died within the institution’s confines, this did not necessarily translate into belief in psychopharmaceuticals as appropriate treatments for mental illness.²⁹¹ Ideally, major tranquilizers altered behavior significantly enough for group, behavioral, or short-term psychotherapy to act therapeutically. Drugs were an adjunct to treatment, not the treatment itself. The JCMIH monograph failed to challenge the dominant

²⁸⁹ JCMIH, *Action for Mental Health*, x-xi.

²⁹⁰ Cumming, Review Article, 392.

²⁹¹ Debates raged over the role of psychopharmaceuticals in decreasing the number of mental patients within institutions. Journal articles show consensus that major tranquilizers changed the face of psychiatry. But there were ongoing discussions whether psychopharmaceuticals treated mental illness or simply allowed techniques such as group therapy and short-term psychotherapy to become more effective. A gradual consensus appears around 1960 that major tranquilizers mitigate symptoms, but do not cure the underlying illness.

understanding that minor tranquilizers or barbiturates treated symptoms, not an underlying problem. If pharmaceuticals remedied the situation it was due to the body's own restitution of health. It is likely the Commission did not discuss treatment with pharmaceuticals because they did not consider use of pharmaceuticals a treatment; like Aspirin, psychopharmaceuticals affected experience of headache, but did not actually make the underlying problem disappear.

Improving the number of facilities and personnel, and access to them, was achievable using a two-pronged approach. There appeared no way to ignore need to upgrade existing psychiatric care institutions, but the committee also promoted the principle that government should fund creation of smaller and more dispersed facilities oriented toward treatment of neuroses, personality disorders, alcoholism, juvenile delinquency, problems within the family, and other emotional stressors. The other means for effectively increasing facilities was, once again, recruiting a wider variety of professions under the umbrella of 'allied mental health professionals.' The national survey reported in *Americans View Their Mental Health* identified a wide variety of professions to which Americans went in the hope they could assist with emotionally disturbing conditions. This group, already involved in informal processes of promoting mental health, included "clergymen, family physicians, teachers, probation officers, public health nurses, sheriffs, judges, public welfare workers, scoutmasters, county farm agents, and others[.]"²⁹² Trained through short courses, they could more formally

²⁹² JCMIH, *Action for Mental Health*, xii

become mental health professionals.

Although there are open questions about the extent of links between the Joint Committee on Mental Illness and Health's final report in 1961, President Kennedy's Special Message to Congress on Mental Illness and Mental Retardation on 5 February 1963, and passage of the Community Mental Health Centers Act later in 1963,²⁹³ the means and ability to fund such a drastic enlargement of the government's role in mental health care remained central to all. Parties involved in drafting and passing the legislation accepted the need to "seek out the causes of mental illness" in part to forestall need for expensive chronic care. "[P]revention is far more desirable for all concerned[.]"²⁹⁴ President Kennedy explained in his message to Congress. *Action for Mental Health*, Kennedy's "Special Message," and text of the Community Mental Health Centers Act, each recognized that extensive new federal government funding would be required, and proffered suggestions how to reduce the fiscal burden on the government's purse.

Kennedy glossed over any need to establish what point on the spectrum from mental health to illness triggered need for assistance. The president did not address the problem presumably because he viewed the program as an effort to nip major mental

²⁹³ Harold L. McPheeters, "Mental Health Programs," *Proceedings of the American Academy of Political and Social Science* 32, no.3 (1977): 159-69.

²⁹⁴ President John F. Kennedy, Special Message to the Congress on Mental Illness and Mental Retardation, February 5, 1963. <http://www.presidency.ucsb.edu/ws/print?phpid=9546> (accessed September 20, 2008), 1.

illness in the bud, to spot “incipient symptoms of illness.”²⁹⁵ Although deserving full kudos for optimism and intent, the wording and approach of the Community Mental Health Centers Act of 1964 contained built in problems that would lead to its own downfall. “All of us have an occasional touch of mental illness,” noted social scientist Joseph Eaton, “[i]n reality, mental health merges imperceptibly and gradually, like the colors of the spectrum, into mental illness.”²⁹⁶ With both prevention of mental illness and promotion of mental health as goals, there was no point when the work of community mental health centers could be considered complete.

Considering mental ill-health in somatic terms and promoting treatment with pharmaceuticals were essential steps toward making mental health care more affordable and accessible. President Kennedy’s proposal, as he saw it, involved a novel emphasis relying “primarily upon the new knowledge and new drugs... which make it possible for most of the mentally ill to be successfully and quickly treated in their own communities and returned to a useful place in society.”²⁹⁷ This was one way to reduce costs. The other was to treat mental health care like other forms of health care; psychiatric pharmaceuticals were part and parcel of putting mental health care within the realm of mainstream medicine.²⁹⁸ “[T]he services provided by these centers should be financed

²⁹⁵ Joseph W. Eaton, “The Assessment of Mental Health,” *American Journal of Psychiatry* 108 (August 1951): 83.

²⁹⁶ Eaton, Assessment of Mental Health, 83.

²⁹⁷ Kennedy, Special Message, 2.

²⁹⁸ Joseph Fazekas, speaking to an audience primarily composed of physicians,

in the same way as other medical and hospital costs[.]” the President reassured Congress. With new technologies, “tranquilizers and new therapeutic methods[.]” mental illness did not require “long and often permanent courses of treatment.”²⁹⁹ Development of psychopharmaceuticals, even though usually considered treatments of symptoms rather than cures, placed treatment or prevention of mental ill-health within the boundaries of mainstream medicine, with its traditional emphasis on physical illness and physical treatment. Health insurance usually applied to physical treatment of physical illness. By somaticizing the problem, it was possible to defray costs by “individual fees for services, individual and group insurance, other third-party payments, voluntary and private contributions, and State and local aid[.]”³⁰⁰ Kennedy promoted passage of The Community Mental Health Centers Act by explaining it as a temporary measure. “Long-range Federal subsidies for operating costs are neither necessary nor desirable[.]”³⁰¹ he assured legislators. He admitted some private sources

explained how psychopharmaceuticals shifted psychiatric care into the hands of primary/family physicians when he stated that “The advent of these drugs makes it possible for the physician to manage many of these patients in the home.... This avoids the stigma currently associated with admission of such patients to a psychiatric hospital, and reduces the costs to the patient.” Fazekas et al., *Ataratics in Medical Practice*, 49; Harold Himwich pointed to financial, as well as medical, benefits of treating mental illness with pharmaceuticals. He explained, “There are other than therapeutic advantages involved. Whether in private practice or in the hospital these treatments are less expensive than the standard ones, and the factor of economy is a large one.” Himwich, *Prospects in Psychopharmacology*, 24.

²⁹⁹ Kennedy, Special Message, 3.

³⁰⁰ Kennedy, Special Message, 4.

³⁰¹ Kennedy, Special Message, 4.

of funding needed adjustment, particularly health insurance, but mental health for all was within America's grasp.

Health Insurance and Access to Physicians

Americans in the post-World War II world expected a personally useful health care system. Greater numbers of citizens had access to in- and out-of-hospital services, partially due to increased affluence in general, and partly resulting from increasing numbers covered by health insurance. Effectively, voluntary health insurance in the United States was a recent development; it began in the 1920s. Melissa Thomasson, an economic historian whose research has focused on development of the United States health insurance system, argues there was neither demand nor mechanisms of supply before that decade. She points out that medical expenditures before the 1920s were relatively minimal and therefore Americans' financial concerns related to ill health focused almost exclusively on loss of wages. Those few policies available were largely sickness insurance, plans that maintained income in the face of short-term disability.³⁰²

Major innovations in health insurance occurred in the 1930s with creation of Blue Cross and Blue Shield plans. Blue Cross developed first, with the earliest plan formed in 1929 by teachers in Dallas who contracted as a group with Baylor University Hospital. In return for a fixed annual payment of six dollars each, the hospital agreed to

³⁰² Melisa A. Thomasson, "From Sickness to Health: The Twentieth-Century Development of Health Insurance," *Explorations in Economic History* 39 (2002): 235.

provide up to twenty-one days of hospitalization per member. Blue Cross plans typically followed this model of contracts between small groups and hospitals; they provided protection against illness for individuals and were beneficial to hospitals which, in the 1930s, faced severe financial constraints.³⁰³ The American Hospital Association organized the umbrella Blue Cross group as an attempt to prevent their member hospitals from undercutting one another. Blue Shield developed as a prepaid voluntary health insurance plan, but arranged with physicians rather than hospitals. Thomasson argues physicians took the initiative in forming Blue Shield plans, even though they were traditionally opponents of health insurance on the grounds that it interfered with physician autonomy and restricted income. But Blue Cross quickly proved popular. There was fear Social Security legislation might include national health care, and hospitals might begin including physician services as well as hospital services in Blue Cross plans. The American Medical Association promulgated a set of ten cardinal rules for voluntary insurance involving physicians. In large part, the focus was on insuring physicians would supervise and control the system, retaining the ability to set their personal fees. Blue Shield subscribers were responsible for paying the physicians, and reimbursed by Blue Shield for a fixed amount per procedure.³⁰⁴

World War II was a turning point in development of health insurance, with establishment of more plans covering a wider variety of medical expenses, which

³⁰³ Thomasson, *From Sickness to Health*, 237.

³⁰⁴ Thomasson, *From Sickness to Health*, 239.

applied to a greater number of Americans. In an effort to stem skyrocketing domestic inflation and costs during the war, the Federal government attempted to control both workers' wages and prices of goods. The 1942 Stabilization Act helped prevent employers from competing among themselves for scarce labor by increasing wages, but allowed and inadvertently promoted, companies using benefits to maintain or increase their own workforce. Health insurance was one of the most important benefits offered, especially as employers did not pay payroll taxes on contributions to their employees' health insurance plans. As a result, increasing numbers of working Americans gained some form of health insurance through their employers during World War II.³⁰⁵

Yet, having more Americans with health insurance did not imply either that a high proportion of Americans had insurance or that there was great breadth of coverage for each member. In 1940 "less than 10 per cent"³⁰⁶ had insurance covering in-hospital medicine (only 40% of this group was thought to have insurance that covered surgery). Typical benefits for hospital treatment covered five dollars per day for room and board and up to thirty days of care.³⁰⁷ The percentage of Americans with insurance covering out-of-hospital, "non-surgical" care³⁰⁸ was a mere two percent. What changed over the

³⁰⁵ Thomasson, *From Sickness to Health*, 240.

³⁰⁶ Herman M. Somers and Anne R. Somers, "Private Health Insurance: Part One. Changing Patterns of Medical Care Demand and Supply in Relation to Health Insurance," *California Law Review* 46, no.3 (1958): 376.

³⁰⁷ E. J. Faulkner, "Meeting Health Care Costs Through Insurance," *The Journal of Insurance* 24, no.1 (1957): 16.

³⁰⁸ Somers and Somers, *Private Health Insurance I*, 376.

1940s and 1950s was that more Americans became aware of, and used, the health care system. Voluntary health insurance became more common, with more group policies and increased coverage of out-of-hospital care. Returning soldiers had experience with health care, including mental health, paid for entirely by their employer, the military. The head of NIMH estimated eighty percent of Americans had some form of coverage, however slight, by 1962. Yet insurance still paid only one-quarter of what individuals were billed for mental health treatments.³⁰⁹ Experience and access to the health care system undoubtedly played an important role in the widespread use of prescription pharmaceuticals from the 1950s to the 1970s.

Specialization of medicine was an important alteration to the mid-twentieth century professional landscape. Herman M. Somers, Professor of Political Science, and Anne R. Somers, Research Associate specializing in industrial relations and “social welfare[,]”³¹⁰ estimated the percentage of medical specialists compared to generalists rose from eleven percent in 1923 to thirty-nine percent in 1955. They documented an even greater shift among physicians in private practice (fifty-two percent by 1949, and fifty-eight percent in 1955).³¹¹ But it is important to recognize most white middle-class Americans dealt almost exclusively with family doctors and group practices when dealing with mental health issues. Some patients saw psychiatrists or psychologists, but

³⁰⁹ Robert H. Felix, “Improving Health Insurance Coverage for Psychiatric Illness,” *American Journal of Psychiatry* 121 (February 1965): 731-35.

³¹⁰ Somers and Somers, *Private Health Insurance I*, 376.

³¹¹ Somers and Somers, *Private Health Insurance I*, 398.

increasingly few entered hospitals or institutions. And when patients interacted with physicians for mental health issues, the treatment they received was generally short-term, and somatic or behavioral. Psychotherapy might be fashionable, but it was expensive and time consuming.³¹²

Mental Health and Health Insurance

Mental health had, and still has, a troubled relationship with health insurance. “There is no such thing today as psychiatric insurance[.]”³¹³ wrote the Assistant director of the AMA’s Department of Economics in 1966. General health insurance policies either covered some or did not cover at all, mental health treatment. Psychiatrists were unique among physicians in having their most common treatments generally excluded from insurance coverage.

In general, Blue plans (Blue Cross and Blue Shield) paid approximately seventy-five percent of hospital bills and forty-five percent of physicians’ bills; they were therefore only partial payment plans and of use mainly to the growing middle class.³¹⁴ Blue plans were not uniform, but overall they either explicitly or implicitly excluded mental illnesses. Some plans paid if physicians found the condition organic in

³¹² Felix, *Improving Health Insurance*, 734.

³¹³ Charles P. Hall, “Mental Disorders and Health Insurance,” *American Journal of Psychiatry* 122 (March 1966): 1021.

³¹⁴ Henry A. Davidson, “Blue Cross Blue Shield and the Blues,” *American Journal of Psychiatry* 111 (June 1955): 931.

cause, or if the patient treatment took place in a general hospital (which rarely had the capacity for specialized psychiatric treatment). Other plans excluded “disorders due to alcohol or drugs[,]”³¹⁵ probably on the grounds that even if addiction was a medical condition it was self-inflicted. The Health Insurance Plan of New York included a psychiatric consultation service, but no psychiatric treatment.³¹⁶ A report by the Joint Information Service of the American Psychiatric Association and the National Association for Mental Health concluded plans were covering in-hospital care of mental illness more than previously, but rarely covered out of hospital treatment. When mental problems were covered, insurance was “characterized usually by multiple limitations.”³¹⁷ Commenting on the situation, Henry Davidson hypothesized that “[b]ehind these conscious reasons lies...the feeling that psychoneurosis is a voluntary, self-induced, basically unreal disability which reflects weakness of character.”³¹⁸ Davidson’s analysis focused on how psychiatrists could adapt to the existing situation. Psychiatry needed to become associated more closely with other branches of medicine, he concluded; “Perhaps we could analogize a psychiatric disorder to a surgical one.”³¹⁹

³¹⁵ Davidson, Blues, 931.

³¹⁶ Edith Alt in Henry A. Davidson, “Health Insurance and Psychiatric Coverage,” *American Journal of Psychiatry* 114 (December 1957): 498.

³¹⁷ Harvey J. Tompkins, “Health Insurance and Psychiatric Therapy,” *American Journal of Psychiatry* 120 (October 1963): 345.

³¹⁸ Davidson, Blues, 931; Doctor Davidson was Parliamentarian of the American Psychiatric Association at the time.

³¹⁹ Davidson, Blues, 932.

The increasing importance of health insurance, albeit mainly to middle-class Americans and veterans, created a strange tension within the post-World War II understanding of mental health and mental illness as a continuum, and neuroses as common conditions.³²⁰ Accepted topics within the purview of mental health professionals now included such broadly dispersed categories as “[m]arriage counseling, vocational guidance, trouble in reading, juvenile delinquency[,]”³²¹ as well as neurotic reactions, personality and mood disorders, alcoholism, and the psychoses. Yet medical insurance plans limited mental health treatment based on insurance principles which required a condition to be voluntary, uncommon, and occurring in a measurable way in terms of rate, costs, and proper treatment.³²² Functional disorders such as neuroses, delinquency, marital problems, drug addiction and alcoholism did not fit their models unless they related to physical conditions, unless medicine and insurance considered the mind, brain, and body a single unit. *A Joint Information System Report* concluded that shorter hospital treatments and greater experience should provide the actuarial information required to show mental health coverage for inpatients would not increase premiums substantially. They foresaw a day in the near future when it would be “possible to have the same coverage for inpatient care on the same basis as

³²⁰ A 1957 estimate by Edith Alt, a consultant on Community resources working for the Health Insurance Plan of Greater New York considered only 10% of the population able to buy psychiatric care entirely out of pocket. Alt in Davidson, *Health Insurance*, 498.

³²¹ Alt in Davidson, *Health Insurance*, 498.

³²² Hall, *Mental Disorders and Health Insurance*, 1022.

physical illness.”³²³ Coverage of ambulatory treatment, however, would require “additional actuarial experience.”³²⁴

What appears the turning point promoting at least moderate coverage of mental ill-health was somaticizing the problem. By 1960, the benefits of psychoanalysis were increasingly questioned; psychiatrists no longer widely accepted it as the gold standard of treatment. It was “appealing and useful only to certain fairly restricted segments of the population.”³²⁵ The utility of psychoanalysis also came under attack, with Charles Hall jr., the Assistant Director of the AMA’s Department of Economics, referring to it as “not only ineffective for treating many forms of psychiatric illness but also forbidding and frightening to large masses of the working population.”³²⁶ The picture of mental health coverage shifted in the late 1950s; while only fifty percent of Blue Cross plans covered even hospital care for mental conditions in 1955, by 1963 eighty-two percent of these policies included coverage without a separate rider. Twenty-one percent of Blue Cross plans nationwide “provided the same benefits as for other types of illness,” although this could require hospitalization, just like somatic illnesses.³²⁷ Benefits under Blue Shield plans changed similarly. Insurance companies recognized

³²³ Thompkins, *Health Insurance and Psychiatric Therapy*, 346.

³²⁴ Thompkins, *Health Insurance and Psychiatric Therapy*, 346.

³²⁵ Hall, *Mental Disorders and Health Insurance*, 1026.

³²⁶ Hall, *Mental Disorders and Health Insurance*, 1026.

³²⁷ Robert H. Felix, “Improving Health Insurance Coverage for Psychiatric Illnesses,” *American Journal of Psychiatry* 121 (February 1965): 731.

use of drugs such as Valium contained costs, compared with psychological treatments.

Treatment with psychopharmaceuticals meant the treatment was physical; drugs acted on body and brain. Physical treatment of neuroses also promoted of short-term treatment on an outpatient basis. President Kennedy, proselytizing for the Community Mental Health Centers explained the necessity and realistic expectation that private business could provide the primary source of funding.

The success of this pattern of local and private financing will depend in large part upon the development of appropriate arrangements for health insurance, particularly in the private sector of our economy. Recent studies have indicated that mental health care – particularly the cost of diagnosis and short-term therapy, which would be major components of service in the new centers – is insurable at a moderate cost.³²⁸

The President was not alone in his optimism. By increasing use of short-term, low-cost, outpatient treatments and also highlighting the somatic aspects of neuroses, modern medicine appeared to create affordable mental health care for the masses. As the American Medical Association's Assistant Director of Economics phrased it, "One of the real problems facing insurance today is to keep their policies up to date with developing modes of treatment."³²⁹

Conclusion

Overall, the period from 1945 to 1963 was characterized by tensions between

³²⁸ Kennedy, Special Message, 4.

³²⁹ Hall, Mental Disorders and Health Insurance, 1024.

increasing demand for services to promote positive mental health and battle mental ill-health, and limits placed by available personnel, facilities, and costs. The resolution developing by 1963 created a situation wherein Valium and other psychopharmaceuticals played a greater role. The focus by 1960 was on obtaining mental health and treating mild, rather than severe, mental illness. Stress and the tensions of everyday life in America were barriers to positive mental health. Physicians differed from other mental health professionals in large part because they could prescribe pharmaceuticals. Valium was suitable for treating neuroses, minor mental ailments, and preventing stress and ongoing everyday tensions from tipping the balance from mental health towards mental illness. Tranquilizers were a short-term treatment, available only from physicians. Because general practitioners wrote most prescriptions for psychotropics, use of drug treatments nicely avoided the problem of health insurance plans which placed limits on the number of visits to psychiatrists.³³⁰

Overarching theoretical structures increased interest in the treatment of tension and anxiety. Hans Selye popularized his theory of the General Adaptation Syndrome in the popular press. Ego and dynamic psychiatry promoted the concept of health involving some form of dynamic tension, a balancing, between intrapersonal forces. Psychosomatic medicine tried promoting a more holistic understanding of illness, with mind and body both involved in ongoing disease. In each case the theories identified tension, stress, and anxiety (including an ongoing feedback loop of anxiety), as an

³³⁰ Hall, *Mental Disorders and Health Insurance*, 1023.

important problem. In 1963, Roche introduced Valium as a treatment useful for the wide variety of cases these three theories—Selye's G-A-S, dynamic psychiatry, and psychosomatics—identified as rooted in anxiety, tension, and stress.

Prescribing tranquilizers was justifiable on multiple levels, it could help father deal with job stress, and mother with the grinding madness of motherhood in the suburbs. It could keep families intact, which many Americans apparently associated with a strong and well regulated democratic society. Minor tranquilizers, those less sedating than ones suited to use within the confines of long-term psychiatric care institutions, served what the American populace and its leaders saw as pressing national needs. Whether used in the short term to treat the psychological aspects of psychosomatic illness, or in the longer term to deal with immature personalities adapting poorly to social roles, few interested Americans questioned tranquilizers' potential medical benefits. The drugs' use fit with what was 'known' about the workings of mind and body. The teachings of contemporary medicine tacitly justified widespread use of minor tranquilizers to treat a wide variety of physical and psychological problems.

The combination of mental health services delivered by the Community Mental Health Centers Act of 1963, focus on neuroses, promotion of positive mental health and rapid diagnosis and treatment of mild mental illness, characterization of more mental illnesses as physical or part of psychosomatic conditions, and widespread use of minor tranquilizers prescribed by general physicians for the stresses and tension that could

lead to neurotic reactions, helped solve the impasse between under supply of mental health services and increased public demand. To promote mental health and stave off mental illness required national mobilization of resources. In the 1950s and 1960s America appeared willing to try eradicating neuroses wholesale, to test Brigadier Menninger's claim that if we "had the manpower and the effort and the time...devoted to preventive aspects of psychiatry...we too could have perhaps demonstrated spectacular achievements comparable to vaccination or DDT."³³¹

Based on this optimistic belief that medical science could meet the widespread need for mental prophylactics, pharmaceutical companies drew on existing knowledge of mental health and illness and contemporary understandings of the nature of neuroses in order to develop valuable treatments. One outcome of their programs was Valium. Whether its usefulness was more akin to vaccination or DDT remained to be seen.

³³¹ Menninger, *Psychiatric Experience*, 585.

CHAPTER 4. DEVELOPING NEUROSES: MENTAL HEALTH THEORY BEFORE VALIUM

Mental health theory provides the context behind Valium's discovery, testing, and marketing. Psyche and somatic-based theories of the mind and brain developed and intertwined from 1900 to 1960. Concepts explaining the nature of neuroses altered; neuroses became things scientists could induce and – at least their correlates – measure in laboratory animals. This opened the possibility of discovering and treating neuroses with drugs such as Valium. The theoretical backdrop helps explain the ways pharmaceutical manufacturers, physicians, and pharmacologists in the 1950s and 60s understood neuroses and anxiety. A combination of theories, including those discussed in this chapter, justified Hoffmann-La Roche putting money into the search for new tranquilizers and development of pharmacologic testing methods used to test Sternbach's compound. Psyche and neural-based theories were not mutually exclusive. They intertwined and complemented each other, possibly because the physicians and scientists involved saw less of a mind/body divide than the average philosopher.

During the 1950s pharmaceutical manufacturers introduced a series of drugs into the psychiatric armamentarium which changed the face of institutional psychiatry. Dominant types of somatic (bodily) treatments altered, with techniques such as psychosurgery and insulin coma nearing extinction. The first pharmacologic antidepressants, including amphetamines, appeared around this time. But of broader

social importance was the discovery of tranquilizers. Chlorpromazine and reserpine, later classified as antipsychotics or major tranquilizers, were the earliest heralds of the flood. Their rapidly proven utility in calming psychotic and manic patients eased life for both institutional patients and doctors. Companies reevaluated substances already on the market, especially antihistamines, which were endowed with sedative, and therefore potentially calming, properties. And toward the end of the 1950s came a new type of tranquilizer...one believed nonaddictive, mild, not dulling the mind, and with little risk of overdose; chlordiazepoxide (Librium) was the first of these benzodiazepines, followed quickly by the drug this dissertation focuses on, diazepam, known by its trade name, Valium.

To understand the peculiarity of Valium's identification and marketing, it is essential to place its discovery in the context of 1950s mental health, as well as developments in behavioral and pharmaceutical research. How mental health professionals understood functional mental illnesses, broadly conceptualized as neuroses, shaped study of potential treatments and guided testing potentially useful compounds.³³² The discovery of major tranquilizers – chlorpromazine and reserpine – affected expectations surrounding potentially useful compounds. Discussions of

³³² The concept of functional mental illness developed from early twentieth century efforts to identify physical lesions or deformities related to dementias, schizophrenia, and psychotic behaviors. By the 1950s functional mental illness could best be defined as those conditions not thought organic-based. Mental retardation, senile dementias, schizophrenia, paresis, mania, and possibly alcoholism were believed to have somatic, bodily, basis. Functional mental illness, in theory, included maladaptations of behavior, affect, or learning, all of which were related to functions of the mind, rather than diseases of the brain.

previously used drugs, including barbiturates and bromides, suggest many physicians and pharmacists thought they affected the body and not the mind. Pharmaceutical companies began looking for compounds that seemingly altered the mind as well as body. The focus on mental health, neurotic reactions, and stress, all melded with one another in ways that created Valium as a social entity, a drug useful for widespread conditions. It was a good solution to a perceived problem. This chapter focuses on changes in conceptualization of neuroses, neurotic reactions, anxiety, and stress from the 1940s through to 1960, in order to help explain development and plans to market Valium (and Librium).

Development of Mental Health Theories

Although an over-generalization, it is useful to divide pre-1940 mental health theory into two broad categories, neural- and psyche-based. Neural theories, often termed behavioral, focused on overt and observable behavior as a window into the mind. Comparatively, mental or psyche-based theories tended to focus on interaction of the unconscious mind with conscious thought and behavior. To illustrate general characteristics of these theories, how they shaped perceptions of mental illness, and mutated into forms influencing discovery of Valium, Pavlovian behavioral conditioning techniques and Freudian psychoanalytic theory will act as exemplars for the two broad categories of theory. It is important to recognize that these theoretical positions are only exemplars. Most of the articles read for this dissertation suggest

many leading physicians and scientists had an eclectic approach, either showing little of their theoretical foundations, or freely using a combination of psyche and neural theories. Discussing the exemplars – at least in the period before 1940 – does, however, provide more clarity. Pavlov's work informed techniques used to identify physiological correlates of neuroses. Freud's theories helped explain links between neuroses and stereotyped behavior.

Ivan Pavlov, 1849-1936: Neural/Behavioral Theories

Ivan Petrovich Pavlov was born in Ryazan, Russia, to an impecunious priest and his wife. After basic educational training in a theological seminary, he studied at the University of St. Petersburg, graduating in general science and moving on to a program in medicine at the Military Medical Academy. He gained a license to practice medicine after completing the program in 1879, but only obtained his M.D. in 1883 after working with a well-known clinician. It was during this period he began working extensively with experimental research animals. From this point a combination of hard work, skill, and connections resulted in a rapid rise from privat-docent in physiology in 1884 to Director of the Physiology Department at the Institute of Experimental Medicine in St. Petersburg in 1890.

Now established head of a research program, Pavlov spent the remainder of his life working, directing research, and garnering increasing renown. Research on physiology of digestion, using dogs as research animals, resulted in a 1904 Nobel Prize

in physiology. Yet by 1902 he and his numerous doctoral students were adapting earlier techniques to “the problem of the higher nervous processes of the brain.”³³³ Around 1923, when his son read one of his lectures before the International Physiological Congress in Edinburgh, Ivan Pavlov’s research gained broader international notice. From that time to his death in 1936 he garnered international awards and memberships, funds and a pension from the Soviet government and, probably most importantly, iconic status sufficient for him to remain professionally successful in Russia while openly anti-Bolshevik.³³⁴

Pavlov’s interest in mental phenomena developed from an interest in physiology, so it is not surprising that he viewed action of the mind as rooted in the brain. Innovative in his focus on long-term studies of conditioning as well as external events,³³⁵ he was the first well-known scientist to recognize neuroses created in animals under laboratory conditions. In 1901, during experiments on animal digestion, he noted his dogs secreted digestive juices before they saw, smelled, or tasted food. Tinkering with environmental conditions suggested these animals had learned to associate a sound before food arrived with the process of eating to the extent their stomachs prepared for

³³³ Anon, “Obituary: Ivan Pavlov,” *The Slavonic and East European Review* 15, no. 43 (1936): 209.

³³⁴ Anon, *Obituary*, passim.

³³⁵ O. Hobart Mowrer, “Learning Theory,” *Review of Educational Research* 22, no.5 (1952): 476.

digestion before ingestion.³³⁶ To isolate the brain area causing this effect, Pavlov tried producing the same learning conditions in decorticated dogs (he excised the brain's cortex) and found the animals unable to associate the bell stimulus with the act of eating. Without the "cerebral hemispheres[.]" the dog became "a helpless invalid, and cannot long survive unless it be carefully tended."³³⁷ He concluded that these animals learned through association, conditioned to recognize events outside the body with those inside the body; furthermore the association formed within the brain's cortex.

Pavlov focused on the influence of environmental alteration and changes in behavior because he considered observation of the physical actions of the brain impossible. Ongoing interaction between the environment and the individual produced "a state of perpetual flux,"³³⁸ of mental activity "changing so rapidly that it becomes practically impossible to observe any aspect of it in an entirely pure and uncontaminated form[.]"³³⁹ Behavior was observable, providing "very definite but purely external signs," useful for deducing how animals learned.

The core of Pavlovian method involved relating unconditioned reflexes (UR)

³³⁶ Open questions remain regarding Pavlov's use of a bell in these original experiments. Roger K. Thomas, "Correcting Some Pavloviana Regarding 'Pavlov's Bell' and 'Pavlov's Mugging'," *The American Journal of Psychology* 110, no.1 (1997): 115-25.

³³⁷ Ivan Pavlov, *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex*, trans. G. V. Anrep (Humphrey, Milford, UK: Oxford University Press, 1927), 1.

³³⁸ Pavlov, *Conditioned Reflexes*, 378.

³³⁹ Pavlov, *Conditioned Reflexes*, 378.

and unconditioned stimuli (US), in order to produce conditioned responses (CR).

Unconditioned reflexes were the natural reactions of the body, innate behaviors such as respiration, digestion, physical sexual response, blinking, fight or flight reflexes.

Certain conditions triggered these innate behaviors, in the presence of unconditioned stimuli such as the body's need for air, eating food, pheromone sensing, avoiding rapid motion toward the eyes, or perceived danger. Conditioned responses developed when unconditioned stimuli and neutral stimuli occurred together or in close time sequence.

This occurred in natural learning, so Pavlov assumed he could reproduce it under controlled laboratory conditions. The result of this pairing preexisting conditions producing a reflex with new stimuli, was association within the brain of the two stimuli, thereby creating a conditioned stimulus. The brain would now react to the stimulus with the conditioned reflex action.

Pavlov explained creation of conditioned stimulus and response by postulating some sort of temporary physical link between a point in the cortex involved in analytical thought and a point in an area of the subcortex responsible for unconditioned reflex. As he explained, "The fundamental mechanism of development of a conditioned reflex depends upon excitation of some definite point in the cortex coincidentally with a more intense excitation of some other point, probably also of the cortex[.]"³⁴⁰ Creation of this link between two points in the brain was the physical essence of conditioning.

He conceptualized the link in terms of excitation, activation, of specific areas of

³⁴⁰ Pavlov, *Conditioned Reflexes*, 384-85.

the physical brain. This connection was an action, perhaps most easily analogized as a wave or tension. Like waves in a pond, the initial activation created a prolonged pattern that gradually weakened; “if such a coincident stimulation of these points is not repeated for a long time the path becomes obliterated and the connection disrupted. But once such a path had been firmly established it remains intact without further practice, for months and years.”³⁴¹ Like a wave, repetition of the same pairing of unconditioned stimulus with neutral stimulus strengthened the connection. By our analogy, repetition of the activation increased the amplitude of the wave.

Pavlov himself was not a clinical practitioner of psychiatry,³⁴² yet his theories informed later treatment approaches. In general, behavioral or environmental approaches find their roots in Pavlovian theory. Essentially the focus is on changing patterns of learning through alteration of stimuli or response to stimuli.

Pavlov considered unconditioned stimulus and reflexes, what he termed ‘natural responses,’ more persistent links than conditioned stimulus-response (S-R) chains. But they were of the same basic type. Repeated use of conditioned stimulus without reinforcement decreased, even possibly extinguished the connection. For example, a dog who learned his owner says “walkies” before taking her out for a walk may learn to

³⁴¹ Pavlov, *Conditioned Reflexes*, 384-85.

³⁴² He did however study with clinicians, and worked “as the director of a laboratory in the clinic of the renowned Botkin for several years.” L. A. Andreyev, “The Great Teacher and Master of Science,” *The Scientific Monthly* 45, no.2 (1937): 163. The laboratory Pavlov directed in the clinic, however, appears to have been that involved in experimental animal work.

pick up a leash and head for the front door. But if the owner uses the term walkies capriciously, the dog is less likely to expect an outdoor expedition is imminent. Although Pavlov's own position on extinction of CS-CR behaviors is unclear, he understood weakening of the association as a process of inhibition (as opposed to excitation). He apparently believed the initial connection persisted, as the inhibition reversed (disinhibition) more quickly than an initial learning pattern created and fixed.

Behaviorism, throughout the early and mid-twentieth century, was about learning. Pavlov associated learning with conditioning of the organism through reaction to the environment; "It is obvious that the different kinds of habits based on training, education and discipline of any sort are nothing but a long chain of conditioned reflexes[.]" he pontificated. "We all know how associations, once established and acquired between definite stimuli and our responses, are persistently and, so to speak, automatically reproduced, sometimes even although we fight against them."³⁴³ But he realized the brain was not a simple machine, because the excitation between points was not a simple and self-contained connection. Excitation of a point within the cortex was akin to setting up a wave, affecting peripheral areas, albeit to a lesser extent the farther away they were. This explained why similar stimuli could evoke the same conditioned responses. Organisms learned through direct conditioning as well as generalizing and differentiating between stimuli. The concept of learning in terms of waves, or links with greater or lesser strength, provided a way to explain

³⁴³ Pavlov, *Conditioned Reflexes*, 395.

tranquilizers as central nervous system depressants. Tranquilizers treated psychoses and neuroses by altering the strength and rate at which CS-CR patterns were established, extinguished, repressed, or altered.

What Pavlov himself learned about the United States was not entirely positive. Already a Nobel Laureate and “one of the most distinguished physiologists in the world,” Pavlov and his son visited the United States for three weeks in 1923. “He was robbed of \$2,000 in a train in the Grand Central Terminal, was forced to become the guest of the Rockefeller Institute because of his predicament and then was refused a British visé to his passport because he was a Russian.” It is hard to imagine being a guest of the Rockefeller Institute was one of the Professor’s negative experiences.³⁴⁴

Pavlovian conditioning was not strictly deterministic. Although some of Pavlov’s statements suggest a stark view in which the individual is a near automaton, simply responding to the environment, his understanding was far more nuanced. Environmental conditions were internal as well as external; Pavlov refers to the “minutest changes in the environment or inside the organism itself” having “a profound effect upon the cortical activities.”³⁴⁵ Yet the constitution of the organism also played an important role, preparing the groundwork upon which conditioning developed. Certain individuals learned more quickly from one form of stimulus than another. In more recent terminology, individuals had learning curves and learned better from

³⁴⁴ Anon, “Professor Pavlov’s Visit to America,” *Science* n.s.58, no.1490 (1923): 45.

³⁴⁵ Pavlov, *Conditioned Reflexes*, 378.

certain types of information. Some constitutions tended to produce overgeneralized responses, applying conditioned responses to diverse related conditions. Others had a remarkably high or low threshold for stimulus in general. Those who persisted in applying a conditioned response, either by overgeneralizing or by delaying the extinction of a response after removal of reinforcement, were the constitutions, in mid-twentieth century terms the personalities, who tended toward neurotic reactions.

Adding to the complexity were the first and second ‘signalizing systems.’ Apart from that portion of the brain responsible for unconditioned reflexes, Pavlov argued there was a first signalizing system which involved the conditioned responses. Initial conditioning was development of connections between these two portions of the brain. What added further complexity was the second signalizing system, widely distributed throughout the brain. This second signalizing system resulted from interplay of primary conditioned responses through interaction and generalization. It was through this signalizing system that human beings gained the capacity for language and abstract thought.

The behavioral model of stimulus-response provided a framework for understanding mental illness that placed few boundaries between organic and functional problems. “Contemporary medicine distinguishes “nervous” and “psychic” disturbances—neuroses and psychoses,” Pavlov complained, “but this distinction is, of course, only arbitrary.” Because he understood mental activity as rooted in the physical interworkings of the brain, it was impossible to understand mental illness as a disease of

the mind that did not involve the brain; “physiology and medicine are inseparable[,]” he told listeners of his 1906 Harvey Lecture.³⁴⁶ By understanding learning in terms of association with innate reflexes, he further blurred any putative boundary between the nervous system and brain. In his own words, “The distinction between “nervous” and “psychic” affections is a distinction made on grounds of greater or smaller complexity and subtlety in the disturbance of the nervous activity.”³⁴⁷ Mental illness was both psychological and physiological.

The extent to which the details of Pavlov’s theories carried over to the operant conditioning theories of the 1950s is a point of debate. As discussed later in the chapter, one of the best known figures in midcentury behaviorism, B. F. Skinner, believed it was only possible to understand behavior, not thought. Whether he was correct is a side issue for the rationale for seeking and using tranquilizers; the more important question is whether Skinner, and others of his theoretical ilk, considered behavior rooted in the physical brain. If neuroses were at least in part physical, they might be directly, physically, treated. Did they understand mental illness as both physiological and behavioral?

Sigmund Freud, 1856-1939: Psyche-Based Theories

³⁴⁶ Ivan Pavlov, “The Scientific Investigation of the Psychical Faculties on Processes in the Higher Animals,” *Science* n.s.24, no.620 (1906): 619.

³⁴⁷ Pavlov, *Conditioned Reflexes*, 396.

The relation between pre- and post-1940s psyche-based theories is more easily described, and how practitioners of these theories understood action of drugs appears more consistent. Depending on the interpretation, Sigmund Freud was either the father of psyche-based theory, or the straw man for alternative interpretations. In the late 1950s and early 1960s, the time of Valium's development and introduction to the American market, talk therapies such as psychoanalysis were the traditional gold standard of treatment. Freud provided the theoretical underpinnings of a system which, with prolonged and intensive treatment, could modify personality enough to protect individuals from developing maladaptive neuroses.

Sigmund Freud's theories and techniques of psychoanalysis were highly influential, especially in the 1940s and 1950s after his death. Freud's writings vary dramatically from his earliest efforts to heal the mind through talk therapy, association, or hypnosis and suggestion. Nevertheless, until the time of his death his own work defined orthodox psychoanalysis. As he wrote in 1914 "...I feel myself justified in assuming that none can know better than myself what psychoanalysis is, wherein it differs from other methods of investigating the psychic life, what its name should cover, or what might better be designated as something else."³⁴⁸ By the 1940s the psychoanalytic school of thought formalized the essential theories considered core to their discipline. Psychodynamics, ego psychiatry, and other post-1940 psyche-based theories were outside the bounds of orthodox Freudian theory.

³⁴⁸ Sigmund Freud, *The History of the Psychoanalytic Movement*, trans. A. A. Brill. (New York: The Nervous and Mental Disease Publishing Company, 1917), 1.

Freudian psychoanalysis is a general methodology based on a certain understanding of human development and the mind. The mind, or psyche, is tripartite, formed of the id, ego, and superego. Although the actual terms refer to more specific and nuanced ideas, it is a useful shorthand to associate the id, ego, and superego with instinct, self, and conscience respectively. The id or instincts were present at birth, the ego developed during infancy, and superego through resolution of the Oedipus conflict (in the traditional Freudian interpretation) or more generally through internalization of social mores and parental teaching.

Freud's understanding ties intimately to physiological thinking. Instinctive drives are similar to energies which are neither created nor destroyed, only temporarily repressed, transferred, or sublimated into other forms. Normal behavior involved development of mechanisms to deal with this energy in ways allowing instinctive drives and expression of the self to meet their desired ends within the bounds of socially acceptable action. When this energy, usually discussed in the early twentieth century as a creative or constructive urge termed either Eros or the libido, was pent up, the individual became neurotic, anxious. Typically, Freudian theory described these conflicts as taking place between the superego and ego over resolution of the id's desires. If neuroses formed because of conflicts within an individual, pharmacologic treatments could not touch the underlying disorder. Psychotherapy was necessary to understand the cause of neuroses and adjust personality, fix current, and prevent future, problems.

Freudian psychoanalytic theory focused on learning; the individual developed according to interplay between inner drives and environmental or social conditions as it attempted to reconcile desires with the limits of social reality. This was a process of negotiation within the individual as well as learning the constraints of society. Transference, projection, sublimation, and repression were efforts to channel drives in order to achieve personal goals within the constraints of the social environment. These efforts to channel energies and conflict between drives to be normal and healthy behaviors...mostly. When the original problem remained unresolved, neuroses might result.³⁴⁹ Psychoanalysis was an attempt to uncover details of the compromise, making the conscious mind aware, and by showing what was “repressed within the id”³⁵⁰ to promote development of responses to the conflict that “correspond better to a psychically mature condition[.]”³⁵¹

Traditionally, writers describe behavioral and psychoanalytic theories as separate philosophies, different ways of understanding. Yet there are remarkable similarities in the underlying assumptions and implications of these pre-1940 theories. Both Pavlov and Freud’s interest focused on individual development and the interaction between internal and external events. In Pavlov’s case, an individual had a constitution which influenced the process of learning and interaction with the environment. In

³⁴⁹ Freud, *History of the Psychoanalytic Movement*, 44.

³⁵⁰ Freud, *Analysis Terminable and Interminable*, 1937, 341.

³⁵¹ Freud, *Analysis Terminable and Interminable*, 1937, 359.

Freud's case the inner drives attempted to reconcile instinct with the social environment. Both theories were about learning. Pavlov's individual learned, through association and generalization, to develop complex conditioned stimulus response chains. Freud's individual learned techniques of accomplishing goals in a realistic fashion, dealing with the requirements of society in ways that channeled internal energies.

Mid-Century Modifications

By the 1950s, purported behaviorists and psychoanalysts worked with significantly modified versions of the initial theories; variants which placed greater emphasis on the roles of stress and anxiety in mental illness, thereby preparing the way for tension reducing drugs. Although many writings of professed behaviorists or psychoanalysts show an eclectic use of both neural and psyche theories, there remained a recognized split between "the two practice groups in psychiatry...the analytic-psychological...and the directive-organic[.]"³⁵² In both cases emphasis increasingly focused on the role of will or self, an assumption that human beings preferred stability, and an association of mental health with adaptation to a changing environment. In theories of both groups, physical and mental life interacted, mainly in one direction; mental processes affected physical. The operant conditioning theories of B.F. Skinner,

³⁵² Thomas A. Gonda, "The Changing Scope of Psychiatry," *Annual Reviews of Medicine* 10 (1959): 292.

as well as Jules Masserman and W. Horsley Gantt's work on conditioning and neuroses, illustrate these changes. Psyche-based theories will be discussed more generally because they were significantly more differentiated, albeit with characteristic similarities.

B. F. Skinner, 1904-1990

Undoubtedly the most famous modification of Pavlov's stimulus-response (S-R) framework was B. F. Skinner's operant conditioning model. Skinner worked at the Biological Laboratories of Harvard University. During his studies on habit formation, he concluded Pavlov's methods and understanding of the conditioning process had limited value. The Russian recognized only two main types of conditioning, Skinner complained, internal only and those impelled by an external stimulus. In one case, the linking of unconditioned reflex and unconditioned stimulus strengthened into a conditioned S-R relationship due to temporal sequence, but the correlation was already in place. In the second form of conditioning, the original stimulus was paired with an external event, a stimulus which "*prepares* the organism by obtaining the elicitation of a response before the original stimulus has begun to act, and it does this by letting any stimulus that has *incidentally* accompanied or anticipated the original stimulus act in its stead."³⁵³ Skinner promoted the idea of a third type of conditioning in which there is no

³⁵³ B. F. Skinner, "Two Types of Conditioned Reflex and a Pseudo Type," *Journal of General Psychology* 12 (1935): 75.

obvious and immediate stimulus. This ‘operant’ conditioning placed greater emphasis on learning through trial and error, or thought, rather than mechanical conditioning through reaction to outside forces.

It is important to note Pavlovian conditioning theory did encompass the conditions Skinner defined as his new idea. Pavlov presumably would have interpreted this form of apparent learning as occurring through the secondary signaling system and the extinction of certain conditioned responses and development of new ones. The organism’s environment reinforced suitable new responses and strengthened the connection between those events and the reflexes.³⁵⁴ Skinner himself was interested in the role of social situations as “techniques of control[,]”³⁵⁵ in other words events reinforcing certain culturally approved behaviors. Pavlov’s presumed interpretation differed substantially from Skinner’s because the former considered the reaction in more deterministic terms, as chains of discrete events, and therefore rooted in different ideas of learning.

As well as a change in understanding the learning process, the operant conditioning model suggested significantly different ways to study learning. If the organism was adaptive rather than acted upon by the environment, whether adaptation was positively or negatively reinforced was important. As Skinner explained in his

³⁵⁴ This interpretation is similar to that offered by J. Konorski and S. Miller, “On Two Types of Conditioned Reflex,” *Journal of General Psychology* 16 (1937): 264-72. See p. 267.

³⁵⁵ Carl R. Rogers and B. F. Skinner, “Some Issues Concerning the Control of Human Behavior,” *Science* n.s.124, no.3231 (1956): 1058.

scathing response to J. Konorski and S. Miller's "On Two Types of Conditioned Reflex,"³⁵⁶ psychologists needed to recognize responses as learning experiences, promoted or hindered because of reinforcement. It was far more important to measure the "rate of occurrence of the response" than the strength of relationship between conditioned S-R.³⁵⁷ Change in rate of occurrence was measurable; alteration in the strength of the S-R connection was poorly quantifiable.

In terms of the experimental conditions used to identify tranquilizers, B. F. Skinner is far more important for promoting study of observable events without interpreting mental events from them. In 1950 he outlined his basic concerns in "Are

³⁵⁶ Konorski and Miller, *Two Types of Conditioned Reflex*, 264-72; Skinner essentially writes off the concerns of these scientists by suggesting they were interested in establishing their priority in the discovery, thereby neatly implying that they must actually be in essential agreement with him; Konorski and Miller were openly working from an initial standpoint of Pavlovian theory. These scientists, working in Warsaw, challenged Pavlov's own explanations and helped initiate/promote Pavlov's focus turning to the interaction between signaling systems. George Windholz, "Pavlov's Conceptualization of Voluntary Movements Within the Framework of the Theory of Higher Nervous Activity," *The American Journal of Psychology* 111, no.3 (1998): 435-43; Within the Soviet Union similar establishment of Pavlovian theories as orthodox doctrine developed. In 1950 the U.S.S.R.'s Academy of Sciences and the Academy of Medical Sciences established the Scientific Council on Problems of the Physiological Theory of Academician I. P. Pavlov. This Council on Problems attempted to promote and ensure current research was conducted within the boundaries of what they defined as the Pavlovian program. They set up conferences and commemorations, as well as arranging publication of Pavlov's writings. Ivan. D. London, "The Scientific Council on Problems of the Physiological Theory of Academician I. P. Pavlov: A Study in Control," *Science* n.s.116, no.3002 (1952): 23-27.

³⁵⁷ B. F. Skinner, *Two Types of Conditioned Reflex: A Reply to Konorski and Miller*, *Journal of General Psychology* 16 (1937): 276.

Theories of Learning Necessary?”³⁵⁸ If “learning is a process in the behavior of the individual[,]”³⁵⁹ he argued, it is inappropriate to use average behavior of a group. Instead, Skinner argued, you needed to study the “*probability of response*” in one creature.³⁶⁰ This was a measurable phenomenon that varied over time, and therefore held the possibility of expressing the change involved in learning. His methods, however, were hijacked by scientists seeking physically observable correlates of mental events. Others recognized that rate of response in laboratory animals provided an experimental shorthand for identifying whether a drug altered the central nervous system, if it was active at the higher levels of integrating perception and learning from the environment.

Use of probability of response as a measure of learning has various implications. The organism learns to adapt to changing conditions. Therefore learning occurs with introduction of stressors, alterations to the usual environment. Because probability of response is a measure of learning over time, it emphasizes speed of adaptation. Skinner’s methodology is part and parcel of a conceptual shift toward focus on quick adaptation to stress as a measure of mental health.

Contemporaneously with Skinner, other behaviorists tried to understand the nature of neuroses. In the 1940s and 50s, Jules Masserman, of the University of

³⁵⁸ B. F. Skinner, “Are Theories of Learning Necessary?” *Psychological Review* 57 (1950): 193-216.

³⁵⁹ Skinner, *Are Theories of Learning Necessary*, 195-96.

³⁶⁰ Skinner, *Are Theories of Learning Necessary*, 198.

Chicago (1936-46) and Northwestern University (beginning in 1946) worked within the operant conditioning model as he conducted animal studies, attempting to understand development of neuroses and their relation to frustration, fear, and aggression.³⁶¹ W. Horsley Gantt, who set up and worked at the Pavlovian Laboratory in Johns Hopkins University, tried to relate development of neuroses to the frustration of uncertain or conflicting learning conditions. Both of these influential behavioral scientists helped shape an understanding of neuroses as physical and emotional reactions based on the internal conflicts induced by changes in external events. Capacity to adapt to environmental changes was an essential part of mental health,³⁶² and lack of viable options prolonged mental illness.

Jules Masserman, 1905-1994

Jules Masserman refined laboratory methods of inducing neuroses in animals, in order to study behavioral changes resulting from modification of the creature's

³⁶¹ These men were neither the first nor the only experimenters working with Pavlov's concept of experimentally created neuroses in animals. For an example see Howard S. Liddell, "Conditioned Reflex Method and Experimental Neurosis," In *Personality and the Behavior Disorders*, ed. J. McV. Hunt. (New York: Ronald Press Company, 1944). Chapter 12. For a more general discussion see Laurence F. Shaffer, "Experimental Contributions to Mental Hygiene," *Review of Educational Research* 16, no.5 (1946): 429-35.

³⁶² In Jules H. Masserman and Curtis Pechtel, "Neurophysiologic and Pharmacologic Influences on Experimental Neuroses," *American Journal of Psychiatry*, 113 (December 1956): 510-14. Adaptation was important enough to be included in 3 of the 8 variables studied.

environment.³⁶³ He identified signs of neuroses which were physical and measurable. These observable features later served as indicators of how well Valium mitigated symptoms associated with neuroses and anxiety.

His neurosis experiments were grounded in his interpretation of Pavlov. “In the Pavlovian system[,]” he wrote, “neurotic behavior was thought to arise when ‘external’ stimuli produced simultaneous but incompatible reactions of excitation and inhibition[.]” He took from this the idea that neuroses resulted from “conflictual incentives and the consequences of their frustration...when he [the animal] could no longer react with more directly adaptive behavior[.]”³⁶⁴

Using laboratory animals such as monkeys, Masserman tested the idea that “conflictive ‘psychological’ traumata”³⁶⁵ could produce neuroses; he provided creatures with a frustrating situation, where expected conditions of cause and positive effect suddenly conflicted with new and often irrational conditions. First, animals learned and therefore expected certain feeding conditions. In one experiment, “[e]ach animal was taught, in from four to six months, to press an electrical switch exactly four times for

³⁶³ Brief obituaries were published in various American newspapers. For example see Anon, “Notable Deaths Last Week,” *Daily Herald* (Chicago, IL) November 13, 1994; for a brief overview of Masserman’s work see Harold M. Vitosky, “Jules H. Masserman, M. D.: One Hundred and Seventh President, 1978-1979,” *American Journal of Psychiatry* 136 (August 1979): 1023-25.

³⁶⁴ Jules H. Masserman, *Behavior and Neuroses: An Experimental Approach to Psychobiologic Principles*, (Chicago: University of Chicago Press, 1943), 17.

³⁶⁵ Jules H. Masserman and Curtis Pechtel “Neuroses in Monkeys: A Preliminary Report of Experimental Observations,” *Annals of the New York Academy of Sciences* 56 (1953): 253.

food, to alternate between two switches, and to choose the correct one of the two as differentially indicated by a bell or light signal.”³⁶⁶ These animals now had a low stress, predictable environment. The investigators then introduced various mobile or vocal representations – new stressors interfering with the monkeys’ predictable environment – outside the cage, and observed the creatures’ reactions to the stressors. The most pronounced effects occurred with presentation of a “toy rubber snake[.]”³⁶⁷ The animals responded with various degrees of “horripilation, alarmed vocalization, rapid breathing, diffuse movements, ejectile defecation, and disturbances of discriminatory patterns in signal-response and switch manipulation that persisted for from 15 to 30 minutes.”³⁶⁸ Stripped of scientific language, the scientists tormented monkeys with a rubber snake, scared the s**t out of them, watched them signal for help, and recorded the entire situation in apparently clinical terminology. These well respected and funded researchers tested a variety of other stimuli such as “a toy rubber lizard, a rubber spider, or a coiled steel spring undulating along its length[.]”³⁶⁹ The results were less dramatic and of shorter duration, and by the time the scientists presented them with “a walking Donald Duck”³⁷⁰ the caged monkeys showed no fear.

³⁶⁶ Masserman and Pechtel, *Neuroses in Monkeys*, 253.

³⁶⁷ Jules H. Masserman, Zoltan Gross, and Curtis Pechtel, “Abnormalities of Behavior,” *Annual Reviews of Psychology* 5 (1954): 263.

³⁶⁸ Masserman and Pechtel, *Neuroses in Monkeys*, 258.

³⁶⁹ Masserman and Pechtel, *Neuroses in Monkeys*, 258.

³⁷⁰ Masserman and Pechtel, *Neuroses in Monkeys*, 258.

The fact that these experiments appear bizarre and cruel to later readers suggests either that the Masserman laboratory at Northwestern University was staffed by psychopaths, or this experiment and its results were understood by the scientists as explaining important aspects of behavior, applicable to humans. Given that the Masserman lab was continually funded, and that he was not driven out of the state when the results were presented to the New York Academy of Sciences, the latter explanation appears more likely. World War II had established that mental health and mental illness were a continuum, with most citizens either neurotic or potentially so. Therefore, understanding neuroses with animal models held broad social importance; they could “shed light on many problems of human behavior.”³⁷¹ Masserman established laboratory experiments in which he could reproduce neuroses at will, and study conditions that prolonged, repeated, moderated, or removed them. For example, he established an association between the anxiety of initial frustration (trauma) and sensitization producing prolonged anxiety. As he explained sensitization, “all animals began showing lowered thresholds of startle to sudden or unusual stimuli in any modality, and marked evidence of anxiety[.]”³⁷² Masserman’s experiments established that similar conditions could produce a wide variety of reactions, physical and psychological, all resulting from a similar underlying condition. Although this experiment did not test the efficacy of tranquilizers in mitigating initial trauma, or

³⁷¹ Anon, “Retirement of Old People is Studied,” *Ames Daily Tribune* (Ames, IA) February 1, 1955.

³⁷² Masserman and Pechtel, *Neuroses in Monkeys*, 261.

ongoing anxiety, it tested two modified versions of psychotherapy. Individual psychotherapy, which worked on all species of monkey except the Rhesus, took the form of petting and reassurance for one female Spider monkey, and requiring a male Vervet to explore the cage in order to acquire food. Rhesus monkeys required group therapy. The female, who would not approach the cage alone, tested the apparatus and then “seemed to encourage similar behavior in her companions.”³⁷³

The relation between neuroses and social behavior, seen in the Rhesus monkeys, was an important thread of Masserman’s research. In an attempt to understand changes in social behavior, dominance and aggression, he trained sixteen cats each to open a box containing a food pellet when a “bell-light”³⁷⁴ signaled the box was unlocked. He paired single cats in various combinations to identify a dominance hierarchy, based on which of a pair of cats ate first (dominant) and which did not try to eat until the dominant cat finished (submissive). Although it might be argued that all cats are neurotic to begin with,³⁷⁵ Masserman induced neurotic behavior in dominant cats by

³⁷³ Masserman and Pechtel, *Neuroses in Monkeys*, 264.

³⁷⁴ Jules H. Masserman and Paul W. Siever, “Dominance, Neurosis, and Aggression” *Psychosomatic Medicine* (1944): 7.

³⁷⁵ Masserman, of course, considered it worthwhile to investigate this potentially troublesome variable. His analysis showed “high ratings on pre-neurotic combativeness correlate significantly with relative resistance to neurotogenic traumata;” but this tendency of non-neurotic cats to resist becoming neurotic was a matter of level of neurotogenic stimuli required. All cats could become neurotic, but not all started that way. Jules H. Masserman and K. S. Yum, “An Analysis of the Influence of Alcohol on Experimental Neuroses in Cats,” *American Journal of Psychiatry* 48 (January 1946): 47.

“exposing them to adaptational conflicts between learned patterns for securing food...as opposed to fear of repetition of a threatening experience.”³⁷⁶ This experiment is typical of his approach and understanding of the conditions producing neuroses; motivation conflicts create neurotic behavior if conditions within the organism and environment were suitable.³⁷⁷ Behavior became “abnormally indecisive, substitutive, diffusely symbolic, and biologically inefficient[.]”³⁷⁸

The effects of drugs played a role in Masserman’s research. Using 142 cats and 43 monkeys, he examined the effects of alcohol, opiates, barbiturates, mephenesin, chlorpromazine (Thorazine), meprobamate (Miltown) and other drugs on animals who were either normal or suffered from experimentally produced neuroses. In monkeys, he found none of the drugs “with the possible exception of alcohol”³⁷⁹ protected against either initial or continuing stress of neuroses.³⁸⁰ In cats, the drugs most similar to Valium (barbiturates, some ataraxic drugs, and alcohol) were those which lessened

³⁷⁶ Masserman and Pechtel, *Neurophysiologic and Pharmacologic Influences*, 510.

³⁷⁷ Masserman, *Behavior and Neuroses*, chapter 11.

³⁷⁸ Masserman, *Behavior and Neuroses*, 204.

³⁷⁹ Masserman and Pechtel, *Neurophysiologic and Pharmacologic Influences*, 513.

³⁸⁰ Similar results were found in his earlier work on alcohol and cats. Mildly neurotic cats returned to normal behavior when given small doses of alcohol. Strongly neurotic cats, he thought, became addicted to booze for psychologic rather than physiologic reasons. It was “a learned adaptation contingent upon inter-current neurotic stresses and reversible when these stresses were removed.” In other words, neurosis could lead to drink. Masserman and Yum, *Influence of Alcohol*, 51.

neurotic symptoms once they formed.³⁸¹

This research highlights parallels between alcohol and tranquilizers which would underlie later debates in the broader social sphere. Masserman identified alcohol (because it depressed the cortex) as a substance reducing action in the portion of the brain thought most important for integrating and synthesizing experience, the cortex. Later explanations of Valium's action sometimes applied this logic. He assumed expectation of anxiety, lack of security, and ability to regress and focus on personal needs were important effects of a "cortical depressant[.]"³⁸² In his own words:

precisely these "pharmacologically decortinant effects might be sought by a neurotic animal to whom its environment had become prevasively[sic] and poignantly threatening, since under such circumstances transient but welcome relief would be afforded by any drug that blurred and disorganized apperceptions provocative of anxiety, diminished inhibition and facilitated a regression to relatively elementary but need-fulfilling behavior."³⁸³

Alcoholism, however, was also partially psychological. Masserman argued "alcoholism is no more a disease than gambling or biting your nails." He followed the statement up by pointing out it was a habit, similar to both gambling and nail biting.³⁸⁴ The physiological and psychological mixed, so although not a true disease alcoholism was a

³⁸¹ Masserman and Pechtel, *Neurophysiologic and Pharmacologic Influences*, 513.

³⁸² Jules H. Masserman, "Neurosis and Alcohol: An Experimental Study," *American Journal of Psychiatry*, 101 (November 1944): 393.

³⁸³ Masserman, *Neurosis and Alcohol*, 393.

³⁸⁴ Anon, "State Medical Society Names President-Elect," *Stevens Point Daily Journal* (Stevens Point, WI) May 3, 1960, 13.

legitimate “social behavior problem[.]”³⁸⁵

Jules H. Masserman provides an excellent example of how behavioral and psyche-based theories intertwined to create an intellectual foundation for the discovery of Valium. Masserman characterized his theoretical foundation as “Dynamic Psycho-Biologic”³⁸⁶ because it applied modified traditional Pavlovian behavioral techniques of inducing neuroses and more contemporary psychodynamic ideas of adaptation and frustration of drives, using both obviously and symbolically related methods of dealing with stresses. Masserman chose muscle tension as one of the three most important items (out of sixty used) for studying neuroses and drugs in cats.³⁸⁷ Roche labs would use small animal tests involving muscle tension to identify potentially marketable tranquilizers.

Masserman’s drunken cat experiments gained popular notice. Dr. Joyce Brothers used the experimenter’s work to reassure one reader there was precedent for their problem beer-drinking cat.³⁸⁸ The Salt Lake tribune ran a report of the research on its front page, focusing on how “cool cats...can come down with anxieties, tensions,

³⁸⁵ Anon, State Medical Society, 13.

³⁸⁶ Masserman, *Behavior and Neuroses*, 202.

³⁸⁷ Jules H. Masserman and Curtis Pechtel, “How Brain Lesions Affect Normal and Neurotic Behavior: An Experimental Approach,” *American Journal of Psychiatry* 112 (May 1956): 865-72. Note that only 3 factors are listed for study in cats, suggesting the researchers saw these as either the most important, or most interesting categories.

³⁸⁸ Joyce Brothers, “Troubled by an Alcoholic Cat?” *The News* (Frederick, MD)

phobias and...[l]ike man, they experience relief of their neuroticism by taking to drink.” The story’s hook, however, was that Masserman, “The Chicago Psychoanalyst[,]” illustrated development of neuroses “in animals that do not have a background of unresolved sex conflicts.”³⁸⁹ Public perception of mental health research assumed both behavioral and psyche-based theories played important roles.

W. Horsley Gantt, 1892-1980

W. Horsley Gantt, working at Johns Hopkins’ Pavlovian Laboratory, focused his animal neuroses studies around behavioral methods, but with a more explicitly mentalist interpretation than Masserman. Gantt’s work tied together observable signs of neurosis with theory of underlying mental behavior. Bringing a broader group of theories into alignment made questioning any of them less likely. Therefore his influence on development of Valium was on both establishing neuroses as externally observable, and therefore testable, conditions and establishing utility of stress mitigating pharmaceuticals, an antineurotics. Gantt’s interests included the relationship between conflict and neuroses in terms of their physiological correlates. But he interpreted frustration and conflict in terms of conflicting drives internal to the animal and inability of adapt to new stressors. Similar to psychologist Gordon W. Allport’s idea of functional autonomy of drives, discussed later in this chapter, Gantt identified

³⁸⁹ Chicago Daily News Service, “Feline Frustrations Drive ‘Em to Drink,” *The Salt Lake Tribune* (Salt Lake City, UT), January 10, 1964.

the roots of neuroses in frustration and conflict, but developing into continuing problems due to associations in the mind and/or brain of the animals.

Gantt saw his behaviorist roots tied to the methods and theories of Pavlov. He focused on both the primary and secondary signaling systems of Pavlov, and used terminology of excitation and inhibition.³⁹⁰ Perceiving himself as the Russian's intellectual offspring, when he focused on the role of constitution – individual factors – he assigned primacy of this discovery to Pavlov. Yet ultimately he focused more than Pavlov on the internal events of an animal's mental life.

Although Pavlov and his followers aimed for objective measurement, they were not as focused on finding statistical norms as would be late twentieth-century scientists. Earlier twentieth-century behaviorists considered temperamental differences between animals important, especially in their research on creation of experimental neuroses. Gantt recognized this element of Pavlovian research; some individuals were prone to develop neuroses more quickly, strongly and persistently than others.³⁹¹ Discussing why initial stresses only developed into neuroses in some of his lab animals, he wrote “The two chief factors seem to be (1) the constitution of the individual, and (2) the severity of the conflict.”³⁹² Pavlov had tied this in to the stability of the animal, its

³⁹⁰ W. Horsley Gantt, “The Origin and Development of Nervous Disturbances Experimentally Produced,” *American Journal of Psychiatry* 98(January 1942): 475-76.

³⁹¹ W. Horsley Gantt, “Principles of Nervous Breakdown- Schizokinesis and Autokinesis,” *Annals of the New York Academy of Sciences*, 56 (1953): 146.

³⁹² Gantt, *Origin and Development*, 477.

capacity to learn quickly.³⁹³

The need to adapt quickly was important when faced with a stressor, which in Gantt's lab was conflict between "the signal for the positive activity (excitation) and the negative (inhibition)."³⁹⁴ As well as conditions producing stresses through instincts – such as fear, fighting, shock – Gantt's methods involved stressful learning conditions, ones producing both excitation and inhibition. One technique used association of one pitch of a sound with availability of food, another without. Experimenters could adjust tones associated with food and not-food until they were too similar to differentiate accurately. This created frustration and anxiety in animals attempting to learn.³⁹⁵ A popular science writer described Gantt's interpretation of the resulting "typical anxiety attack" as the outcome of "conflict when the animal could no longer discriminate[.]"³⁹⁶ In this experiment Gantt feigned no hypotheses (in other words, 'pulled a Newton'), writing "I shall omit discussion of the theoretical considerations[.]"³⁹⁷ but then turned to only two possible interpretations "a physical one of overlapping of cortical processes of excitation and inhibition, or whether the conflict is based on a more highly organized

³⁹³ Gantt, *Principles of Nervous Breakdown*, 148.

³⁹⁴ Gantt, *Origin and Development*, 475.

³⁹⁵ Gantt, *Origin and Development*, see pp. 475-76.

³⁹⁶ Anon, "Unbalanced Nerves Can Cause Heart Disease and Ulcers," *The Science News-Letter* 33, no.16 (1938): 244.

³⁹⁷ Gantt, *Origin and Development*, 475.

psychobiological level, such as is indicated by ‘frustration.’”³⁹⁸ Implicitly, Gantt favored the second interpretation.

Articles by Hoffman and Gantt, as well as Whitehorn, reported that in animals previously introduced to conflicting stimuli, heart rate sped up before muscle action; the animal was hyper alert, keenly expecting something to happen. This suggested to them the nervous system must be excited (in some specific portion), leading to the physical action. When learning new conditioned responses, the cardiac response appeared earlier in training and persisted longer when there was no reinforcement of response. Gantt viewed this as an important clue to the nature of “nervous dysfunction on the higher level of behavior[.]”³⁹⁹ Physical stress reactions developed from frustration.

Neuroses were extensions of the conflict frustration over a long period. Neurosis was maladaptation, dysfunctional behavior, continuing after removal of external stressors. Neurosis was not a good adaptation, but it was an adaptation according to Gantt. Organisms preserved an equilibrium with their environment through conditioned reflex actions.

Counterproductive reactions were learned behaviors showing poor adaptation to the stress, dysfunctional behaviors. They tended to produce new strains on the nervous system because they retained “visceral reactions, based on earlier maladaptive

³⁹⁸ Gantt, *Origin and Development*, 476.

³⁹⁹ Gantt, *Principles of Nervous Breakdown*, 146.

behaviors.”⁴⁰⁰ These maladaptations to initial stress formed a condition Gantt termed schizokinesis. This was more common in man than animals because of more changes in the modern human environment, and internal factors which often produced a compromise rather than continuous adaptation.⁴⁰¹ As science writer Patricia McBroom explained Gantt’s theory:

A single episode –shock or traumatic emotional experience– may produce permanent heart changes that linger in the central nervous system as a source or a trace of pathology. This source then becomes capable of disturbing the body physically and mentally, long after its original usefulness is past.⁴⁰²

Laboratory study of developing neuroses was essential to identifying observable factors useful for predicting who would “break under a certain psychic load.”⁴⁰³ Useful signs included: muscular activity and metabolism, gastrointestinal symptoms, respiratory, cardiac, urinary, and sexual symptoms, certain social behaviors, and generalization of neurotic behavior to multiple physiologic systems.⁴⁰⁴

Studying physiological reactions to initial stress offered the possibility of

⁴⁰⁰ Gantt, *Principles of Nervous Breakdown*, 159.

⁴⁰¹ Gantt, *Principles of Nervous Breakdown*, 158-59.

⁴⁰² Patricia McBroom, “Building on Pavlov,” *Science News* 91, no. 21 (1967): 498.

⁴⁰³ Gantt, *Principles of Nervous Breakdown*, 148.

⁴⁰⁴ W. Horsley Gantt, *Experimental Basis for Neurotic Behavior: Origin and Development of Artificially Produced Disturbances of Behavior in Dogs*, (New York: Paul B. Hoeber, 1944), xiv.

identifying “the spread of the nervous imbalance...before it is overtly expressed.”⁴⁰⁵

This was essential. Human mental health required identifying and treating the incipient neurotic before the maladaptation had progressed too far, becoming a generalized condition. This was an essential step in maintaining mental health because “[o]nce the disturbance is thoroughly established, therapy is difficult.”⁴⁰⁶

To understand why Valium was so widely prescribed, it is important to note the wide variety of physiological problems associated with neurotic personalities. These conditions were warning signs of mental illness. The strains of, and causing, mental illness needed mitigating before a neurosis became fixed, thoroughly established. Muscular tension, gastrointestinal ills, asthma, heart palpitations, high blood pressure, frequent urination, impotence or nymphomania, and antisocial behavior could be observable warning signs of an underlying neurosis. They needed treatment for the core disorder before the problems spread, became fixed, and caused further health problems. Ignoring early signs risked ongoing bodily dysfunctions and damage, but more importantly allowed the neuroses to become fixed and relatively untreatable. In contrast to other tranquilizers, Roche’s marketing of Valium would highlight treatment of the physiological symptoms Gantt identified.

W. Horsley Gantt’s understanding of neuroses – linking physiological symptoms to mental ones, development in some personalities from distress in one

⁴⁰⁵ Gantt, *Experimental Basis*, vii.

⁴⁰⁶ Gantt, *Origin and Development*, 481.

physiological system to others, and as forms of maladaptation that had taken on a life of their own – are all neatly packaged in the case of Nick, the neurotic dog. Coincident with other research, Gantt and his colleagues discovered two animal cases providing in-depth and continuous evidence of neurotic personalities. Nick, studied for thirteen years, retained Gantt’s fascination, driving him to seek professional help and treatment for the creature. The other dog, studied for six years, had the simple moniker V3.⁴⁰⁷

Personality types of the two were opposite. When introduced to the lab at one year of age, Nick seemed a normal dog whereas V3, who had been in the laboratory since birth, showed a frightened and unfriendly personality from the start. Nick began

⁴⁰⁷ Gantt recognized the study of individual cases, as well as longer term studies of animals larger than mice, was expensive. In 1951 he responded to a letter in *Science* by A Moneyed Man who sarcastically lamented the unfairness that in Europe a scientist, “plain university professors who, in all their lives, saved perhaps \$1000 apiece...” could get streets, banners, or even societies named after them, while the maltreated rich remained less known. “I am fed up. I strike.” wrote the putative scion of wealth, “I quit money-making for purest scientific endeavor.” The Moneyed Man asked readers of *Science*, “Have you any suggestion as to what I should discover first?” A Moneyed Man, “Lament of a Moneyed Man,” *Science* 113, no.2934 (1951): 332-33. Gantt responded with his own letter, offering “the secret whereby your name can go down in fame,” and outlined a plan similar to that practiced in academia today. “Now,” Gantt wrote, “our laboratory is very much in need of a name like yours with big money. We will take part of the money –if there is enough– to buy a marble tablet, a portrait, a bust, an autographed photograph, an album bound in gold of some of the letters you have dictated, plus your name in big letters over the door and on every article, reprint, letterhead, and word of wisdom that issues from this laboratory.” He assured his potential investor, “Wherever the human being, his conditional reflexes, neuroses, psychoses, are being discussed, your name will inevitably be tagged on.” Well versed in salesmanship, Gantt applied the carrot and stick, “I am already making plans to replace the present wooden sign with an appropriate marble slab. Owing to the great demand, there are not enough good laboratories and universities to go around. In order not to be disappointed, please act quickly.” W. Horsley Gantt, “Gantt to the Rescue!” *Science* n.s.114, no.2961 (1951): 332-33.

showing signs of neuroses after a month of experimentation, “running violently in and out of the experimental room, barking, panting, refusing to eat, negativism.”⁴⁰⁸

Admittedly the experimental conditions were suited to producing troublesome behavior since Gantt designed the stimulus or reward and punishment system to conflict with itself.

What Gantt considered evidence that Nick was a neurotic dog was that symptoms seen during the conflict experiments were minor compared with those developed more than one year after the experiments ended. According to the behavioral scientist, the cause was earlier events; “Overwhelming evidence of the relation of these late symptoms to the original conflict were brought out by appropriate experiments[.]” he claimed.⁴⁰⁹ V3, on the other hand, received no conflict experience from experiments. Gantt referred to V3 as an “extremely pathological animal, persistently neurotic[.]”⁴¹⁰ V3 was already neurotic, formed maladaptive associations easily, and retained them strongly.

V3 took part in experiments relating sexual excitement to alcohol consumption, and showed a ridiculously strong reaction, apparently learning to associate use of the camera, alcohol and sexual stimulation. When cut off by the end of the experiment he

⁴⁰⁸ Gantt, *Principles of Nervous Breakdown*, 151.

⁴⁰⁹ Gantt, *Principles of Nervous Breakdown*, 152.

⁴¹⁰ Gantt, *Principles of Nervous Breakdown*, 154.

returned to behaving strangely and in an increasingly “stereotyped”⁴¹¹ manner, “showing many interesting features reminding one of compulsions, echopraxia, panic, and catatonic behavior with catalepsy.”⁴¹² Left alone, V3 behaved normally. Opening his paddock made him run in circles, dash to the back corner with tail tucked, dash past the scientist (“frightened hypermanic flight”⁴¹³), head into the experiment room and wait standing on three legs. He waited, oblivious to noise or strong stimuli (but affected by mild ones). Unless the scientist stayed in the closed experiment room for a minute with V3, the canine refused to return to the paddock. Although a near caricature of neurotic behavior, V3 showed the same diffuse symptoms, in roughly the same physiological systems that Gantt identified in other lab work.

Nick, in contrast had a good personality to begin with, and Gantt had no intuitive explanation why an apparently normal dog developed neurotic behavior well after the initial experiments. Pavlov had suggested the possibility of conflict-creation through stimulation of contradictory responses, and believed there were different temperaments to begin with, but Nick’s temperament showed no initial signs suggesting a neurotic personality. Existing knowledge did not adequately explain the results.

As Gantt’s explanation of human neurotic development continued, he gained insight into Nick’s condition. Based on experimental neurosis work, Gantt concluded

⁴¹¹ Gantt, *Principles of Nervous Breakdown*, 155.

⁴¹² Gantt, *Principles of Nervous Breakdown*, 155.

⁴¹³ Gantt, *Principles of Nervous Breakdown*, 155.

humans subject to nervous breakdown were responding to internal, rather than external, events. These neurotic individuals did not harmoniously intertwine their internal and external reactions; “It involves a basic discrepancy between the more external expressive movements (which, being in our consciousness, appear to us usually as voluntary and purposeful) and the generally hidden visceral responses, which are ordinarily out of consciousness[,]” Gantt explained.⁴¹⁴ In humans, symbolic behavior helped hide the tensions; the basic bodily reactions, such as a startle reaction, appeared well before observable effects in main physiological systems. In Gantt’s words:

The very function of symbolization responsible for our marvelous ability to adapt is also the function at the basis of disturbed behavior. Due to the characteristics of excess reaction to symbols, and the property of split function, there is a greater retention of the visceral components than of the more external motor and secretory ones. That the organism may be superficially at rest but violently disturbed internally has a physiological basis as well as a Freudian one.⁴¹⁵

Gantt focused on the possibility of ties between Nick’s neuroses and the initial experiments. Therefore understanding the link could lead to treatment. Perhaps the symbolic associations continued, appearing in externally noticeable behaviors a year after the experiments concluded. Indicative of the links between behaviorist and psychoanalytical approaches, the behaviorist Gantt turned to a group of psychoanalysts for their interpretations of links between the experiments and Nick’s neuroses.

The psychoanalysts’ answers were similar, gliding easily between behavioral

⁴¹⁴ Gantt, *Principles of Nervous Breakdown*, 157.

⁴¹⁵ Gantt, *Principles of Nervous Breakdown*, 160.

and psychoanalytic terminology. Their letters were characteristic of the Freudian tradition, discussing the role of internal conflicts between drives as an individual seeks to fulfill his needs in ways acceptable to society. They were also characteristic of midcentury psychiatry in focus on the individual as a social animal.⁴¹⁶ Talk therapy might not work with a dog, but the four psychoanalysts appeared comfortable interpreting the problem leading to Nick's neuroticism.

One correspondent, Dr. French, pointed out direct links between behaviorism and psychoanalysis, tying a positive conditioned response to "an affective association" and suggesting inhibition of learned behavior was "parallel to Freudian repression." Both internal and external factors played a role; the experiment created fear and the dog faced "failure of gratification" when he could not resolve his conflicting responses.⁴¹⁷

Dr. Leon Saul was also able to put the behavior into psychoanalytic terms. Nick faced a conflict between desire to flee the experiment area, an instinctive drive, and a social desire to please his master. The dog faced a troubling conflict. Dr. Saul pointed out how Nick's situation was remarkably similar to a problem commonly seen in clinical psychiatry:

in the second generation son, conditioned by his father to ideals of success, independence, self-made man, etc., but by his mother to being soft, dependent, indulged, spoiled by her. It has always seemed to me that this type of conflict is quite analogous to that seen in animals conditioned to salivate to one stimulus and not to salivate to a closely similar one. However, the level at which this conflict takes place is not

⁴¹⁶ Gantt, *Experimental Basis*, 181.

⁴¹⁷ Gantt, *Experimental Basis*, All quotes on page 182.

clear. It is probably at a rather low level, far from consciousness although higher levels could be secondarily involved.⁴¹⁸

In Nick's case, Saul diagnosed, the initial conflict became internal. The experimental situation was "very disturbing"⁴¹⁹ when Nick desired the security of a stable world. Nick wanted to find a solution, to adapt, to please, but he was in an untenable situation and conflict between drives appeared unresolvable. The dog's strong attachment to Dr. Gantt was "of the normal canine variety."⁴²⁰ Faced with another stress-inducing experiment his instinct was to flee, but when Dr. Gantt, his master who he loved, depended on, and obeyed, took him into the laboratory the instinct to flee conflicted with his feelings towards Dr. Gantt. "Because the dog must remain well behaved his excitation cannot be adequately discharged in direct and primitive action. It is pent up and seeks discharge in other directions. This is apparent in the diffused excitement of the animal[.]"⁴²¹ Nick developed an unpleasant association with the man he loved, resenting both the laboratory and Dr. Gantt, "his master who is the experimenter who treats him this way."⁴²²

Before consulting the psychoanalysts, Gantt and his colleagues tried various treatments based on their understanding of the problem. In behavioral terms, the dog

⁴¹⁸ Quote from Dr. Leon Saul in Gantt, *Experimental Basis*, 182.

⁴¹⁹ Saul quoted in Gantt, *Experimental Basis*, 182.

⁴²⁰ Saul quoted in Gantt, *Experimental Basis*, 183.

⁴²¹ Saul quoted in Gantt, *Experimental Basis*, 183.

⁴²² Saul quoted in Gantt, *Experimental Basis*, 182.

faced “two antagonistic nervous waves[,]”⁴²³ conditioned responses in conflict within the brain. They probably were in the secondary signaling system because of the semi-symbolic nature of the conflict, then radiating from the initial conflict to other areas, resulting in a “conditioned-reflex connection by indirect signalization[.]”⁴²⁴ In 1934, Gantt tried cortin on the dog. It was a drug known to diminish motor hyperactivity in sheep. Ineffective. In 1935, he tried moving the experiment area to a different part of the room, but Nick remained frightened and hyperaware of the original location.⁴²⁵ Periods of rest in another environment produced more pronounced symptoms. In the summers of 1938 and 1939, on the advice of Doctor Alan Gregg, they gave Nick alcohol, a drug known to relieve tensions temporarily.⁴²⁶ Although the alcohol did relieve some symptoms, it “removed the inhibitory effect of the camera on sexual reflexes” which he had learned earlier, when Nick got off the booze his sexual problems were even worse.⁴²⁷

Made aware of the social conflict (“reciprocal relations were definitely found to be operative[.]”⁴²⁸) Gantt tried to reduce Nick’s anxiety by having people spend time

⁴²³ Gantt, *Experimental Basis*, 181.

⁴²⁴ Gantt, *Experimental Basis*, 181.

⁴²⁵ Gantt, *Experimental Basis*, 156.

⁴²⁶ Gantt, *Experimental Basis*, 159.

⁴²⁷ Gantt, *Experimental Basis*, 160-61.

⁴²⁸ Gantt, *Experimental Basis*, 182.

with him. As a science writer for *The Science News-Letter* explained Gantt's new approach, "Social factors, such as the presence of a human in the room or of a friendly dog, reassures the nervous animal so that he does not have an attack."⁴²⁹ Nick did not respond well to this therapeutic approach, in fact he "developed a negativistic attitude with marked respiratory and cardiac changes toward these persons."⁴³⁰ By 1939, the experimenters had only found one method of temporarily alleviating his symptoms, "putting the dog in the same paddock with a female in estrus[.]"

After consulting psychoanalysts, Gantt changed his approach. He moved Nick to his farm for a year and a half, giving the dog "an opportunity to develop new relationships toward me."⁴³¹ Nick strengthened his friendship with the experimenter and at first appeared healthy when returned to the lab. But the neurotic behavior quickly recurred. Gantt took him back to the farm and within two days his heart rate had fallen from 200 to 110 beats per minute.⁴³² In the summer of 1940 Nick returned to the farm and more intensive therapy (quality time) with Dr. Gantt. Gradually the symptoms lessened, and although reminders of the experiment continued to act as stressors, strengthening and reassuring him of his social role effected a cure. "[H]e

⁴²⁹ Anon, *Unbalanced Nerves*, 243.

⁴³⁰ Gantt, *Experimental Basis*, 182.

⁴³¹ Gantt, *Experimental Basis*, 163.

⁴³² Gantt, *Experimental Basis*, 164.

became a most devoted companion, following me everywhere,”⁴³³ Dr. Gantt reported. The experience with Nick solidified his conviction that once full-blown neuroses developed it took extensive measures, social and environmental, to alleviate the symptoms. Cure remained a problem, therefore identification and prevention of developing neuroses was crucial.

Links Between Neural and Psyche Theories

Developments within the psyche framework in the late 1940s and 1950s paralleled those in the neural. They promoted the idea that humanity desired stability as well as an outlet for creative and destructive energies. Adaptation of the individual was key; rapid and realistic adaptation to environmental change reduced stresses and restored stability. As Peter Madison of Swarthmore College explained, “Repression and defense are the heart of the contemporary conception of mental illness. Together with their sister concept of anxiety, they have become the core of modern psychiatric theories, even when these disclaim a Freudian orientation in a narrower sense.”⁴³⁴

Science writer Patricia McBroom pointed out the links between behavioral research and Freudian-type analysis, in an article outlining Horsley Gantt’s work. His work, she wrote, “has taken Pavlovian concepts far beyond their original mechanistic rigidity.”

⁴³³ Gantt, *Experimental Basis*, 165.

⁴³⁴ Peter Madison, “Freud’s Repression Concept: A Survey and Attempted Clarification,” *The International Journal of Psycho-Analysis* 37 (1956): 75.

The course of his research brought him “closer to Freud than to Pavlov.”⁴³⁵ The idea that a single traumatic episode earlier in life could create neurosis, part of the popular interpretation of Freud, appeared similar to Gantt’s focus on the “latent excitation” which was “capable of acting independently of additional external influences.”⁴³⁶

Walter Cannon’s influential idea of homeostasis illustrates the common assumption that physiological concepts included psychological aspects. Cannon studied medicine at Harvard then proceeded to a distinguished career including thirty-six years as the George Higginson Professor of Physiology at Harvard, and President of the American Academy for the Advancement of Science. During undergraduate studies on digestion he noted the dramatic influence of emotion. He began investigating interactions between emotion and bodily systems, which led him to the concept of homeostasis. The sympathetic nervous system and adrenal medulla played an important role in regulating widespread bodily systems in order to restore balance, he noted.⁴³⁷ Homeostasis referred to the body’s tendency to adjust to internal and external stresses in order to preserve stability of physical functions. Cannon himself associated emotional reaction to external events with change in the body; they triggered the nervous system’s efforts to adjust. “[E]motional upsets,” he remarked, “in the nervous

⁴³⁵ McBroom, *Building on Pavlov*, 498.

⁴³⁶ McBroom, *Building on Pavlov*, 498.

⁴³⁷ Walter B. Cannon, “The Body Physiologic and the Body Politic,” abridged version of Presidential Address to AAAS (originally published in *Science* 93, no. 1 (1941)), *The Scientific Monthly* 79, no.1 (1954): 20-26.

pathways, have concrete and obvious effects[.]”⁴³⁸ Scientists needed to recognize this interaction and find ways to identify the early physiologic signs of stress, if they wanted to prevent overwhelming of homeostatic action and development of dysfunctions, in turn creating chronic disorders. “It is stupid[.]” Cannon declared, “to belittle or neglect such complaints. The powerful influence which emotional states can exert on bodily functions needs no argument.”⁴³⁹

Nigel Walker explicitly attempted to apply Cannon’s idea of homeostasis to Freud’s theories, seeking the sources of important contemporary physical/mental concepts as well as errors, compared to knowledge in the 1950s. Shoe-horning homeostasis into psychoanalytic theory, he argued Freud’s statement that “the nervous system is an apparatus having the function of abolishing stimuli”⁴⁴⁰ anticipated cybernetic focus on feedback mechanisms and physico-psychological concepts of homeostasis. The defense mechanisms used by the ego to mediate demands of the id with reality and requirements of society, Freud understood as attempts by the central nervous system (CNS) to reduce internal stimuli, according to Walker. Freud’s error was his focus only on the ego’s attempts to lessen stimuli. This led the originator of psychoanalysis to identify a death instinct – what Freud termed Thanatos – as the effort

⁴³⁸ Walter B. Cannon, “Problems Confronting Medical Investigators,” *Science* 94, no. 2434 (1941): 174.

⁴³⁹ Cannon, *Problems Confronting Medical Investigators*, 174.

⁴⁴⁰ Sigmund Freud, “Instincts and Vicissitudes,” *Collected Papers*, 1915, vol. IV.

to reduce stimuli to nothingness. Walker held homeostasis as true and tried to either find signs of it in Freud, or find Freud in error. He found parallels between development of neuroses into psychoses, through swamping the ego's defenses by overwhelming demands of the id, and homeostatic mechanisms restoring norms until they "reach a point at which the mechanism of homeostasis ceases to operate in such a way as to restore the end-state." This was the "point of breakdown[.]"⁴⁴¹ Human beings craved stability, dealing with stress and restoring psychologic and physiologic balance, as well as a stimulating environment, allowing id and ego to act in moderate and healthy ways. Problems arose with overstimulation.

The idea of equilibrium as an underlying state needs to be understood in the context of Allport's concept of functional autonomy, and the more general field of dynamic psychology. Gordon W. Allport was an early proponent of dynamic psychology, which he saw as a more useful replacement for Freudian psychoanalysis. What made this approach dynamic was recognizing the historical context and its influences on a man's life, but focusing on the current situation, focusing on change.

The problem with psychoanalysis, according to Allport, was its ridiculous belief that "a very few basic motives suffice for explaining the endless varieties of human interests."⁴⁴² Eros and Thanatos, the constructive and destructive drives, had to apply in

⁴⁴¹ Nigel Walker, "Freud and Homeostasis," *The British Journal for the Philosophy of Science*, 7, no. 25 (1956): 63.

⁴⁴² Gordon W. Allport, 1937, "The Functional Autonomy of Motives," *American Journal of Psychology* 50: 142.

such a myriad of forms to explain actual cases as to make them useless. Even with addition of one or two more drives, the psychoanalytic approach could only describe events, not explain why they occurred. It was an “over-simplified theory[,]” Allport concluded.⁴⁴³

A dynamic approach included historical dimensions, but placed more emphasis on the contemporary situation. The man grew from the child, there was no doubt about it. But this was no simple unfolding in which you could trace the roots of current problems back to infancy. Allport promoted the concept of ‘functional autonomy’ of the individual. As a sense of self-developed, will supplanted the mechanistic drives, and the individual became autonomous, separate from the initial drives. Mental health professionals needed to understand the mature adult in terms of motives, “infinitely varied, and self-sustaining[.]”⁴⁴⁴ Functionally, man was separate from any core drives that might, or might not, still exist. The dynamic aspect of functional autonomy placed the frame of reference in the present, and therefore actions existed with reference to a steady state rather than a historical process.

Dynamic psychiatry still accepted that the individual tried to negotiate with the environment to fulfill needs, it simply did not accept ties between those needs and historic, basic, drives. As Allport explained:

The pursuit of literature, the development of good taste in clothes, the use of cosmetics, the acquiring of an automobile, strolls in the public

⁴⁴³ Allport, Functional Autonomy of Motives, 143.

⁴⁴⁴ Allport, Functional Autonomy of Motives, 143.

park, or a winter in Miami -- all may first serve, let us say, the interests of sex. But every one of these instrumental activities may become an interest in itself, held for a life time, long after the erotic motive has been laid away in lavender. People often find that they have lost allegiance to their original aims because of their deliberate preference for the many ways of achieving them.⁴⁴⁵

The drives were diverse, and their manifestations took on a life of their own. Current behavior was not understandable as a simple manifestation of drives.

The individual discussed in midcentury psyche theories was not the mechanistic individual of Freud, he was an individual who lived in society and was a social animal. Social psychology gained prestige during the 1950s. Kurt Lewin, who came to the United States from Berlin shortly after Hitler formalized his autocracy, played an important role in development of social psychology. He introduced the concept of 'life space,' the totality of dynamic forces within and surrounding an individual. Internal forces, drives in the earlier Freudian parlance, were now motivations and purposes as well as needs. These internal forces interacted, through the self, with the external environment. The individual acted through society and tried to maintain a sort of equilibrium between internal and external requirements. He construed environment broadly, with greater focus on society and its expectations, roles, and norms.

At a time when psychology implicitly defined individualism through the individual's relationship with society,⁴⁴⁶ it is unsurprising that another major therapy

⁴⁴⁵ Allport, *Functional Autonomy of Motives*, 146.

⁴⁴⁶ The individual was a fundamentally social animal who tried "to satisfy individual desires and tendencies by means of group values and to institute group recognition and acceptance...". H. E. Eisler, "The Development of the Individual," *The*

gaining ground in the 40s and 50s was ‘client-centered’ therapy, associated with the work of Carl Rogers.⁴⁴⁷ In a nutshell, the approach was to focused on feeling than content in a clinical setting, and assumed patients had a natural motivation to develop insight. “If the therapist accepts, recognizes, and clarifies the feelings expressed by the client,” Rogers’ theory suggested, “there will be movement from negative feelings to positive ones, followed by insight and positive actions which are initiated by the client.”⁴⁴⁸ The approach focused on the role of social interaction, acceptance of the client by the therapist, and focusing on promoting interaction. Carl Rogers was particularly in favor of counseling to help an individual promote realistic and mature recognition of problems.⁴⁴⁹

Psychoanalytic Review 42 (1955): 388.

⁴⁴⁷ Important and influential works by Rogers include *Counseling and Psychotherapy*, 1942; *Client-Centered Therapy*, 1951; and *On Becoming a Person*, 1961.

⁴⁴⁸ Fred M. Zimring and Nathaniel J. Raskin, “Carl Rogers and Client/Person-Centered Therapy,” 629-56 in *History of Psychotherapy: A Century of Change*, ed. Donald K. Freedheim (Washington, D.C.: American Psychological Association, 1992), 630.

⁴⁴⁹ For examples of Rogers’ approach see: Carl R. Rogers, “War Challenges Family Relationships,” *Marriage and Family Living* 5, no.4 (1943): 86-87; Carl R. Rogers, “Wartime Issues in Family Counseling,” *Marriage and Family Living* 6, no.4 (1944): 68-69, 84; Carl R. Rogers, “Counseling,” *Review of Educational Research* 15, no.2 (1945): 155-63; Carl R. Rogers, “Counseling with the Returned Serviceman and His Wife,” *Marriage and Family Living* 7, no.4 (1945): 82-84; Carl R. Rogers, “A Personal Formulation of Client-Centered Therapy,” *Marriage and Family Living* 14, no.4 (1952): 341-61; Carl R. Rogers, “A Counseling Approach to Human Problems,” *The American Journal of Nursing* 56, no.8 (1956): 994-97; Carl R. Rogers and B. F. Skinner, “Some Issues Concerning the Control of Human Behavior,” *Science* n.s.124, no.3231 (1956): 1957-66.

Conclusion

In the 1940s and 1950s, when events shaping development of Valium solidified – psychology and the theory of mental health, whether behaviorist, psychodynamic, client-centered or otherwise defined – had several commonalities. Individuals were social creatures with motivations and desires. Individuals were the core units of society, but they were not apart from it. Stability or equilibrium was the basic state of man. And adaptation, whether to new stimuli and stressful conditions, or negotiating the needs of ‘self’ within the environment, was a key aspect of mental health.

Merging and interaction of behavioral and mental theories provided background assumptions guiding development of tranquilizers. Both theories similarly explained how psychoactive drugs worked, the nature of neuroses, and the developing feedback relationship of body and mind tying initial stress into more incurable maladaptions, detrimentally affecting a wider variety of bodily systems. Stress, therefore, led to a wide variety of physical problems. Some individuals adapted poorly to stress, psychologically and physiologically; in Masserman’s terms, “alleviation of anxiety is an integral part of all psychiatric therapy.”⁴⁵⁰ Neurotic reactions, as well as response to overwhelming stressors in more ‘normal’ personalities, were identifiable through physiologic measurements. Objective measurements of dysfunctional behavior in animals included maladaptive fight or flight responses, including continued rapid heart

⁴⁵⁰ Anon, “No Simple Prescription For Treating Anxiety,” *The Science News-Letter* 87, no.15 (1965): 226.

rate, high blood pressure or muscle tension, as well as poor adaptation to changing conditions, seen in learning, righting reflexes, aggression, or climbing behaviors.

Just as the pre-1940 behavioral and psyche-based theories had underlying similarities, post-1940 modifications in both realms were similar. Both theoretical perspectives began to focus more on drives, which were now more broadly construed, adaptation (reactive attuning) to the physical and social surroundings, and a broad variety of behaviors which were manifestations of developing or full-blown neuroses.

Mental health professionals understood action of drugs on the central nervous system in similar ways, whether they advocated behavioral or psyche-based treatments. Either drugs modified development, generalization, and extinction of conditioned responses, or they released inhibitions and previously repressed material. In both cases the physical mechanism of the action was unknown. But, researchers including Pavlov, Masserman, and Gantt, had elaborated measurable physiologic correlates of maladaptive responses to stress, of incipient or full-blown neuroses. This understanding could be applied to identification and testing of new chemical compounds, such as Valium.

**CHAPTER 5. FINDING TRANQUILITY, DEVELOPING REASON:
COMPETITOR COMPOUNDS
AND STERNBACH'S SYNTHESIS OF DIAZEPAM**

Valium was a drug well suited to its time. Although a trite statement, following necessarily from the fact of a drug being successful in the marketplace, the conditions surrounding Valium's identification, development, and marketing were particular to its time. These conditions shaped what Valium was.⁴⁵¹ Pharmacologists would have vetted the same chemical compound identified twenty years earlier with different tests. Roche might have ignored it as not useful, or marketed it for a different purpose, perhaps as a sedative or muscle relaxant. But ataractics, pharmaceuticals giving a feeling of active tranquillity, fit the spirit of the age. Physician H. Angus Bowes declared, "The 'emotional aspirin' is likely to become just as much a part of our way of life as the epileptic's anticonvulsant, the alcoholic's amphetamine, the executive's antacid, the salesman's hip flask, and the socialite's sedative."⁴⁵²

⁴⁵¹ In the terminology of organic chemistry Valium is 7-chloro-1,3-dihydro-1-methyl-5-phenyl 2H-1,4-benzodiazepin-2-one.

⁴⁵² H. Angus Bowes, "The Ataractic Drugs: The Present Position of Chlorpromazine, Frequenel, Pacatal, and Reserpine in the Psychiatric Hospital," in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 10-22, 18.

Naming Pharmaceuticals

Richard Ruge, a Harvard-trained lawyer writing on “Regulation of Prescription Drug Advertising,” explained the tripartite naming system used for naming drugs in a manner that parallels development of Valium. “A discrete drug substance may be known by three types of names[,]” he explains. “Its chemical name simply lists every part of a drug’s molecular structure.” Leo Sternbach synthesized, or discovered, the chemical compound. Ruge continues, “Its generic name abbreviates the components but still informs a doctor of the drug’s chemical composition, from which he can determine its general effect on the body. Ordinarily a drug will have only one generic or nonproprietary name.” Lowell Randall and his team of pharmacologists identified the general effects of this compound. Clinical trials illustrated its potential uses in humans. This effectively turned it into the benzodiazepine diazepam, a tranquilizer. “Finally,” Ruge explained, “a drug is sold under a trade or brand name which identifies the drug with a particular manufacturer but conveys little information about its nature or composition.” This process of market positioning and marketing created Valium, a tranquilizer associated with images, uses, and experiences different from other tranquilizers. Roche marketed Valium for specific conditions, and identified it with particular benefits and problems.⁴⁵³ This chapter focuses on Valium’s development up to Sternbach’s synthesis, his discovery of a chemical compound, in an effort to explain

⁴⁵³ Richard B. Ruge, “Regulation of Prescription Drug Advertising: Medical Progress and Private Enterprise,” *Law and Contemporary Problems* 32, no. 4 (1967): 650-73, 654.

why anyone would care to look or be prepared to find the molecule later called Valium.

The intellectual background surrounding identification and development of Valium shaped it, helped define its meaning, and suggested it was worth testing. Because in hindsight we view it mainly as a psychotropic drug, and because contemporary understandings of psychosomatic disorders informed their treatment with psychopharmaceuticals, it is necessary to examine the identification, testing, and shaping of Valium as a drug acting on mind and body via the central nervous system (CNS), a drug acting in the locus, the trope, of the mind/brain/psyche as well as the autonomic and sympathetic nervous systems.

Existing medicinally used psychotropic and psychosomatic drugs provided a comparative framework for Valium's development, testing, and marketing. Valium's synthesis occurred within a specific context which included availability of other tranquilizers, each with perceived uses, modes of action, and problems. The conditions of Valium's birth helps explain why and for what purposes it was marketed. Public concern about mental health encompassed a broader group of people and conditions than ever before. Medical knowledge informed appropriate use of tranquilizers. Anxiety, tension, and adrenal feedback were privileged causes of widespread illness, physical and mental. Existing sedatives and tranquilizers suggested promising areas of research, especially where existing compounds either failed to work, or had undesirable effects. Valium's identification occurred within the confines of expectation and knowledge of the times. That Valium was a drug well suited to its time is trite, but true.

Previous tranquilizers, sedatives, and hypnotics

Humanity in most times and places has proven ingenious at ferreting out psychotropic substances. Acquiring drugs from physician or pharmacist, as well as self-medication, for mental effects was not new in the 1950s. Opiates played an important role in treating insomnia or anxiety, and coping with the stresses of life in the nineteenth century.⁴⁵⁴ By mid-twentieth century America, the drugs of choice for dealing with stresses of life, neuroses, and functional rather than organic disorders, included bromides, barbiturates, and alcohol.⁴⁵⁵ Bromides, first used in treatment of epilepsy, were used as hypnotics in the mid-1860s.⁴⁵⁶ By the 1950s they were in declining use,⁴⁵⁷ and appear to bear little relationship to development and marketing of

⁴⁵⁴ For further information on opium use in the 19th century see Diana L. Ahmad, *The Opium Debate and Chinese Exclusion Laws in the Nineteenth-Century American West* (Reno, Nevada: University of Nevada Press, 2007), or David T. Courtwright, *Dark Paradise: Opiate Addiction in America Before 1940* (Cambridge, MA: Harvard University Press, 1982).

⁴⁵⁵ At the time, functional disorders were those assumed probably unrelated to permanent physical changes or dysfunctions in the brain; they did not have an organic basis. A functional disorder related to the functions of the mind, the psyche, or the behavior of an individual in society; before 1950 the only medically accepted drugs for reducing mental excitation “were the aliphatic depressants, such as barbiturates, chloral hydrate, and paraldehyde, and the bromides.” Joseph F. Fazekas, James G. Shea, and Paul D. Sullivan, “Ataratics in Medical Practice,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 42-49, 42.

⁴⁵⁶ Sollmann, Torald. *A Manual of Pharmacology and its Application to Therapeutics and Toxicology*, (Philadelphia: W. B. Saunders Company, 1942), 774.

⁴⁵⁷ Irvin M. Cohen, “Drugs Recently Introduced in the Treatment of Psychiatric Disorders,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology*

Valium. Barbiturates, however, were both widely used in the 1950s and prescribed in a manner overlapping that of Valium in the 1960s.⁴⁵⁸ Phenobarbital was one of the “most commonly used medications” for anxiety neuroses, and barbiturates in general had “been employed for many years to control the emotional surmenages found in neurotic and so-called ‘nervous’ patients.”⁴⁵⁹ Although the rates of use for these sedatives are surprisingly high, they pale by comparison to the main drug serving to insulate Americans from tension and stress – alcohol.⁴⁶⁰

Barbiturates

By 1950, barbiturates, especially phenobarbital, held a long established place

and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 60-66, 65.

⁴⁵⁸ Valium is usually associated with anxiety, tension and stress related conditions. Barbiturates were used as sedatives, hypnotics, anesthetics, anti-convulsants, and potentially as analgesics. Daniel M. Perrine, *The Chemistry of Mind-Altering Drugs: History, Pharmacology, and Cultural Context* (Washington, D.C.: American Chemical Society, 1996), 149. Valium was tested for similar properties.

⁴⁵⁹ Wallace Marshall, “Ambulatory and Comparative Treatment of the Anxiety Neurosis Syndrome with Chlorpromazine, Phenobarbital and Dimethylane,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 382-87, 383.

⁴⁶⁰ Inclusion of a drug among the grouping ‘sedatives’ depended on how it was subjectively experienced; they reduced anxiety and tension, thereby inducing a feeling of calm, of relaxation. Carl F. Essig, “Addiction to Barbiturate and Nonbarbiturate Sedative Drugs,” in *The Addictive States, Proceedings of the Association for Research in Nervous and Mental Diseases* (New York, December 2-3, 1966) ed. Abraham Winkler (Baltimore, OH: Williams & Wilkins, 1968), 188-98, 188; hypnotics were sleep-aids.

among pharmaceuticals in the United States. Their wide use as sedatives and hypnotics – treatments for tension, anxiety, and insomnia – made them competition for any tranquilizers Roche planned to market. The barbiturate class of drugs, all derived from barbituric acid, were of longstanding use by midcentury. Barbituric acid's initial synthesis was by von Baeyer in 1883⁴⁶¹ or Concord and Gut-zeit in 1882,⁴⁶² depending on the source of information. Scientists developed specific medicinal compounds based on barbituric acid early in the twentieth century; barbital in 1904, phenobarbital in 1912.⁴⁶³ Used mainly for disorders associated with 'nerves,' situations related to the central nervous system (CNS) – inability to sleep, anxiety, tension – their use boomed after World War I. By 1948, annual production of barbiturates within the United States was around 336 tons, "...or about 24 therapeutic doses per each man, woman, and child in the country!"⁴⁶⁴ Consumption continued to grow.

⁴⁶¹ Joel Fort, "The Problem of Barbiturates in the United States of America," *United Nations Office of Drug Control Bulletin* 1, no. 1 (1964): I; Joel Fort was a lecturer in criminology and Director of the Center for Treatment and Education on Alcoholism at the University of California at Oakland; Perrine, *Chemistry of Mind-Altering Drugs*, 148.

⁴⁶² I. Phillips Frohman, "The Barbiturates," *The American Journal of Nursing* 54, no. 4 (1954): 432.

⁴⁶³ Perrine, *Chemistry of Mind-Altering Drugs*, 148; Sollmann, *Manual of Pharmacology*, 774.

⁴⁶⁴ Frohman, *The Barbiturates*, 433; This type of estimate is in a common format, total amount of barbiturates produced in the United States, divided by the number of citizens. It probably over estimates the number of people taking large doses, and underestimates the number taking barbiturates in some form. In the 1950s a wide variety of compounds contained small amounts of barbiturates. The New York Academy of Medicine, "Report on Barbiturates: The New York Academy of

Despite booming interest in newer tranquilizers among mental health and pharmacology professionals after 1953,⁴⁶⁵ barbiturates remained the most widely used psychopharmaceuticals from the 1940s through to 1970. In 1963, approximately one decade after the first major tranquilizer, chlorpromazine (Thorazine), began its meteoric institutional career, phenobarbital remained both the most widely sold generic drug and the most commonly used of the barbiturate class.⁴⁶⁶ Of the approximately 374 million new prescriptions issued in that year, barbiturates accounted for 14.59 million new prescriptions, each of which could be enough for a month or more. Refills accounted for another 30.18 million scrips.⁴⁶⁷

Legislation passed in the early 1950s, specifically the Durham-Humphrey Act,⁴⁶⁸ restricted writing prescriptions for barbiturates to licensed medical practitioners,

Medicine,” *Public Health Reports* 71, no. 11 (1956): 1147.

⁴⁶⁵ Sherman Ross and Jonathan O. Cole, “Psychopharmacology,” *Annual Review of Psychology* 11 (1960): 416.

⁴⁶⁶ Statistics compiled from *National Prescription Audit: General Information Report- College Edition*, R. A. Gosselin & Co.: Dedham, Massachusetts. Reports for 1962, 1963, 1967, 1969; Phenobarbital was a long acting barbiturate and therefore more susceptible than other forms to intoxication due to accumulation of the drug over repeated dosing. In contrast, Amytal/amobarbital was relatively short acting, and Seconal even shorter. S. J. Holmes, “Barbiturates Create Many Problems,” *Alcoholism Research* 1 (1954): 7.

⁴⁶⁷ Gosselin and Company, *National Prescription Audit-1964*, passim; Comments on likely duration of prescriptions during this time are based on conversations with pharmacists at Theilen Student Health Center Pharmacy, Iowa State University.

⁴⁶⁸ The New York Academy of Medicine, Report on Barbiturates, 155-56. Peter Temin, “Origin of Compulsory Drug Prescriptions,” *Journal of Law and Economics* 22,

and required written or oral permission for renewal of prescriptions.⁴⁶⁹ Rates of benzodiazepine use continued to climb. Periodically, there were swells of public concern that long-term repeated use of original prescriptions, and sale without prescription, contributed to addiction.⁴⁷⁰ But barbiturates were most commonly obtained by physicians' prescriptions, and this continued.⁴⁷¹ By 1960, a conservative estimate suggested 852 tonnes of barbiturates, in a variety of forms, were sold in the United States each year, sufficient to give every man, woman, and child 33 one-grain (66.7 milligrams) doses.⁴⁷² G. P. Grabfield, in 1931, placed the dose of barbital required to guarantee a full night sleep in any hospital patient at 160 milligrams, amytal at 94 milligrams, pentobarbital at 46 milligrams, and phenobarbital at 72 milligrams. A one-grain dose, 66.7 milligrams, is therefore close to that required to knock out a

no.1 (1979): 91-105.

⁴⁶⁹ Frohman, *The Barbiturates*, 434; The Durham-Humphrey Act of 1951, section 503 required habit-forming drugs—narcotics and hypnotics—be prescribed by a physician and refills authorized by that physician either in writing or verbal authorization to a pharmacist. New York Academy of Medicine, *Report on Barbiturates*, 1155-56.

⁴⁷⁰ H. Isbell, "Addiction to Barbiturates and Barbiturate Abstinence Syndrome," *Annals of Internal Medicine* 33 (1950): 108-09.

⁴⁷¹ Isbell, *Addiction to Barbiturates*, 109; G. P. Grabfield, "Hypnotics" *JAMA*, 96, no.1865 (1931).

⁴⁷² Fort, *Problem of Barbiturates*, III; Grabfield, *Hypnotics*; Sollmann, *Manual of Pharmacology*, 776-77; one gram contained 15.4324 grains. Charles Caspari, jr. *A Treatise on Pharmacy for Students and Pharmacists*, 6th ed., revised by E. F. Kelly. (Lea & Febiger: Philadelphia, 1920), 35; The quantity reported by Fort is within the boundaries of the *National Prescription Audit*.

hospitalized adult with phenobarbital. Sedation, rather than sleep, required a fraction of this dose. Assuming most children consumed less than average, and poorer members of society could not afford this tax deductible martini, the quantity in circulation appears sufficient to ensure a good night's sleep, or at least perpetual mellowness, among a substantial portion of America's citizenry.⁴⁷³ Barbiturates were so widely prescribed for ailments major and minor, that J. Phillips Frohman, Chairman of the General Practice Section of Washington D.C.'s Medical Society, quipped, "If Macbeth were representative of modern man, his serious mental illness and symptomatic insomnia would warrant a prescription for phenobarbital, at least – if not one for Seconal, or even Amytal."⁴⁷⁴

⁴⁷³ Fort, Problem of Barbiturates, III; In addition more than 1 billion doses of a "barbiturate-like" pharmaceutical, Doriden was not included in the above estimate. Fort, Problem of Barbiturates, III; Essig cites a similar estimate of 24 doses of 1.5 grains (100mg) for each man, woman and child in 1962. Essig, Addiction to Barbiturate, 191.

⁴⁷⁴ Frohman, The Barbiturates, 432; Increased use of barbiturates over the 1950s and early 1960s was not unique to the U.S. Between 1951 and 1962 the quantity of barbituric acid and barbiturates imported into Canada more than doubled. Barbiturate manufacture did not exist in Canada at the time, and therefore the increase does not reflect a decline in domestic manufacture; there was an increase in the use of barbiturates in Canada. England faced similar increases; prescriptions in 1951 accounted for 90,000 pounds of barbiturates, in 1959 162,000 pounds. The quantity also reflects how widely this class of drugs was used compared to other pharmaceuticals; in 1959 barbiturates accounted for seven percent of all prescriptions written in England. S. J. Holmes, "Barbiturates –Friend or Foe?" *Addictions* 9 (1963): 25.

Long acting	phenobarbital barbital
Midrange	amobarbital/Amytal butabarbital/Butisol
Short acting	hexobarbital/Evipal pentobarbital/Nembutal secobarbital/Seconal

Figure 3. Types of Barbiturates and Duration of Action⁴⁷⁵

Medical and nonmedical writers alike widely considered barbiturates mentally but not physically addictive, even after English language reports published in the 1940s identified a consistent pattern of physical withdrawal symptoms. Because physicians often assumed physical addictiveness of drugs was specific to opium and its derivatives, and characterized by a single pattern of withdrawal symptoms, only with identification of a regular withdrawal profile did the medical community begin associating barbiturates with physical as well as mental addiction. In “recent years this mistaken concept [that barbiturates are not physically addictive] has been shaken by the appearance of reports of convulsive seizures following withdrawal of barbiturates[.]” wrote Harry Isbell, one time Director of the National Institute of Mental Health’s Addiction Research Center.⁴⁷⁶ In an act emblematic of the complexities of how the

⁴⁷⁵ Holmes, *Barbiturates –Friend or Foe*, 25-6.

⁴⁷⁶ Isbell, *Addiction to Barbiturates*, 109; The groundbreaking reports were: H. S. Dunning, “Convulsions Following Withdrawal of Sedative Medication,” *International Clinics* 3 (1940): 254; Kalinowsky, Lothar. B., Convulsions in Non-Epileptic Patients on Withdrawal of Barbiturates, Alcohol and Other Drugs, *Archives of Neurology and Psychiatry*, 47 (1942): 946; Brownstein, S. R., and Pacella, B. L., “Convulsions Following Abrupt Withdrawal of Barbiturate: Clinical and Electroencephalographic Studies,” *Psychiatric Quarterly*, 2 (1943): 112; Osgood, C. W.,

educated medical community at large understood addiction even after publication of these reports, Isbell continued to consider barbiturate addiction substantially mental; he believed similar types of “personality defect” largely explained who “succumbed to morphine and barbiturate addiction.”⁴⁷⁷

Most discussions of drug addiction continued to separate narcotic and barbiturate addiction, in part because they separated tolerance, habituation, and physical dependence. Tolerance involved requiring increased doses over time, to achieve similar effects. Habituation referred to psychological addiction, while the term physical dependence described the body developing a requirement for the drug to such an extent a predictable syndrome of withdrawal symptoms occurred upon stopping consumption.⁴⁷⁸

Physicians and popular press authors regularly compared barbiturates’ effects with those of alcohol.⁴⁷⁹ Symbolic of this link is how they described cumulative effects

“Convulsive Seizures Following Barbiturate Withdrawal, *Journal of the American Medical Association* 133 (1947): 104; Although these reports brought physical addiction of barbiturates to the attention of English speaking physicians, similar reports were published earlier in German. K. Pohlisch, “Ein Fall Akuter Psychose bei Chronischer Trional-Varonal-Vergiftung” *Monatsschrift für Psychiatrie und Neurologie* 69 (1928): 351-67; L. Von Muratt, “Über Psychische Reaktionsformen bei Arzneimittel-Vergiftungen” *Zeitschrift für die Gesamte Neurologie und Psychiatrie*, 22 (1914): 122-32.

⁴⁷⁷ Isbell, *Addiction to Barbiturates*, 109.

⁴⁷⁸ In the mid-1950s control of addictive drugs was guided by the Harrison Act which did not include barbiturates. It only covered opium and its derivatives, cocaine, marijuana, and synthetic versions of these substances.

⁴⁷⁹ For example, see Marie Nyswander, “Drug Addictions,” in *American Handbook of Psychiatry*, volume 1, ed. Silvano Arieti (New York: Basic Books, 1959), 614-22.

of barbiturates, as intoxication.⁴⁸⁰ Jules Masserman's research on changes in behavior under the influence of various psychoactive substances showed similar effects with alcohol and barbiturates; they were all drugs providing "relief of neurotic tension."⁴⁸¹ In their "Report on Barbiturates," a committee of the New York Academy of Medicine referred to concerns that people used barbiturates as a substitute for alcohol, writing, "Addiction is probably limited to persons who, if barbiturates were not available, would take excessive quantities of alcohol or other drugs."⁴⁸² Underlying these comparisons is description of both barbiturates and alcohol as tranquilizers, substances used to relieve tension. Alcoholism could also be interpreted as an outcome of alcohol's imperfect tranquilizer activity. Ebbe Curtis Hoff, explains how alcoholism can result if the alcoholic does not "effectively learn from his drinking experience and alcohol is therefore not a good tranquilizer."⁴⁸³ In this way barbiturates and alcohol were both similar to, and competitors for, the formally marketed tranquilizers such as Valium.

⁴⁸⁰ For example, see Karl M. Bowman, "Some Problems of Addiction," in *Problems of Addiction and Habituation*, eds. Paul H. Hoch and Joseph Zubin. (Grune & Stratton: New York, 1958) 161-176; the term intoxication was also used in reference to the effects of opiate use.

⁴⁸¹ Jules H. Masserman, "Experimental Psychopharmacology and Behavioral Relativity," in *Problems of Addiction and Habituation*, eds. Paul H. Hoch and Joseph Zubin. (New York: Grune & Stratton, 1958), 110-48, 130.

⁴⁸² New York Academy of Medicine, Report on Barbiturates, 1147.

⁴⁸³ Ebbe Curtis Hoff, "Current Advances in the Ambulatory Medical Treatment of Alcoholics," *Academy of Medicine of New Jersey Bulletin* 9, no.3 (1963): 146.

Valium as a better barbiturate

Barbiturates had unwanted side effects, leaving them prone to displacement on the market by drugs with similar benefits, but fewer detrimental side effects. Apart from the issue of addiction, intoxication and lethality remained important barbiturate side effects. In sufficient doses, long acting barbiturates such as phenobarbital produced intoxication; they “cloud the patient’s sensorium.”⁴⁸⁴ The problems associated with bromides were similar but greater than those in barbiturates; “in effective doses they commonly produced such a deep state of sedation that the patient was rendered useless and helpless in his environment.”⁴⁸⁵ Repeated doses of long-acting barbiturates compounded the effect.⁴⁸⁶ Because they were respiratory depressants they could cause death, whether the taker intended suicide or not.⁴⁸⁷ Almost one-quarter of all patients

⁴⁸⁴ Lothar B. Kalinowski, “Chlorpromazine and Reserpine, and their Relation to Other Treatments in Psychiatry,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 343-50, 347.

⁴⁸⁵ Fazekas et al., *Ataractics in Medical Practice*, 42.

⁴⁸⁶ Fort, *Problem of Barbiturates*, II.

⁴⁸⁷ Fort, *Problem of Barbiturates*, II; Publication of reports arguing barbiturates had detrimental autonomic depressant effects, that in large enough doses they depressed respiratory reflexes, did not translate into immediate recognition of a problem. Even pharmacologists well versed in the subject did not necessarily take the reports of barbiturate dangers as a proven fact. In a 1961 publication, Lowell Randall classified phenobarbital as a drug without autonomic blocking effects, along with Miltown and Librium. Chlorpromazine was listed as an autonomic blocker. It appears from this publication, that Librium in 1961 could not have been marketed as less dangerous than precursors on these grounds. L. O. Randall, “Pharmacology of Chlordiazepoxide (Librium),” *Diseases of the Nervous System* 22, section 2, suppl. 7 (1961): 7-15.

admitted to hospitals for poisoning in the early 1960s had taken barbiturates.⁴⁸⁸

Overall, American physicians and the public underestimated both the risks and benefits barbiturates offered; for every noted addict or suicide there were hundreds, probably thousands, for whom the drug appeared unconditionally beneficial.⁴⁸⁹ “There is hardly an organic disturbance in which the administration of a tranquilizing agent would not be beneficial,”⁴⁹⁰ enthused Joseph Fazekas of Albany Medical College.⁴⁹¹ Writing for the *United Nations Office of Drug Control Bulletin*, in 1964, Joel Fort explained that “many physicians in the United States appear to think and act as though barbiturates are completely harmless drugs that can be prescribed in unlimited quantities.”⁴⁹²

The concept of legitimate medical use remained nebulous, a harbinger of the widespread ailments considered suitable for treatment with Valium in the 1960s and 1970s. They were drugs for nerve-related problems, and the central nervous system interacted extensively and intimately throughout the body. Within institutions, wrote Harold Himwich, physician in Albany Medical College’s Department of Physiology and

⁴⁸⁸ Fort, *Problem of Barbiturates*, IV; note this does not imply greater abuse, as was often assumed in the press, but that this class of drugs was more widely used; Barbiturates were in the system of these patients, they were not necessarily the reason for admission to hospital.

⁴⁸⁹ The New York Academy of Medicine reached this conclusion in its Report on the Barbiturates, 1144-58.

⁴⁹⁰ Fazekas et al., *Ataractics in Medical Practice*, 46.

⁴⁹¹ Joseph F. Fazekas was in the Department of Physiology and Pharmacology.

⁴⁹² Fort, *Problem of Barbiturates*, IV.

Pharmacology, “Barbiturates bring surcease to the patient and to the physician who attends him, but the results are usually ephemeral.”⁴⁹³ In ambulatory patients, those with neuroses or ‘nerve’-related conditions, effects were mixed. Barbiturates masked rather than cured psychological ills, thus reducing the likelihood of patients ever seeking more thorough treatment.⁴⁹⁴ Yet barbiturates met a widespread perceived need in American society. They reduced anxiety and tension, as well as fighting insomnia. The New York Academy of Medicine concluded “The wide prevalence of psychiatric complaints among the population must add up to a large volume of legitimate therapeutic need.”⁴⁹⁵

Physicians prescribed barbiturates because they were the best available option, the Academy recognized; to reduce barbiturate use it would be necessary to either prevent “the prevalent unrest and anxiety”⁴⁹⁶ or find better treatments. Given the high rate of barbiturate prescribing, a large number of Americans saw pharmacologic treatment more viable than the possibility of preventing widespread unrest and anxiety.

The search for better drugs, effective in treating tension, anxiety, sleeplessness, alcoholism or addiction, and epilepsy, was a major impetus for pharmaceutical

⁴⁹³ Harold E. Himwich, “Prospects in Psychopharmacology,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 23-35, 23.

⁴⁹⁴ Fazekas et al. *Ataractics in Medical Practice*, 42.

⁴⁹⁵ New York Academy of Medicine, Report on the Barbiturates, 1145.

⁴⁹⁶ New York Academy of Medicine, Report on the Barbiturates, 1157.

manufacturers to develop and market drugs treating neuroses; these were all symptoms or conditions associated with neurotic reactions or neuroses. Barbiturates were widely sold and associated with detrimental side effects. A mild sedative or hypnotic which did not depress respiration would be safer, more salable.

Focus on reducing the physical effects of withdrawal also promoted efforts to identify new drugs useful for treating drug and alcohol addiction, as well as introduction of substitute pharmaceuticals with less addiction potential, into the medical arsenal.

Marie Nyswander, the Senior Supervising Psychotherapist at New York's Postgraduate Center for Psychotherapy, as well as consultant to the New York City Department of Health wrote, in 1959, "of prime importance in the treatment of this addiction is the use of the same drug for withdrawal. *There is no substitute drug for withdrawal.*"⁴⁹⁷

Pharmacologic and clinical trials tested most tranquilizers for capacity to aid in drug or alcohol addiction,⁴⁹⁸ either as a substitute or alternate treatment form. It was an expected part of the tranquilizer profile. Physicians regularly faced the "combative and assaultive acutely inebriated individual."⁴⁹⁹ Treatment with major tranquilizers, what physicians in the late-twentieth century termed antipsychotics, were "most suitable for management of

⁴⁹⁷ Nyswander, *Drug Addictions*, passim.

⁴⁹⁸ Hirsch L. Gordon, "Introduction," in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), xi-xviii, xiv.

⁴⁹⁹ Fazekas et al. *Ataractics in Medical Practice*, 47.

such patients[.]” in part because “of their immediate onset of action,”⁵⁰⁰ and sedation while leaving patients able to care for themselves.⁵⁰¹

In theory, major tranquilizers also ameliorated longer term side effects of alcohol or barbiturate addicts shifting to teetotaler status. “The majority of patients suffering from the after-effects of continued overindulgence in alcohol require treatment for insomnia, anxiety and tremors. Here again the immediate control of the disorder is best accomplished by one of the phenothiazine derivatives. Sleep will be induced within 30 to 45 minutes[.]”⁵⁰²

Part of this benefit arose from the tension reducing nature of tranquilizers; “In chronic alcoholics [they reduce] the tension that finds release in inebriety.”⁵⁰³ Tranquilizers could function through supplanting an addictive and less specific tension-reducing agent, alcohol, for one less addictive and more specific in action. Some physicians claimed meprobamate (Miltown), aided alcohol withdrawal, as well as “menstrual stress, neurodermatitis and the reaction to pain.”⁵⁰⁴ Premarketing trials

⁵⁰⁰ Fazekas et al., *Ataratics in Medical Practice*, 47.

⁵⁰¹ J. Campbell Howard, Jr. and Frank J. Vinci, “Use of the Tranquilizing Properties of Reserpine,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York: Philosophical Library, 1958), 114-21, 118.

⁵⁰² Fazekas, Shea, and Sullivan, *Ataratics in Medical Practice*, 47.

⁵⁰³ Gordon, Introduction, xiv.

⁵⁰⁴ Gordon, Introduction, vx.

suggested Valium was useful for its ability to aid withdrawal from addiction to alcohol and other drugs.⁵⁰⁵ Ebbe Curtis Hoff, Chairman of the Division of Psychiatric Research at the Medical College of Virginia, argued his clinical tests proved Valium useful in the battle against addiction.

Barbiturates were a medical marvel in treatment of epilepsy. There was hope that minor tranquilizers would mirror barbiturates in suppressing seizures.

Phenobarbital, a long acting barbiturate, allowed countless epileptics to lead fairly normal lives. “In this they were the first miracle drugs of their day,” writes academic chemist Daniel Perrine, “it was more than 50 years before antiseizure medications other than phenobarbital became available”⁵⁰⁶ and the side effects of the first alternative antiseizure medications could be life threatening, especially to offspring.⁵⁰⁷

Pharmacologists tested for antiseizure properties in the first generations of major tranquilizers. For example, Leonore Koploff and his colleagues at the New York State Psychiatric Institute and Hospital tested chlorpromazine’s effect on epileptic monkeys and found rapid administration during a seizure caused “flaccidity, diminished

⁵⁰⁵ Hoff, *Current Advances*, 152.

⁵⁰⁶ Perrine, *Chemistry of Mind-Altering Drugs*, 148.

⁵⁰⁷ Phenytoin was known as a substance altering response to EEG patterns, in the 1930s. By 1950, it “became the drug of choice for tonic-clonic seizures, since it produced less intellectual impairment and little sedation relative of phenobarbital.” Perrine, *Chemistry of Mind-Altering Drugs*, 152. Cleft lip or palate could be produced in offspring. Long term use also produced changes in the user, including excessive hair growth, and “coarsening of facial features.” Perrine, *Chemistry of Mind-Altering Drugs*, 152.

responsiveness, reduced aggressiveness, lethargy and somnolence[.]”⁵⁰⁸ As a preventative it could not compete with phenobarbital; unfortunately chlorpromazine tended to sedate or reduce responsiveness in epileptics not currently suffering seizures. Tranquilizing drugs had existing associations with both physical muscle relaxation and relief from mental tension, each of which related to epileptic seizures. Therefore, continued testing of new tranquilizers for these properties was reasonable. If Valium could provide a safe alternative, there was a ready market among epileptics concerned by the side effects of barbiturates.

Any nonaddictive antineurotic, tranquilizer, or sedative would be a highly marketable alternative to barbiturates. Although majority opinion in the medical community continued to be that barbiturate addiction was not true addiction, as it did not result in classical symptoms associated with opiates,⁵⁰⁹ it continued to accept psychological addiction to barbiturates as fact. Barbiturate users were unfortunates, like alcoholics in having a definite moral failing, and possibly a physical one. As I. Phillips Frohman characterized the situation, barbiturate addicts were “psychically impoverished individuals” who tried “to escape from the responsibilities and challenges of ordinary living, and they resort to their use to create a state of insulation against reality whenever

⁵⁰⁸ Leonore M. Kopeloff, Joseph G. Chusid, and Nicholas Kopeloff, “Effect of Chlorpromazine Upon Epileptic and Normal Monkeys,” *Proceedings of the Society for Experimental Biology and Medicine* 90 (1955): 283.

⁵⁰⁹ Frohman, *The Barbiturates*, 432; Essig, *Addiction to Barbiturate*, 188.

they can.”⁵¹⁰ Addicts did not engage properly with society, which automatically identified their behavior as unhealthy within 1950s and early 1960s terms. Similarly, underlying later debates on the nature and physical reality of Valium addiction are questions of whether smooth interaction within a social environment shows mental health, and under what conditions long-term drug taking is itself a medical condition.

Widespread use and risks associated with barbiturates created a climate of opportunity for any pharmaceutical company developing an alternative compound with more specifically beneficial effects and fewer risks. The early major tranquilizers, chlorpromazine and reserpine, were of seminal importance within psychiatric institutions⁵¹¹ but took little away from the main markets for barbiturates, those seeking relief from insomnia, situational or ongoing stress, tension, and epilepsy. Harold Himwich accurately prophesied:

These drugs are effective not only for disturbed patients with psychomotor overactivity but also for emotionally tense ones with acute anxiety. The value of these drugs is being tested for various clinical categories, and in general one might predict that in many conditions for which bromides were formerly used and now barbiturates are prescribed, the new drugs will receive preference.⁵¹²

Major sedatives had strong sedating effects. Barbiturates were widely used in outpatient

⁵¹⁰ Frohman, *The Barbiturates*, 432.

⁵¹¹ Harold Himwich describes tri-fold benefits: increasing the number of patients who can be discharged, making ambulatory treatment of psychoses and neuroses possible, and allowing the mentally ill to continue a normal life “with less effort.” Himwich, *Prospects in Psychopharmacology*, 24.

⁵¹² Himwich, *Prospects in Psychopharmacology*, 34.

populations, those people seeing general physicians, psychiatrists, or psychoanalysts. The new tranquilizers, whether minor tranquilizers or low doses of major tranquilizers, could substitute for barbiturates. As Dr. Lothar Kalinowski enthused, “The neurotic patient falls ever more into the domain of the general practitioner and non-psychiatric specialist. For this group you will prescribe the new drugs in the same way as you prescribed Phenobarbital or other barbiturates in former times.”⁵¹³ Ideally, a barbiturate substitute would treat anxiety, tension, related psychosomatic complaints, control seizures, and help alleviate insomnia.

Although critics later condemned Roche’s Valium marketing for widening the boundaries of mental illness and the limits of acceptable anxiety, barbiturates were applied with a similarly wide brush. Use of pharmaceuticals for ‘nerve’ related conditions, construed broadly, was an acceptable clinical practice well before Valium’s introduction. Most Americans taking barbiturates presumably did not consider themselves sick, only needing a little something to deal with a minor issue, such as sleeplessness or the stresses of work or home life. Concern about individuals refilling prescriptions repeatedly over long periods of time, which led to legislation increasing control over barbiturates, including limits on the number of refills allowed, also illustrates a popular understanding of appropriate barbiturate use. Many barbiturate users did not consider it necessary to see a physician regularly, they believed it appropriate to continue refilling the same prescriptions. Boundaries between healthy

⁵¹³ Kalinowski, Chlorpromazine and Reserpine, 349.

use, inappropriate use, and addiction were debatable, but the vast number of barbiturates consumed each year in the United States suggests use of these drugs for widely existing conditions, or at least to alleviate concerns shared by a substantial portion of the adult population.

Relationship Between Valium and Alcohol

Less obviously an alternative to barbiturates, sedatives, hypnotics, and tranquilizers, was the far more widely used drug, alcohol. In the mid-twentieth century United States, most adult men and women drank. As with barbiturates, medical professionals only considered a fraction of those imbibing as drug abusers. In *Aspects of Alcoholism*⁵¹⁴ Ebbe Hoff, Chair of the Medical College of Virginia's Division of Psychiatric Research, estimated the number of alcoholics in the early 1960s at roughly five million citizens. Considering that moderate social drinking, or a tippie after work most days, was generally not considered symptomatic of alcoholism, the popular assumption that most adult males drank a few times a week seems reasonable.⁵¹⁵ Early twenty-first century definitions of alcoholism are broader, including regular social

⁵¹⁴ This book was written and published under the auspices of Hoffmann-La Roche as part of their "Aspects of..." series.

⁵¹⁵ S. C. Franco, writing in *Industrial Medicine and Surgery* 26 (1957): 221 identifies daily drinking in moderation, but for "relief from inner tension"(Hoff, 13) as pre-alcoholic behavior. Alcoholism is associated with needing a drink in the morning just to face the day ahead, drinking alone, hiding drinking from others and rationalizing it to oneself. Ebbe Curtis Hoff, *Aspects of Alcoholism* (Philadelphia: J. B. Lippincott company, 1963), 13.

drinking as a sign of alcoholism.

Medical professionals mainly diagnosed alcoholism in men, with 5.8 diagnosed for every woman. Most were working age and living within a family, although Hoff only goes so far as to say “[m]ore than half” were living with their wives.⁵¹⁶ He tries to show the social life of alcoholics are not those of social misfits; these were mainly men with a stable life, ongoing jobs, no recent moves, living within a household. Unstable social conditions, he implicitly argues, are not major causes of alcoholism. Alcoholics might not be statistically normal Americans, but their profile fit with widely held social ideals regarding normalcy.⁵¹⁷

During the 1950s and 60s, medical opinion was making a slow and wide turn toward considering alcoholism, as well as drug addiction, as medical issues.⁵¹⁸ There remained a strong tendency within the medical community, like the public at large, to identify alcoholism as a personal failing. But the way of defining a person – in terms of personality, typical behavior patterns, or ways of interacting with society – placed

⁵¹⁶ Hoff, *Aspects of Alcoholism*, 11. Hoff is summarizing a survey by R. Straus and S. D. Bacon, published in *Quarterly Journal of Studies of Alcoholism* 12 (1951): 231.

⁵¹⁷ Similar focus on the importance of positive social behaviors and preventions of ‘anti-social’ actions exists in definitions of the benefits of other psychopharmaceuticals. Gordon, for example, praises meprobamate’s ability in terms of reducing “muscular tension associated with anxiety and hyperemotionalism and returns the patient to social productivity.” Gordon, Introduction, xv.

⁵¹⁸ Robert W. Rasor, “Narcotic Addicts: Personality Characteristics and Hospital Treatment,” chapter 1 in *Problems of Addiction and Habituation* (Grune & Stratton: New York, 1958).

alcoholism into the broad category of mental illnesses, a medical categorization. In psychiatric classification it usually fell into the character disorders,⁵¹⁹ or was specifically categorized as alcoholism or addiction based on the need for specialized treatment.

Valium has an interesting relationship with alcohol; clinical trials and to an extent medical practice suggested its usefulness as a treatment for alcoholism, and both Valium and alcohol served as tension reducers. Each drug potentiated effects of the other. Valium was effectively and explicitly conceptualized by some medical professionals as an improved alternative to alcohol; a more scientific and specifically acting compound with similar beneficial effects alongside fewer detrimental side effects.

In the late 1950s and 1960s, early clinical trials for any tranquilizer included testing usefulness as treatment for acute alcoholism. Major tranquilizers, those used in institutional psychiatry and their derivatives, provided a more effective means to get alcoholics through the first stages of withdrawal, when behavior was similar to psychoses. Unfortunately, these phenothiazine derivatives and rauwolfia compounds not only caused severe blood pressure drop in some patients, they occasionally caused extrapyramidal side effects in alcoholics, just as they did in other patients given them.⁵²⁰

⁵¹⁹ Zigmunt A. Piotrowski, Nolan D. C. Lewis, W. M. Miksztal, and Maurice Phillips, "The Alcoholic Looks at Himself: The Role of Self-Image with Respect to Craving for Alcohol," chapter 12 in *Problems of Addiction and Habituation* (Grune & Stratton: New York, 1958); for further examples addiction interpreted as mental illness see page 191 in *Problems of Addiction and Habituation* for a diagram showing conflict areas and diagnostic categories.

⁵²⁰ Angelo D'Agostino and John D. Schultz, "Clinical Experiences with Chlordiazepoxide in Acute Alcoholism," *Psychosomatics* 2 (September 1961): 362-65.

Some alcoholism researchers and clinicians saw benzodiazepines as a boon to treating alcoholism. Although they acted on different parts of the brain, clinicians tested minor tranquilizers as alternatives; they fit the public's expectation of a medical cure for alcoholism. Ebbe Hoff complained of the widespread belief among alcoholics that physicians will give them something to get them through withdrawal quickly, and the patient's erroneous belief that continued abstinence will be easy afterwards.⁵²¹ Some physicians chose to treat alcohol addiction by substituting another substance, transferring the addiction "from alcohol to sedative, tranquilizers, or other addictive modalities."⁵²² Hoff argued alcohol's addictive nature derived, in part, because it was "not a good tranquilizer[;]"⁵²³ it could only reduce tension moderately, and in alcoholics the tension turned to fear and guilt. Alcohol did not remove tension when used as more than "a social beverage" because it only suppressed tension, possibly by depressing the "alerting mechanisms to the cortex[.]"⁵²⁴ Pharmacologic trials of diazepam suggested it helped relieve tension, but differed from sedatives and major tranquilizers by not stunning the mind's ability to react; it did not depress alerting mechanisms. Laboratory tests and clinical trials with Valium suggested it was not physically addictive, and it was less

⁵²¹ Hoff, *Current Advances*, 143-153; the same opinion is seen in Hugh H. Haden, "Experiences with a Tranquilizing Agent in the Treatment of Chronic Alcoholism," *Psychosomatics* 2 (July 1961): 279-82.

⁵²² Hoff, *Current Advances*, 150.

⁵²³ Hoff, *Current Advances*, 146.

⁵²⁴ Hoff, *Current Advances*, 145.

likely to cause psychological addiction than euphoriant or quick acting substances such as alcohol.

Although alcohol was socially acceptable, at least in moderation, members of the American media, and the medical community, recognized how its use paralleled that of compounds such as barbiturates and minor tranquilizers, substances viewed as medicinal. A tittle after work relieved the tension of the day, but ongoing tensions created risk of over-consumption and addiction. Tranquilizers marketed by pharmaceutical firms were more effective at targeting tension; they were a safer, and tax-deductible, martini. Whether Valium was physiologically addictive became a contested issue around 1970. Previously, most physicians appear to have associated it with active tranquillity, reduction of tension without removing alerting mechanisms. In this, Valium was an improved version of alcohol.

Drug Classification

Classification of psychoactive drugs in the 1950s was basic and fluid. Psychiatry and psychotherapy used four main types, defined by their action and effects: shock producing, sedative-hypnotic, analeptic, and tranquilizing. No standard typology for psychopharmaceuticals existed before the 1960s.⁵²⁵ Shock producing agents, which fell

⁵²⁵ Hirsch Gordon, for example, classified drugs by presumed area of action within the body. He differentiated “central nervous system depressants and stimulants[.]” into four groups, “The autonomic drugs: sympathomimetic (adrenergic), sympatholytic (adrenergic blocking), parasympathomimetic (cholinergic) and parasympatholytic (cholinergic blocking)[.]” Gordon, Introduction, xi.

largely out of use for mild neuroses in the 1950s, created convulsions. These drugs (most commonly insulin and metrazol) had proven efficacy, but there was no consensus on how or why they worked. Although used for schizophrenia and manic-depression, shock treatment was most useful in cases of depression. Sedatives-hypnotics were sometimes simply called sedatives, with the implicit understanding that induction of sleep was always a property of sedatives. Sedative drugs, widely used at midcentury, included barbiturates, alcohol, and morphine. The dominant interpretation in medical and pharmacologic literature assumed these drugs had a general depressant effect on the central nervous system (CNS). Analeptic drugs – caffeine, amphetamines, methamphetamines, and autonomic agents such as epinephrine (adrenalin) – appear associated with CNS stimulants. Three drugs dominated the tranquilizer market before Sternbach discovered the benzodiazepines: chlorpromazine (marketed as Thorazine in the United States and Largactil in the United Kingdom), reserpine,⁵²⁶ and meprobamate

⁵²⁶ Reserpine played a lesser role in the late 1950s than chlorpromazine, and will only be mentioned in passing through the remainder of this dissertation. Reserpine represents a purified version of a “resin fraction[.]” Gordon, Introduction, xi. from roots of the plant *Rauwolfia Serpentine*, a plant “known for centuries in India for a variety of healing powers for the body and the mind[.]” Gordon, Introduction, xi. Efforts to isolate sub-portions of the plant, to isolate specific effects, occurred at least as early as 1931 when “Drs. Salimuzza-man Siddiqui and Rafat Hussain Siddiqui isolated from its roots five alkaloids used with disappointing results (1931).” Reports from “Drs. Cananath Sen and Kartick Chanra Bose,” boosted interest in developing pharmaceuticals from the plant when they “claimed that it reduced high blood pressure and controlled ‘insane mania.’” Gordon, Introduction, xi. Once the ‘Gupta Group’ identified a resin in the plant’s root as conveying most pharmacological activity, European pharmaceutical manufacturers and physician-scientists took more note. “Ciba started its *Rauwolfia* research in 1947 and a year later it sent one hundred grams of Ajmaline (prepared by the Siddiquis) to Sir Robert Robinson in Oxford for further study.” Gordon, Introduction, xi. From 1949 to 1953 testing focused on hypertensive

(marketed by separate companies as Miltown and Equanil). Other drugs in this category were derivatives of the major three, or forms of antihistamines.⁵²⁷

Although medical writers could explain tranquilizers' effects in a plethora of ways, most framed explanations in the context of over- or under-activity of electric, metabolic, or chemical components of the central, sympathetic, or parasympathetic nervous systems. As John Ferguson, a doctor from Michigan's Traverse City State Hospital, explained to an audience of physicians interested in the new psychopharmacology, "Behavior is like a teeter-totter." Healthy people went through periods when they were more or less active, but there was a general balance. The healthy could voluntarily rein themselves in when overactive, and stimulate themselves into action as appropriate. "It is when one factor - overactivity or underactivity is

properties, but links to tension were quickly made. "H. J. Bein of Ciba experimenting on rabbits found that reserpine has an anti-hypertensive and sedative action, but the animals could easily be aroused." Gordon, Introduction, xi-xii. After Robert W. Wilkins, in 1953, reported on reserpine in hypertension and in 1954 at a symposium held in the New York Academy of Medicine he reported that it relieves psychoneurotic symptoms." Gordon, Introduction, xii, half a dozen pharmaceutical manufacturers quickly placed fractions, isolates, and modifications of reserpine (the CIBA isolate) on the market under names including "Serpasil (Ciba), Serfin (Parke-Davis), Reserpoid (Upjohn), Rau-Sed (Squibb), Rauwiloid (Riker), Moderil (Pfizer), and Raudixin (Squibb)[.]" Gordon, Introduction, xii.

⁵²⁷ The best known of these antihistamines was marketed as Atarax which had both a sedating and antihistaminergic effect. The generic name is hydroxyzine and it is currently mainly prescribed for allergic reactions in which psychosomatic factors may be a component. Marketed by J. B. Roerig & Company, its generic name was hydroxyzine hydrochloride. "Its sedative properties are greater in intensity than the common side effect of antihistaminic drugs. It modifies psychosomatic manifestations when they were caused by an increase in emotional tension. In states of excitation, anxiety neurosis and arteriovisceral conditions the therapeutic results are particularly effective." Gordon, Introduction, xvi.

clinically manifested - that we have abnormal behavior[.]”⁵²⁸ Ferguson argued. This is not to say behavioral change was mental illness, it was a visible sign. Scientifically minded physicians usually held to a combination of biological, social, and psychological factors as the ‘causes’ of mental illness. Literature in psychopharmacology tended to focus on stimulation or inhibition in brain or nerves, possibly mediated by neural humors, what in hindsight we identify as neurotransmitters. For example, Pollack claimed “[i]t is quite obvious that mental illness is the product of multifactorial changes which seem to be related to an interference with the major enzyme systems.”⁵²⁹

Drugs useful in promoting mental health helped restore balance between over and under activity. Stimulants, such as amphetamines, coffee, or methylphenidate (Ritalin), increased activity. Before 1950, drugs prescribed “for the management of hyperexcitable states[.]”⁵³⁰ CNS depressants, included chloral hydrate and paraldehyde as well as the more commonly used barbiturates.⁵³¹ Pharmaceutical companies introduced dozens of mental depressants to the United States market in the 1950s;

⁵²⁸ John T. Ferguson, “What’s New and Usable in the Chemical Treatment of Abnormal Behavior,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York, NY: Philosophical Library, 1958), 50-59, 56.

⁵²⁹ Pollack comments on Bowes in Bowes, *Ataratic Drugs*, 20; presumably Pollack is Seymour L. Pollack a physician at Illinois’ Galesburg State Research Hospital.

⁵³⁰ Fazekas et al., *Ataratics in Medical Practice*, 42.

⁵³¹ Both these drugs continued to be used in hospitals through the 1960s.

chlorpromazine (Thorazine), reserpine, and meprobamate (Miltown, Equanil) are among the best known, in part because they were the first of their types and remained the archetype for each category. Each of these drugs depressed, inhibited, tranquilized, or otherwise reduced over-activity in portions of the brain. Pharmacologic research suggested “reserpine and chlorpromazine depress the hypothalamic mechanisms, particularly that part concerned with the patterns for emergency, for fight and flight.” The more general and apparently stronger effects of chlorpromazine (Thorazine) arose from it depressing “not only these mechanisms but also the sympathetic and parasympathetic nervous systems.”⁵³² This schema of stimulation, and depression or inhibition of the central nervous system offered an explanation for the benefits and problems of a broad spectrum of sedating drugs, including alcohol, opiates, and the prescribed major and minor tranquilizers.

The bumper crop of new CNS depressants identified in the 1950s and 1960s forced changes in drug classification, mainly dividing existing categories by focusing on physical location and extent of de-excitation, inhibition, or tranquilization produced.⁵³³

⁵³² Morris Fishbein, “The Tranquilizing Drugs,” in *The New Chemotherapy in Mental Illness: The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations*, ed. Hirsch L. Gordon (New York, NY: Philosophical Library, 1958), 3-5, 3.

⁵³³ Phenothiazine compounds (chlorpromazine and related substances), in general, were “assumed to exercise a depressant action at the myoneural junction and directly on the muscle, an inhibiting action on the diencephalic centers and a dampening effect on the arousal mechanism in the reticular substance.” Gordon, Introduction, xiii. The effect was widespread throughout the brain and central nervous system “acting primarily at the subcortical level in cerebrum, diencephalon, medulla and, to a lesser extent, on the peripheral autonomic system.” Gordon, Introduction, xiii.

“The discovery of new drugs of this type invariably sets off a chain reaction[.]” doctor Morris Fishbein, editor of *JAMA*, declaimed “in which new fields are investigated and various combinations of new and old drugs are tested for specific effects.”⁵³⁴

Tranquilizers, the developing typology implied, were similar to sedatives but with effects on more specific parts of the CNS. As a result, most physicians or mental health professionals who did contemplate the relative merits of pharmaceuticals, identified tranquilizers with drugs calming agitation of the body, or the nerves, while not clouding consciousness nor interfering with intentional action. They were milder versions of sedatives.

Depending on your theoretical bent, these drugs either disrupted/modified learned connections in the brain/mind, or altered the balance between id, ego, and superego, thereby forcing the ego to relearn and adapt.⁵³⁵ Written descriptions of psychotherapeutics in medical journals flow smoothly between behaviorist and mentalist descriptions; it appears mid-twentieth century physicians, pharmacologists, and behavioral scientists saw less of a divide between behavioral theory and analytic descriptions than some late twentieth-century books suggest.⁵³⁶

One possible explanation for assumptions of links between externally visible

⁵³⁴ Fishbein, *The Tranquilizing Drugs*, 4.

⁵³⁵ Abraham Winkler, *The Relation of Psychiatry to Pharmacology* (Baltimore, MD: American Society for Pharmacology and Experimental Therapeutics, 1957) Section 2.

⁵³⁶ Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (Toronto: John Wiley & Sons, Inc., 1997), 26.

behavioral patterns and patterns physically or psychically existing in the brain, is interpretation of learning and thought as patterns of electric activity. The link between psyche and somatic theories can be understood in terms of electrical patterns or tensions, which could be modulated, take different forms when an individual was awake or asleep, and develop or lose paths between areas of activity. This possible interpretation also ties understanding of human physiology and psychology to medical technologies rising to greater use and precision, such as the electroencephalogram (EEG).

Doctors prescribed a wide array of drugs for psychological and somatic problems. Insulin, for example, was prescribed to treat narcotic addiction,⁵³⁷ but more commonly used to produce convulsions and coma or hibernation. During World War II, doses too low to produce coma or convulsions found application in treating ‘combat fatigue,’ and other conditions associated at the time with psychoneuroses. Although earlier physicians thought the therapeutic mechanism rooted in rest and allowing time for the body to adapt,⁵³⁸ by the 1950s explanations turned to disruption of learned maladaptive behavior patterns,⁵³⁹ or destroying the fragile equilibrium within the psyche

⁵³⁷ Winkler, *Relation of Psychiatry to Pharmacology*, 5.

⁵³⁸ Sakel, who introduced insulin shock as a therapy, discussed the rationale in M. Sakel, “The Classical Sakel Shock Treatment: A Reappraisal,” *Journal of Clinical Psychopathology* 15 (1954): 255-316.

⁵³⁹ Gellhorn and his research group conclude the effect of insulin shock is removing inhibitory processes. E. Gellhorn and H. Minatoya, “The Effect of Insulin Hypoglycemia on Conditioned Reflexes,” *Journal of Neurophysiology* 6 (1943): 161-71; E. Gellhorn, “Is Restoration of Inhibited Conditioned Responses Specific for Pavlovian Inhibitions?” *Archives of Neurology and Psychiatry* (Chicago) 56 (1946): 216-21; M. Kessler and E. Gellhorn, “The Effect of Electrically and Chemically

and forcing the ego to adjust in more practical ways. There were no consistent results, or overwhelming proof, that coma or chemical convulsant treatments improved a patient's condition by the time pharmaceutical manufacturers introduced tranquilizers.⁵⁴⁰ Drug-based convulsive therapies fell from favor with introduction of safer alternatives.⁵⁴¹ Sedatives and analeptics found use in psychoexploration, narcoanalysis, narcosynthesis, and elevation of mood. Psychoexploration typically involved combining psychoanalysis with drugs to reshape the relationship between patient and analyst, either by altering consciousness or reducing repression, and as a result allowing the patient consciously to explore events and emotions previously repressed.⁵⁴² Analeptics produced bursts of speech, useful in therapy, and improved energy level as part of treating depression. Barbiturates, widely used by the American public in the mid-twentieth century as all-purpose tranquilizers/sedatives/hypnotics, served similar purposes; in theory, they removed inhibitions, allowing instinctive or subconscious thoughts and behavior to

Induced Convulsions on Conditioned Reflexes," *American Journal of Psychiatry* 99 (March 1943): 687-91. Winkler explains the traditional Pavlovian explanation would be allowing development of protective processes if insulin was used to produce coma. Winkler, *Relation of Psychiatry to Pharmacology*, 228.

⁵⁴⁰ Winkler, *Relation of Psychiatry to Pharmacology*, 7.

⁵⁴¹ It is important to notice that the declining use of electroconvulsive therapies did not lead to their disuse. How they work remained a point of debate throughout the twentieth century, that they were highly effective in certain cases, particularly depression without history of mania, was not questioned.

⁵⁴² L. S. Kubie and S. Margolin, "The Therapeutic Role of Drugs in the Process of Regression, Dissociation and Synthesis," *Psychosomatic Medicine* 17 (1945): 147-51.

surface, and prevented patients from guarding their speech. Narcosynthesis, whether with sedatives or analeptics such as methamphetamine, served either to force a cathartic experience, relive trauma, or otherwise shake up the balance between id, ego, and superego in order to produce a resynthesis of the individual's psyche.⁵⁴³ In terms of learned behavior, Simon Dworkin of McGill University's Laboratories of Physiology characterized the effects of sedatives as impairing ability to recognize if conditioned responses were positive or negative. As a result, creatures felt free to try different responses and could therefore more easily learn and adapt.⁵⁴⁴ E. Wentink noted phenobarbital's ability to extinguish conditioned responses in rats, if used at high enough doses.⁵⁴⁵ Dworkin tried applying essentially the same technique to humans.

Explanations of analeptics, such as amphetamines and methamphetamines often

⁵⁴³ Narcosynthesis, narcoanalysis, drug induced abreaction, and similar methods gained notice during World War II. At the time there was a focus on high rates of war neuroses and the need to get soldiers back to duty as quickly as possible. For examples see: R. R. Grinker, "Brief Psychotherapy in War Neuroses," in *Proceedings of the 2nd Brief Psychotherapy Council*, volume 1, 6-19. (Chicago: Institute for Psychoanalysis, 1944); S. J. Horsley, *Narcoanalysis* (Oxford University Press: London, 1943); H. L. MacKinnon, "Narcoanalysis and Allied Procedures," *American Journal of Psychiatry* 105 (September 1948): 224-25; J. S. New and A. R. Kelley, jr. "Narcosynthesis in Civilian Practice," *Southern Medical Journal* 40 (1947): 349-55; D. W. Orr, "Psychiatric uses of Sodium Pentothal. Experiences in a Forward Area," *Naval Medical Bulletin* (Washington, D. C.) 49 (1949): 508-16; and J. F. Wilde, "Narco-Analysis in the Treatment of War Neuroses," *British Medical Journal* 2 (1947): 4-7.

⁵⁴⁴ S. Dworkin, W. Bourne, and B. B. Raginsky, "Changes in Conditioned Responses Brought About by Anesthetics and Sedatives," *Canadian Medical Association Journal* 37 (1937): 136-39.

⁵⁴⁵ E. A. Wentink, "The Effects of Certain Drugs and Hormones Upon Conditioning," *Journal of Experimental Psychology* 22 (1938): 150-63.

use atypical interpretations. These drugs improved mood in depressed patients, but laboratory measures suggested they sometimes functioned as sedatives. On EEG tests, the results were similarly cloudy, in fatigue states they restored normal patterns, in large doses they often desynchronized expected alpha and beta wave patterns.⁵⁴⁶ B. F. Skinner, with his usual diplomacy, declared amphetamines and caffeine simply outside understanding, “We may just as well say that the effect...is to cause the organism to release energy at a higher than normal rate whether it is in a state of inhibition or not. The surplus energy is used by the animal in doing what it is accustomed to doing[.]”⁵⁴⁷

Tranquilizers were fairly new at the time Sternbach began modifying them. Derived from antihistamines, muscle relaxants, and traditional hypotensive medicines, the earliest psychopharmaceuticals, given the moniker ‘modern tranquilizers’ – because they acted specifically on the CNS and functional behaviors – were chlorpromazine, and reserpine.

Doctors mainly used chlorpromazine, the first major tranquilizer introduced, in mental institutions because of side effects identified during its intended use; originally developed to prevent shock during surgery, it also appeared to calm conscious patients. Physicians charged with running institutions, who often were administrators more than clinical practitioners, immediately identified the practical and possibly therapeutic benefits of chlorpromazine; their patients were less violent, more calm, and approachable both

⁵⁴⁶ Winkler, *The Relation of Psychiatry to Pharmacology*, 176-77.

⁵⁴⁷ B. F. Skinner and W. T. Heron, “Effects of Caffeine and Benzedrine Upon Conditioning and Extinction,” *Psychological Record* 1 (1937): 340-46.

physically and psychologically. The drug appeared to act on both the CNS and autonomic nervous systems, and as a result “strikingly reduces the patient’s sensitivity to his own emotions and to his environment.”⁵⁴⁸ In theory, this offered improved possibility of treatment through traditional psychoanalytic methods, or the more recent group therapy, and the learning of life skills and socially acceptable behaviors necessary to leave the institution. Chlorpromazine’s effectiveness in other areas was at least equally important to some administrators; with fewer violent patients, employee turnover decreased and costs reduced, coincident with cleaner, less destructive, more self-maintaining patients.

The neural action of chlorpromazine involved “synchronization of spontaneous cortical electrical activity”⁵⁴⁹ on electroencephalograph (EEG) tests. In some ways the drug behaved similarly to stimulants, in others akin to central nervous system depressants. Neurologically, chlorpromazine acted mainly on the reticular system, but to an extent on more brain areas than traditional sedatives.⁵⁵⁰

Pharmaceutical firms quickly developed drugs with similar behavioral and EEG profiles, but fewer side effects. Existing theoretical links between psychoses and neuroses suggested doctors could prescribe the same drugs at lower doses, or milder tranquilizers, to outpatients with less severe mental illnesses. Outpatients formed a far larger market.

In the mid- and late-1950s there were few studies, especially animal and behavioral,

⁵⁴⁸ Robert B. Bross, “The Modern Mood-Changing Drugs,” *The American Journal of Nursing* 57, no. 9 (1957): 1142-43 & 1146, 1142.

⁵⁴⁹ Winkler, *Relation of Psychiatry to Pharmacology*, 177.

⁵⁵⁰ Winkler, *Relation of Psychiatry to Pharmacology*, 188.

on the newer tranquilizers, the best known of these being reserpine and meprobamate (Miltown and Equanil).⁵⁵¹ Yet even the scanty published trials suggested newer tranquilizers better suited treatment of the widespread neuroses; they had relatively clean side effect profiles and apparently lesser sedative effects.

The concept of major and minor tranquilizers fit with the popular and professional interpretation that neuroses were similar to, but more mild than, psychoses. Sometimes physicians assumed psychoses were organic in cause, while neuroses were maladaptive functional behaviors; therefore psychopharmacologic treatments for neuroses did not require strong physically sedative effects. Because actions of meprobamate and benzodiazepines were more specific and mild, they appeared suitable for treating neurotic responses to stress in ambulatory patients, while the stronger tranquilizers, such as chlorpromazine (CPZ) appeared the best choice for treating psychoses within institutions.

One tradition of historical discussions of psychopharmaceutical development places meprobamate on the border between major (CPZ and reserpine) and minor (benzodiazepines, hydroxyzine) tranquilizers. David Herzberg, in *Happy Pills in America: From Miltown to Prozac*, explains how officials at Wallace Laboratories intentionally positioned Miltown “by calling it a tranquilizer rather than a sedative, while also distinguishing it as a minor rather than major tranquilizer[.]”⁵⁵² This marketing effort, to link meprobamates with the psychopharmaceutical revolution heralded by chlorpromazine (Thorazine), downplays the

⁵⁵¹ Winkler, *Relation of Psychiatry to Pharmacology*, 114-15.

⁵⁵² David Herzberg, *Happy Pills in America: From Miltown to Prozac* (Baltimore: The Johns Hopkins University Press, 2009), 24.

logic of Miltown's development. It fits well with Doctor Seymour Rosenblatt and Reynolds Dodson's reference to Miltown's creation as a scientific accident.⁵⁵³ This explanation is insufficient. One important anomaly is mephenesin, a drug appearing on the market before the beginning of the psychopharmaceutical revolution (1953) and leading more directly than the major tranquilizers to development of minor tranquilizers such as meprobamate (Miltown), chlordiazepoxide (Librium), and diazepam (Valium).⁵⁵⁴

Mephenesin and Meprobamate

The history of mephenesin, marketed as Myanesin or Toserol, begins before CPZ heralds onset of the psychopharmaceutical revolution. Discovered in 1946 by Berger and

⁵⁵³ Seymour Rosenblatt and Reynolds Dodson, *Beyond Valium: The Brave New World of Psychochemistry* (New York: G. P. Putnam's Sons, 1981), 39.

⁵⁵⁴ A second anomaly is not discussed in this dissertation, for reasons of brevity; antihistamines, which tended to have a sedative or hypnotic side effect profile, were identified, modified, and/or marketed for their sedative properties. Reviewing recent developments in psychopharmacology, J. D. French divides tranquilizers into four groups, based on chemical type: (1) reserpine, (2) chlorpromazine and related phenothiazines, (3) meprobamate and other propanediols, and (4) azacyclonol and related diphenylamines. Reserpine comes into western psychiatry through recognition of a naturally occurring compound (*Rauwolfia*) with a long history of use outside Euro-America. Azacyclonol was the isomer of an existing stimulant, and its broader history is not significant to this dissertation. Chlorpromazine/phenothiazines are derived from antihistaminergic compounds. J. D. French, "Drug Actions Upon the Brain: 'Psychopharmacology'," *Annual Reviews of Medicine* 9 (1958): 333-46.

Bradley⁵⁵⁵ while systematically working through the “ α substituted ethers of glycerol,”⁵⁵⁶ screening showed mephenesin had the widest dosage range of anti-curare effects between that causing paralysis and that resulting in death of the tested compounds. Obviously from this test battery, these chemists did not uncover mephenesin in a search for tranquilizers; Berger and Bradley cared about muscle control properties of chemical compounds. Yet within a year, readers of the *Journal of the Canadian Medical Association* learned that humans given mephenesin intravenously gained a feeling of “euphoria and relaxation.”⁵⁵⁷ Either chemists, pharmacologists, and medical professionals already assumed links between muscle and mental relaxation preexisted or they rapidly made this connection.

Although mainly prescribed to ameliorate effects of curare, muscle paralysis, tension, or spasm,⁵⁵⁸ that small doses of mephenesin caused “a generalized muscular relaxation without, however, impairing voluntary muscular control”⁵⁵⁹ led researchers to test usefulness in psychiatric institutions where damage from physical spasms associated with ECT

⁵⁵⁵ F. M. Berger and W. Bradley, “The Pharmacological Properties of $\alpha\beta$ -dihydroxy-(2-methylphenoxy)-propane (myanesin),” *British Journal of Pharmacology* 1 (1946): 265-72.

⁵⁵⁶ John Hay, “Observations on the Use of Myanesin in Psychiatric Cases,” *Canadian Medical Association Journal* 60 (March 1949): 224.

⁵⁵⁷ E. H. Hare, “The Effects of Mephenesin in Neurotic Anxiety,” *Journal of Mental Science* 101, no. 422 (1955): 172-74.

⁵⁵⁸ John Hay uses the comparison of mephenesin and curare in “Observations on the Use of Myanesin in Psychiatric Cases,” *Canadian Medical Association Journal* 60 (March 1949): 224-27.

⁵⁵⁹ Hay, Observations on the Use of Myanesin, 224.

remained a problem. It reduced or removed symptoms associated with Parkinson syndrome, such as tremors and muscle rigidity. The results were best explained by positing some effects occurred within the cerebral cortex;⁵⁶⁰ psychiatric patients in general experienced “psychic phenomena, chief of which appears to be a feeling of relaxed well-being[.]”⁵⁶¹ wrote John Hay. In 1952, while physicians first read of chlorpromazine (Largactil) in *Archives Internationales de Pharmacodynamie*, Veterans Administration physicians published comments on mephenesin’s use for psychiatric conditions. They studied neurotic individuals with symptoms including anxiety and tension; in twenty-six of thirty patients, the drug produced “a feeling of reduced muscle and psychic tension, often with a sense of well-being[.]”⁵⁶² Mephenesin produced results similar to the widely used barbiturates, including reduction of stress and anxiety, as well as improved sleep, but was less toxic and, because it reduced tension in “voluntary muscles without affecting the muscles of the diaphragm[.]”⁵⁶³

⁵⁶⁰ Birger R. Kaada used knowledge derived from a variety of the drug’s specific actions to conclude it effected the central nervous system in general and had a selective depressant or inhibition action. Birger R. Kaada, “Site of Action of Myanesin (Mephenesin, Tolserol) in the Central Nervous System,” *Journal of Neurophysiology* 13, no. 1 (1950): 89-109; a similar study in 1954 appears to link questions about the CNS localization of muscle and mental relaxation with reflex experiments similar to those used by Lowell Randall in showing diazepam was a potentially useful tranquilizer. Ellen Eva King and Klaus R. Unna, “The Action of Mephenesin and Other Interneuron Depressants on the Brain Stem,” *Journal of Pharmacology and Experimental Toxicology* 111, no. 3 (1954): 293-301.

⁵⁶¹ Hay, *Observations on the Use of Myanesin*, 226.

⁵⁶² Louis Paul, “Mephenesin in Anxiety-Tension States,” *Psychosomatic Medicine* 14, no. 5 (1952): 381.

⁵⁶³ Bross, *Modern Mood-Changing Drugs*, 1143.

– muscles associated with breathing – it should have proved less of an overdose risk.⁵⁶⁴

Mephenesin had a short shelf life as a chemical treatment for anxiety and tension,⁵⁶⁵ compared to longer term use as a muscle relaxant. In 1958, the inaugural report on psychopharmacology in *Annual Reviews of Medicine* identified mephenesin only as a muscle relaxant,⁵⁶⁶ but noted its benefits and defects played a major role in development of meprobamate (Miltown) and the benzodiazepines. Existing medical and scientific theories suggested muscle tension was a measure of stress, that the body responded to stress in both physical and psychological ways, and therefore reduction of muscle and psychic tension should relate to overall well-being. E. B. Squibb and Sons developed mephenesin carbamate in an effort to create a more potent version with longer duration of effect.⁵⁶⁷ Of more lasting importance, scientists at Carter Laboratories developed a “somewhat related”⁵⁶⁸ compound,

⁵⁶⁴ Note that the comparison is mine, but the facts of its action are matters of record. For example the effects of Mephenesin on the diaphragm is noted in Bross, *Modern Mood-Changing Drugs*, 1143.

⁵⁶⁵ For examples of physicians’ desires to find an effective antianxiety medication becoming bogged down in complexities of proof, see Paul, *Mephenesin in Anxiety-Tension States*, 378-82; John A. Ewing, “Clinical Evaluation of the Effects of Mephenesin on Anxiety,” *Journal of Mental Science* 99, no. 416 (1953): 464-72; Hare, *Effects of Mephenesin in Neurotic Anxiety*, 172-74; and P. A. L. Scott, “A Controlled Study of the Effects of Mephenesin on Psychiatric Out-Patients,” *Journal of Mental Science* 101, no. 422 (1955): 163-71.

⁵⁶⁶ French, *Drug Actions Upon the Brain*, 333-46.

⁵⁶⁷ M. Engler, “Mephenesin (Tolserol) and Mephenesin Carbamate in Spastic Conditions,” *Journal of Mental Science* 101, no. 423 (1955): 391-98.

⁵⁶⁸ F. M. Berger, C. D. Hendley, B. J. Ludwig, and T. E. Lines, “Central Depressant and Anticonvulsant Activity of Compounds Isomeric with 2-Methyl-2- η -Propyl-1,3-Propanediol Dicarbamate (Miltown),” *Journal of Pharmacology and*

meprobamate, with a better activity profile as an antianxiety, anti-tension agent.

Carter Laboratories developed meprobamate as part of efforts to improve on mephenesin as a muscle relaxant and antianxiety agent. They theorized that mephenesin was active in the body for only a short period because the primary hydroxyl group oxidized rapidly, thus changing the compound.⁵⁶⁹ Efforts to prevent oxidation resulted in a series of new compounds⁵⁷⁰ of which one discovered in 1950, meprobamate,⁵⁷¹ possessed a longer duration of action, a wider spectrum of activity, and more consistent pharmacologic properties.⁵⁷²

Meprobamate proved an effective muscle relaxant and fit with the profile of existing tranquilizers; it appeared to prevent convulsions and have a calming effect on behavior.⁵⁷³

Experimental Therapeutics 116, no. 3 (1956): 337-42.

⁵⁶⁹ F. M. Berger and R. F. Riley, "The Preparation and Pharmacological Properties of the Acid Succinate of 3-(*o*-toloxy)-1,2-propanediol (Myanesin)," *Journal of Pharmacology and Experimental Therapeutics* 96, no. 3 (1949): 269-75; F. M. Berger, "The Pharmacological Properties of 2-Methyl-2-*n*-Propyl-1,3-Propanediol Dicarbamate (Miltown), A New Interneuronal Blocking Agent," *The Journal of Pharmacology and Experimental Therapeutics* 112 (1954): 413.

⁵⁷⁰ Berger and Riley, Preparation and Pharmacological Properties, 269-75; F. M. Berger and B. J. Ludwig, "The Anticonvulsant action of 2,2-diethyl 1,3-propanediol (DEP) and some of its Homologues and Esters," *Journal of Pharmacology and Experimental Therapeutics* 100, no. 1 (1950): 27-39.

⁵⁷¹ Berger, Pharmacological Properties of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown), 414.

⁵⁷² F. M. Berger, "The Anticonvulsant Activity of Carbamate Esters of Certain 2,2-disubstituted-1,3-propanediols," *Journal of Pharmacology and Experimental Therapeutics* 104, no. 2 (1952): 229-33.

⁵⁷³ Charles R. Boddington Joyce, ed., *Psychopharmacology: Dimensions and*

Wallace Pharmaceuticals began marketing the new drug in 1955, as the tranquilizer Miltown. Also under license from Carter, Wyeth marketed it as Equanil. Marketing focused on a larger population than institutionalized patients; as a compound “producing a profound tranquilizing effect without impairment of alertness,”⁵⁷⁴ physicians could prescribe it to outpatients without fear it would interfere with their regular activities.⁵⁷⁵ This opened an enormous potential market to Wallace and Wyeth, the majority of Americans whose mental health was not absolute yet did not require institutional care. This “vast number of neurotics and mild psychotics”⁵⁷⁶ were those interacting primarily with general physicians. Barbiturates were the main preexisting alternative and their limitations were well-known.⁵⁷⁷

Perspectives (Philadelphia: Lippincott, 1968), 120.

⁵⁷⁴ Abraham Gardiner, “Meprobamate—A Clinical Study,” *American Journal of Psychiatry* 114 (December 1957): 524.

⁵⁷⁵ Clinical trials focused on treatment of psychoses suggested meprobamate could be used as an adjunct to other pharmacotherapies. Veronica M. Pennington, “Use of Miltown (Meprobamate) with Psychotic Patients,” *American Journal of Psychiatry* 114 (December 1957): 257-60; Other clinical studies focused on relief of tension associated with alcohol or drug withdrawal, or anxiety in general. Gardiner, Meprobamate, 524-26; Arnold H. Zucker, Stanley D. Machlin, and Winfield Scott, “An Evaluation of Meprobamate in Opiate Withdrawal,” *American Journal of Psychiatry* 115 (September 1958): 254-55; John H. Medenhall and John A. Ewing, “Further Psychometric Evaluation of the Effect of Mephenezin on Anxiety,” *Journal of Mental Science* 100, no. 418 (1954): 262-66.

⁵⁷⁶ Frank J. Ayd, “Meprobamate: A Decade of Experience,” *Psychosomatics*, 5 (March-April 1964): 82.

⁵⁷⁷ As a result grants from Wallace funded research establishing relative efficacy of meprobamate and phenobarbital, the most commonly used barbiturate. E. H. Uhlenhuth, Arthur Canter, John O. Neustadt, and Henry E. Payson, “The Symptomatic Relief of Anxiety with Meprobamate, Phenobarbital and Placebo,” *American Journal of Psychiatry* 115 (April 1959): 905-10.

The meprobamates quickly became the most commonly prescribed psychopharmaceuticals, continuing in this position until at least 1964.⁵⁷⁸

Published research identified three characteristic behaviors of meprobamate in mice and rats: sedation at low levels, loss of righting reflex at medium doses, and paralysis at high doses.⁵⁷⁹ Compared with the barbiturates, the drug produced sedation and aided sleep without an initial period of restlessness.⁵⁸⁰ Its action was stable, predictable, and fit the concept of tranquilizers as CNS depressants. Obviously another improvement for future drugs would be a wider range of doses between that producing ataraxia, active tranquillity, and mental or physical sedation.⁵⁸¹

Therefore, when Sternbach set out on the trail of new tranquilizers, doctors recognized these drugs as useful adjuncts to psychiatry and general medicine, but medical scientists knew few details about how they functioned. Contemporary knowledge of

⁵⁷⁸ Ayd, *Meprobamate: A Decade of Experience*, 82-87.

⁵⁷⁹ Berger, *Pharmacological Properties of 2-methyl-2-n-propyl-1,3-propanediol dicarbamate* (Miltown), 413-23.

⁵⁸⁰ Berger, *Pharmacological Properties of 2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate* (Miltown), 414.

⁵⁸¹ Clinical research regarding addictiveness of meprobamate was published in the late 1950s. Considering later debates over addictive potential in benzodiazepines, such as Valium, it should be noted that physicians John Ewing and Thomas Haizlip identified withdrawal symptoms similar in barbiturates and meprobamate. Rather than warning against use, they suggested the drug be started and stopped slowly. The authors note their gratitude for Wyeth's support, therefore they did have ties to companies marketing meprobamates. John A. Ewing and Thomas M. Haizlip, "A Controlled Study of the Habit Forming Propensities of Meprobamate," *American Journal of Psychiatry* 114 (March 1958): 835.

psychopharmaceuticals suggested to psychoanalysts that they should act on repression, and in behaviorist translation that they should modify conditioned responses and reduce excessive or ongoing physical responses to stress. Both approaches were consistent with interpreting events in terms of stimulation and depression or repression of the physical brain. Existing tranquilizers suggested observable signs and behaviors to look for in identifying new versions, EEG patterns, muscle tension, righting reflex, changes to learning and learned responses, and reduction in signs of anxiety or tension.

Research and Development at Roche

By the late 1930s, Hoffmann-La Roche was a major pharmaceutical company with a substantial research and development commitment. Headquarters and facilities in Switzerland complemented those at Nutley, New Jersey. Pharmaceutical development encompassed a wide variety of fields, including the two main areas in which Sternbach worked, vitamins and tranquilizers.⁵⁸² The work of Otto Schneider had already produced Narconumal in 1939 and Persedon in 1943.⁵⁸³ Initially, Roche hired Dr. Leo Sternbach to work on vitamin research.

Sternbach, upon completing a doctorate in Chemistry at the University of Cracow in 1931, continued to serve as a teaching assistant for six years. In reminiscences, Sternbach

⁵⁸² For an overview of the company's history see Hans Conrad Peyer, *Roche: A Company History, 1896-1996* (Basel, Switzerland: Editiones Roche, 1996).

⁵⁸³ Narconumal was a sedative-hypnotic form of narcotic, while Persedon was a more mild hypnotic. Peyer, *Roche: A Company History*, 128.

regularly tied his later interest in benzodiazepine-like substances to his early research. Attempts to develop heterocyclic dyestuff compounds failed, but he remembered his love of these compounds' basic properties, synthesis in large quantities was rather simple and the compounds crystallized "beautifully."⁵⁸⁴

Postdoctoral work in Zurich not only improved his career, it allowed him to leave Poland in 1937, slightly ahead of the Nazi advance. Both research and life at his boardinghouse were instrumental factors moving him from academe to corporate work. At the Eidgenössische Technische Hochschule he worked with Leopold Ruzicka, soon to be a Noble Laureate for his work on sex hormones. At his boardinghouse the fascination was with Herta Kreuzer, daughter of the landlord. Realizing a postdoc did not provide sufficient funds to support a family, he moved on to Roche in Basel, with his new wife Herta. With World War II looming, even near Switzerland, the company moved its more vulnerable employees to Nutley, New Jersey, effectively Roche's wartime headquarters. Sternbach, a Polish Jew, was at serious risk should the Nazis take Switzerland. In New Jersey, Roche set the young chemist to work synthesizing vitamins. By 1954, members of the board at Roche faced declining income from vitamin sales. The two-pronged approach taken explains Sternbach's work history at the firm. First, Roche leaders wanted to lessen costs of producing vitamins. At the time, vitamins were fairly new synthetic pharmaceutical compounds, and therefore highly profitable if produced in large amounts through inexpensive processes. Quick development of an economical process creating biotin and

⁵⁸⁴ Lloyd Shearer, "The Man Who Invented Valium," *Oakland Tribune* June 27, 1976.

intermediate compounds for riboflavin improved Sternbach's status within the company. Second, Roche leadership put greater resources into the search for new and marketable pharmaceuticals.⁵⁸⁵ Around 1955 Sternbach gained a new task, although exactly what that task was, and the parameters given him is debatable. Perhaps supervisors told him to develop a tranquilizer, although the methods used to test it suggest the company either wanted a muscle relaxant, anticonvulsant, or improved mild sedative along the lines of barbiturates or meprobamates.⁵⁸⁶

Profiles of existing tranquilizers included these properties; tranquilizers were pharmaceuticals reducing forms or manifestations of stress and tension, including muscle tension. If they calmed but did not substantially dull the mind you could call them tranquilizers. These compounds, minor tranquilizers or ataractics, first entered the market in the early 1950s. By 1955, it was apparent that Miltown was a financial success, and there were few improved compounds successfully competing with it.⁵⁸⁷ Gaining a strong market share depended on developing and marketing a useful substance before competitors, and entering with a drug whose properties were at least slightly better than those already on sale.⁵⁸⁸ In some versions of written recollections, Sternbach's task was similar to that driving

⁵⁸⁵ Peyer, *Roche: A Company History*, 170.

⁵⁸⁶ Peyer, *Roche: A Company History*, 172.

⁵⁸⁷ Even in 1957 there were only a few tranquilizers on the market and meprobamates were the sole alternative to chlorpromazine and reserpines. Bross, *Modern Mood-Changing Drugs*, 1146.

⁵⁸⁸ These qualifications for financially remunerative drug development are outlined in O. L. Burns, "Some Statistical Considerations in the Selection of Research

development of Miltown, start with the short acting muscle relaxant Mephenesin and find a stronger and longer acting version. In other branches of hindsight, Sternbach wrote of efforts to create tranquilizers based around a new core molecule.⁵⁸⁹

Roche's interest in tranquilizers or sedatives is understandable. Institutional psychiatrists in the United States and abroad were fascinated with chlorpromazine, but side effects made it impractical for outpatient use. Based on the common assumptions – that psychoses were either organic or functional; that neuroses were milder versions of functional psychoses; that there was a spectrum from mental health to mental illness with most Americans falling between the two poles; and that muscle relaxation as well as antihistaminergic activity were associated with sedative tranquilizers – there was an obviously large market for less dangerous and milder versions of tranquilizers; especially because in the broader public market they were a safer substitute for barbiturates. Pharmaceutical manufacturers knew from past experience that slight modifications to existing compounds could produce similar beneficial activities and better side effect profiles. Wyeth's development of meprobamate illustrated the size of the market. If Roche could get a slightly better compound to market quickly, profits might be enormous.

Exactly what task Roche gave Sternbach remains debatable.⁵⁹⁰ The main point of

Projects in the Pharmaceutical Industry," *Applied Statistics* 11, no. 3 (1962): 170-83.

⁵⁸⁹ Tonya Koeppel, *Leo H. Sternbach*, transcript of interview 12 March 1986, unpublished (Philadelphia: The Beckman Center for the History of Chemistry, Chemical Heritage Foundation, 1986), 25.

⁵⁹⁰ For example, Sternbach patented a spasmolytic in 1953. Leo Henryk Sternbach, assignor to Hoffmann-La Roche, Inc. 1953. Esters of 1-Azabicycloalkanols.

confusion lies in just why the chemist was playing with heterocyclic compounds; these were quite different from existing tranquilizers, muscle relaxants, sedatives, or hypnotics.⁵⁹¹

Sternbach did know a great deal about the compounds he chose. He spent many of his postdoc years studying them, but as potential dyestuffs. Established methods were to modify known marketable compounds. This was less risky and faster than beginning with a random molecule that appeared, but was not yet proven, useful. However, a new core molecule was more likely patentable. Some of Sternbach's writings suggest his supervisors were unhappy with the track his research was taking.⁵⁹² Five years of research produced nothing; he spent years developing new molecules before hitting on one with desirable properties.

Sternbach's work appeared a dead end, so Roche directed his efforts elsewhere.

Perhaps he ate the memo, or simply ignored it.⁵⁹³ Luckily for Roche, when faced with

U.S. Patent 2,648,667, filed April 18, 1951, and issued August 11, 1953; Washington Post Staff Writer B. D. Colen, after interviewing Sternbach, wrote that the chemist was told to create a tranquilizer similar to meprobamate, and start with the same basic molecule. B. D. Colen, "Adventurous Chemist and His Pill; Valium: The Most Popular Most Abused Prescription Pill," *The Washington Post* January 20, 1980.

⁵⁹¹ Excellent diagrams for the structures of chlorpromazine, meprobamate, phenobarbital, chlordiazepoxide (the first of Sternbach's benzodiazepine series) can be seen in Randall, *Pharmacology of Chlordiazepoxide (Librium)*, 7-15.

⁵⁹² In an interview, Sternbach speaks of the research and chemical synthesis leading to the benzodiazepines in terms suggesting his work was driven more by personal interests than a planned program of research. His supervisor, Dr. Goldberg, appears resentful of Sternbach's inability to accept direction. Koeppel, *Leo H. Sternbach*, 26-27.

⁵⁹³ Sternbach recalled working on these compounds after the project officially ended. Koeppel, *Leo H. Sternbach*, 26.

tidying up lab space to set up new projects, Sternbach sent two compounds, synthesized years earlier, to Lowell Randall in the Pharmacology Lab.⁵⁹⁴ Why he did not submit them earlier remains an open question. Roche might be cutting their losses at the lab, but at least testing might produce a publishable paper or two. Sternbach's colleague Earl Reeder asked "Shouldn't we test these compounds?"⁵⁹⁵ They sent the substances off for testing and within a few days received a note from Lowell Randall, calling the compound "interesting[.]"⁵⁹⁶

⁵⁹⁴ The compounds leading to Librium were synthesized in 1955 and submitted for testing in 1957. Leo H. Sternbach, *The Benzodiazepine Story* (Basel, Switzerland: Editiones Roche, 1980). p. 11.

⁵⁹⁵ Koepfel, *Leo H. Sternbach*, 28.

⁵⁹⁶ According to Sternbach he only submitted one of the two remaining compounds for testing. The molecule tested formed the basis of Librium. Valium derived from the same compound, but formed from the precipitate's decomposition. It therefore was synthesized as part of a more complex substance in 1955, and as a separate substance in 1959. Koepfel, *Leo H. Sternbach*, 28-31.

CHAPTER 6. THE MOUSE THAT ROLLED.
FROM DIAZEPAM TO VALIUM™:
TESTING THEORIES AND FINDING USES

Most existing histories of the ‘discovery’ of Valium focus on Leo Sternbach’s role.⁵⁹⁷

However, there is an essential connection between synthesis of the compound and identifying diazepam as potentially useful, and useful in novel ways. The connection resulted from the battery of screening tests used by Lowell O. Randall in the Roche pharmacology labs, followed by clinical testing by outside physicians. Randall earned a Ph.D. in biochemistry at the University of Rochester. After four years working for the state of Massachusetts, he moved on to Burroughs-Wellcome,⁵⁹⁸ then five years later to

⁵⁹⁷ Possibly the focus on synthesis as discovery relates to requirements of the patent system. Compounds could be patented, proof of utility could not. Date of synthesis, being earlier than date at which efficacy was established, helped establish priority.

⁵⁹⁸ Based on published articles in *Journal of Pharmacology and Experimental Therapeutics*, Randall moved up the ranks in the Experimental Research Laboratories of Burroughs Wellcome & Company in the United States; between 1940 and 1942 publications listed him as third or fourth author, by 1943 he ranked position as either the first or second author. He tested compounds linked to later concepts of tranquilizers, such as modification of epinephrine and amine oxidase inhibition. Axel M. Hjort, Edwin J. DeBeer, and Lowell O. Randall, “Experiences with the Biological Assay of Several Sympathicotropic Substances Including Epinephrine,” *Journal of Pharmacology and Experimental Therapeutics* 71 (1941): 105-13; Axel M. Hjort, Edwin J. DeBeer, Johannes S. Buck, and Lowell Randall, “Relative Pharmacological Effects of 2,2-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochlorides,” *Journal of Pharmacology and Experimental Therapeutics* 76 (1942): 71-74; Axel M. Hjort, Edwin J. DeBeer, Johannes S. Buck, and Lowell O. Randall, “Relative Pharmacological Effects of 2-alkyl-1,2,3,4-tetrahydroisoquinoline hydrochlorides,” *Journal of*

Hoffmann-La Roche. Both major pharmaceutical firms put him to use in pharmacological testing. By 1957, he headed the pharmacology lab that tested compounds developed by Sternbach's team.⁵⁹⁹ Randall's position involved overseeing administration of pharmacological tests for various psychotropic development projects. He worked with Dr. Alfred Pletscher in the 1950s development of mono amine oxidase inhibitors (MAOI), an enzyme modifying group of antidepressants.⁶⁰⁰

In 1951, Lowell Randall and his colleagues at Hoffman- La Roche were already looking at compounds which, a few years later, they might have considered tranquilizers. In an article titled "The Adrenergic Blocking Action of Some Dibenzepine Derivatives[,]” they reported results of studies on one of a series of eighteen dibenzepine derivatives. The pharmacologists identified drug Ro-2-3248 the most promising member of the series because

Pharmacology and Experimental Therapeutics 76 (1942): 64-72; Axel M. Hjort, Edwin J. DeBeer and Lowell O. Randall, "Relative Pharmacological Effects of 3-methyl-3,4-dihydro- and 3-methyl-1,2,3,4-tetrahydroisoquinoline Derivatives," *Journal of Pharmacology and Experimental Therapeutics* 76 (1942): 258-262; Lowell O. Randall and George H. Hitchings, "Effect of Tyrosinase on Phenethylamine Derivatives," *Journal of Pharmacology and Experimental Therapeutics* 81 (1944): 77-83; Lowell O. Randall, "Oxidation of Phenethylamine Derivatives by Amine Oxidase," *Journal of Pharmacology and Experimental Therapeutics* 88 (1946): 216-20; Axel M. Hjort, Lowell O. Randall, and Edwin J. DeBeer, "The Pharmacology of Compounds Related to β -2,5-dimethoxy phenethyl amine: I. The Ethyl, Isopropyl and Propyl Derivatives," *Journal of Pharmacology and Experimental Therapeutics* 92 (1948) 283-90.

⁵⁹⁹ Mary Ellen Bowden, Amy Beth Crow, and Tracy Sullivan, *Pharmaceutical Achievers: The Human Face of Pharmaceutical Research* (Philadelphia, PA: Chemical Heritage Press, 2003), 122-24.

⁶⁰⁰ Hans Conrad Peyer, *Roche: A Company History, 1896-1996* (Basel, Switzerland: Editiones Roche, 1996), 172.

of its “maximal adrenergic blocking action[;]”⁶⁰¹ it appears Roche was already looking at drugs which effectively served as tranquilizers by blocking adrenal feedback mechanisms associated with Hans Selye’s General-Adaptation-Syndrome. Yet Randall and his colleagues did not refer to these compounds as tranquilizers.⁶⁰²

⁶⁰¹ Lowell O. Randall and T. H. Smith, “The Adrenergic Blocking Action of Some Dibenzepine Derivatives,” *Journal of Pharmacology and Experimental Therapeutics* 103, no.1 (1951): 10.

⁶⁰² Randall’s earliest articles based on research at Roche focused on the sympathetic nervous system, modified antibiotics (paralleling the research program leading to mephenesin), ganglionic blocking agents (meprobamates fell into this category), modified narcotics, adrenalin blockers, antispasmodics, and curare or anti-curare agents (muscle tension related). G. Lehmann and Lowell O. Randall, “Pharmacological Properties of Sympathomimetic Diamines,” *Journal of Pharmacology and Experimental Therapeutics* 93 (1948): 114-25; Lowell O. Randall and G. Lehmann, “Pharmacological Studies in Analgesic Piperidine Derivatives,” *Journal of Pharmacology and Experimental Therapeutics* 93 (1948): 314-28; E. Grunberg, Lowell O. Randall and R. J. Schnitzer, “The Chemotherapeutic and Pharmacological Properties of the L-Ephedrine Salt of Penicillin G (Tersavin),” *Journal of Pharmacology and Experimental Therapeutics* 95 (1949): 336-48; Lowell O. Randall, William G. Peterson, and G. Lehmann, “The Ganglionic Blocking Action of Thiphanium Derivatives,” *Journal of Pharmacology and Experimental Therapeutics* 97 (1949) 48-57; Lowell O. Randall and G. Lehmann, “Pharmacological Properties of Some Neostigmine Analogs,” *Journal of Pharmacology and Experimental Therapeutics* 99 (1950): 16-32; Lowell O. Randall and G. Lehmann, “Analgesic Action of 3-hydroxy-n-methyl morphinan hydrobromide (Dromoran),” *Journal of Pharmacology and Experimental Therapeutics* 99 (1950): 163-70; Lowell O. Randall, “Anticurare Action of Phenolic Quaternary Ammonium Salts,” *Journal of Pharmacology and Experimental Therapeutics* 100 (1950): 1-5, 83-93; Lowell O. Randall and Thomas H. Smith, “The Adrenergic Blocking Action of Some Dibenzepine Derivatives,” *Journal of Pharmacology and Experimental Therapeutics* 103(1951): 10-23; Lowell O. Randall, Wilbur M. Benson, and Paul L. Stefko, “Spasmolytic Action of Bicyclic Basic Alcohol Esters,” *Journal of Pharmacology and Experimental Therapeutics* 104 (1952): 284-90; Lowell O. Randall, “The Conversion of Decamethonium-Like Agents to Tensilon-Reversible Agents by Aromatic Substituents,” *Journal of Pharmacology and Experimental Therapeutics* 105 (1952): 16-26; Lowell O. Randall, “Synthetic Curare-like Agents Which are Reversible by Tensilon,” *Journal of Pharmacology and Experimental Therapeutics* 105 (1952) 7-15.

The term tranquilizer became associated in the early 1950s with compounds such as chlorpromazine and reserpine, which had a deeply sedating action, causing tranquillization of highly agitated patients. It referred to substances which were central nervous system depressants, but those with a broad spectrum of action, usually including sedation at high doses. These substances gained notice within the American psychiatric profession, especially among hospital administrators in the mid-1950s, after publication of Randall's article on Dibenzepine derivatives. Because the popular press brought use of major tranquilizers in institutional psychiatry to the public's attention, pharmaceutical manufacturers chose to market products such as diazepam (Valium) as minor tranquilizers, drugs treating milder mental illnesses by tranquilizing without sedating. Advertising and professional medical literature often treated minor tranquilizers as milder versions of compounds like chlorpromazine.⁶⁰³

Use of the term 'blocking action' by Randall and colleague T. H. Smith, to describe their debenzapine derivatives, is significant because of similarity to descriptions of meprobamate's mechanism of action. G. Mengoli and G. Maccagnani, who tested meprobamate in an Italian provincial psychiatric hospital, considered it settled knowledge that the drug acted "on the central nervous system by blocking the interneuronic synapses

⁶⁰³ For a list of characteristics considered common to tranquilizers see p. 499 of J. Delay and P. Denneker, "Caractéristiques Psycho-Physiologiques Des Médicaments Neuroleptiques," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 485-501. Note these characteristics are those associated with compounds later termed major tranquilizers, such as chlorpromazine, rather than minor tranquilizers, such as Valium.

selectively, particularly on a level with the thalamus and the caudate nucleus.”⁶⁰⁴ Blocking agents that acted on the sympathetic nervous system were usually termed adrenergic blocking agents. In hindsight, the link between these substances and other psychopharmaceuticals appears obvious. Adrenergic blocking agents included those affecting two major neurotransmitter types, “epinephrine [adrenalin] and norepinephrine in particular[,]” as well as any substance blocking their action or distribution.⁶⁰⁵ They interfered with the anxiety feedback loop.

Already immersed in development of methods to screen new muscle relaxant and adrenal blocking compounds, and compare them to existing ones,⁶⁰⁶ Randall knew how to assess the potency of tranquilizers, muscle relaxants, sedatives, and hypnotics. At least as important, he knew some procedures tested the usefulness of potential drugs, others tested theories. Screening tests identified potentially useful compounds, theory testing provided leads in development of new and more accurate measurements.

⁶⁰⁴ G. Mengoli and G. Maccagnani, “Laboratory and Clinical Observations on a Group of Psychiatric and Neurological Patients Treated with Meprobamate,” in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 561-562, 561.

⁶⁰⁵ Frederick F. Yonkman, “Sympathetic Blocking Agents,” *Annual Reviews of Medicine* 7 (1956): 195.

⁶⁰⁶ Randall and Smith, Adrenergic Blocking Action, 10-23; In 1960 he published a study similar to his work on diazepam, but looking at meprobamate’s effects on aggression, activity, and conditioned avoidance behavior. Lowell O. Randall, William Schallek, George A. Heise, Eaden F. Keith, and Robert E. Bagdon, “The Psychoedative Properties of Methaminodiazepoxide,” *Journal of Pharmacology and Experimental Therapeutics* 129 (1960): 163-71; Randall and Smith, Adrenergic Blocking Action of Some Dibenzapine Derivatives, 10-23.

For use at Roche, screening methods needed to be efficient financially and temporally, provide a yes or no answer whether the compound should continue down the testing pipeline, and do so by testing properties easily observable and associated with the drug's intended purpose. Long-term studies of animals with induced neuroses were not feasible because hundreds, if not thousands, of compounds needed screening each year. However, induced neurosis experiments informed simpler, faster, tests because they identified easily observable factors, which in turn appeared to identify neurotic reactions and states. For pharmacologic tests to be viable they had to use small animals.

Pharmacologists could not directly test tranquilizing effects; these were experiences or sensations whose observable features included well-known side effects of other effective tranquilizers.⁶⁰⁷ Randall began with a simple mouse-based test for muscle relaxation and speed of response, a test for avoidance of conditioned stimuli, and a simple test for reflex responses. Each test was quick. They identified properties already associated with tranquilizers and early identification of neuroses, and were quantifiable.

Pharmacological Testing of Diazepam

The first published pharmacology reports for diazepam (Valium) and chlordiazepoxide (Librium) show use of a similar battery of tests used to compare toxicity

⁶⁰⁷ Neal E. Miller, "Objective Techniques for Studying Motivational Effects of Drugs on Animals," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 83-103, 91.

with muscle relaxant and taming effects.⁶⁰⁸ In both cases, the pharmacologists observed effects of these drugs on mice trying to keep their footing on an inclined screen (the mouse roll test) and when placed in conditions designed to make them fight. The scientists tested how well the drugs blocked induced seizures. They studied muscle relaxation and EEG patterns in cats, while rats provided a biological tool to identify changes in overall activity level, and capacity to mitigate physically caused aggressive behavior. The battery of tests provided information on the expected effects of a tranquilizer: reduction of tension, activity, or aggression, whether it caused problems of coordination, affected convulsion threshold, caused changes in conditioned avoidance behavior, and if it had an effect on the physical brain as well as behavior.⁶⁰⁹ The tests established differences from existing tranquilizers, including barbiturates, information useful to decide if the drug had strong marketing prospects.⁶¹⁰ Employing a battery of tests, the scientists could “cross-check” results by using “a variety of diverse techniques.”⁶¹¹

⁶⁰⁸ L. O. Randall, “Pharmacology of Methaminodiazepoxide,” *Diseases of the Nervous System* 21, section 2, suppl. 3 (1960): 7-10; L. O. Randall, G. A. Heise, W. Shallek, R. E. Bagdon, R. Banziger, A. Boris, R. A. Moe and W. B. Abrams, “Pharmacological and Clinical Studies on Valium™ a New Psychotherapeutic Agent of the Benzodiazepine Class,” *Current Therapeutic Research* 3 (September 1961): 405-25.

⁶⁰⁹ Results of the initial pharmacological tests were published as a ‘Therapeutic Monograph’ in the journal *Clinical Therapeutic Research*. Randall et al, Pharmacological and Clinical Studies on Valium, 405-25.

⁶¹⁰ George A. Ulett, Anton Heusler and Joseph Callahan, “Objective Measures in Psychopharmacology (Methodology),” in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 401-09.

⁶¹¹ Miller, Objective Techniques, 91; Use of a battery of tests for tranquilizers,

Published results on diazepam (Valium) focused on distinguishing how this drug differed from the already marketed Roche benzodiazepine, chlordiazepoxide (Librium). Proof of basic efficacy was not the issue, diazepam was a derivative of chlordiazepoxide (Librium), therefore assumed also useful. Overall, Randall's research approach was to compare the dose at which the drug produced an effect in fifty percent of cases.

The ratio of effective dose₅₀ for a task (ED₅₀) to lethal dose₅₀ (LD₅₀) was a quick measure of risk that effects would occur at a dosage similar to that causing life-threatening danger.⁶¹² The results were numerical; ratios of the ED₅₀ for diazepam compared to that of Librium allowed the Roche pharmacologists to assert Valium was "5 times as potent as Librium as a tranquilizer and muscle relaxant in animals and 10 times as strong as an anticonvulsant."⁶¹³ That the point of comparison for the effective and lethal dose was that at which there was a fifty percent response, suggests a typically mid-twentieth century assumption that psychotropic drugs were rarely effective in the vast majority of cases; there might not be an ED₉₀ to find.

The use of an LD₅₀ also fits with an assumption that lethality of tranquilizers came

"to establish each new drug's range of action compared to other similar agents[,]” was normal in the late 1950s. Ulett, Heusler and Callahan, *Objective Measures in Psychopharmacology*, 401; For a contemporary explanation of the need for test batteries in dealing with tranquilizers, see R. Wein, "Experimental Methods of Examining Tranquilising Agents," in *Psychotropic Drugs* eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 369-70.

⁶¹² The assumption being that risk of death was linear or exponential with increased dose.

⁶¹³ Randall et al., *Pharmacological and Clinical Studies on Valium*, 405-25.

from suppression of central nervous system responses, including respiration, and that risk of death rose suddenly and sharply with increased dosage. Contemporary research justified pharmacologists seeing a spectrum of behavior associated with depression of the central nervous system as they increased dosage of tranquilizers, from effects on more complex reasoning, to more dramatic effects on the brain including sedation, followed by induction of sleep, coma, and with high enough doses, death. Tranquilization was a stage on a continuum of action. The LD_{50} identified the dosage at which half the study group died, while those remaining presumably suffered a lesser rate of central nervous system suppression or depression, probably resulting in sleep, sedation, or some form of tranquilization. By comparing the ED_{50} with the LD_{50} , Roche's pharmacology team showed two points on this spectrum of action. Wider difference in dosage between the two measures suggested a safe dosage range at which the drug had desirable properties.

Randall and his colleagues studied most of diazepam's effects at six or fewer dosage levels, signaling the experimenters' assumptions of great individual variation, and that the drug interacted with the body as a whole. Tight gradation between dosages made sense if the experimental population's responses were fairly uniform; using a small number of dosage levels suggests the experimenters had preexisting expectations of the effective dosage level and they expected individual variation too great for a tighter gradation of dosages to show 'real' results. The pharmacologists measured dosage based on the animal's weight rather than a per animal dosage, suggesting they thought results showed a drug's interaction with the body as a whole. Whether the important effects resulted from interaction between drug

and body, or drug and brain with the body, is not clear. In either case, fixing dosage by total weight heightened the difference between amounts given to individuals in the study group; dosage based on extrapolated brain weight or size subjected the results to greater error and resulted in lesser differences between doses given. The choice to use a small number of dosage levels, each based on body mass, tied to underlying assumptions that individuals varied widely in mental and behavioral responses to drugs having a physical interaction with the body and/or brain.

The battery of tests Randall used to show the compound promising enough to begin clinical trials illustrates how he expected tranquilizers to act. He assumed a relationship existed between muscle relaxation, rate of response, the capacity to learn or unlearn avoidance behaviors, and anticonvulsant properties; phenobarbital affected each. Both EEG patterns and nocturnal activity levels of mice gave insight into effects of a drug on alertness; chlorpromazine (Thorazine) altered both. EEG (electroencephalograph) patterns differed between individuals on major versus minor tranquilizers.⁶¹⁴ Medical professionals already knew barbiturates and alcohol caused a mixture of agitation and sedation; they referred to these results as paradoxical. Technicians could incite aggression in more than one way, for example by creating physical lesions in the brain, or putting mice into environments designed to induce conflict; meprobamates altered aggression. Tests focused on more than one area of the brain; psychopharmacologists believed minor tranquilizers affected fewer and

⁶¹⁴ Marcel Monnier, "Topic Action of Psychotropic Drugs on the Electrical Activity of Cortex, Rhinencephalon and Mesodiencephalon : (Excitement, Tranquilization, Sedation and Sleep)," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 217-34

more specific areas of the brain and nervous system than did major tranquilizers and barbiturates.⁶¹⁵

The tests chosen did not identify all testable effects of tranquilizers; Randall chose procedures to identify responses he considered indicative. Large doses of tranquilizers usually put patients to sleep. Physicians often prescribed them for conditions barbiturates had earlier treated, for example as sleep aids. Yet Randall and his colleagues did not directly test the hypnotic properties of benzodiazepines; the most relevant test involved the nocturnal activity of rats. They tested activity during a period when the animals were most alert, therefore testing reduction of alert behavior rather than induction of sleep.⁶¹⁶ Roche pharmacologists chose and adapted tests thought appropriate for their needs.

Randall and his colleagues sought to identify potential tranquilizers, then distinguish them from similar drugs. The wide range of phenomena studied, in establishing the basic pharmacological properties of diazepam through animal tests, suggests the broad scope of ideas such as psychosomatic disorders and the hypnotic-sedative-tranquilizer spectrum. They could test for variety of observable actions. Tranquilizers presumably affected a group of symptoms; as Yale Psychologist Neal E. Miller phrased it, "Fear, anxiety, guilt, tension, and worry seem to form a related cluster and probably involve certain physiological mechanisms in common."⁶¹⁷ Potentiation or blocking the effects of barbiturates or

⁶¹⁵ Randall, *Pharmacological and Clinical Studies on Valium*, passim.

⁶¹⁶ Randall, *Pharmacological and Clinical Studies on Valium*, 407.

⁶¹⁷ Miller, *Objective Techniques*, 92.

convulsants served as means to show the individuality of diazepam, how its profile varied from that of potential competitors. By establishing how a cat's EEG pattern differed from normal, experimenters illustrated diazepam's place within the spectrum of tranquilizers; cats on diazepam produced patterns similar to those produced by chlordiazepoxide (Librium).⁶¹⁸ Results of earlier experiments suggested a relation between EEG frequency patterns in the cortex, hippocampus, amygdala, and septum and sedation. Higher doses of sedative-tranquilizers produced greater change in the brain's electrical patterns, coincident with inducing sleep.⁶¹⁹ Muscle relaxation, sedation, reduction of anxiety, tension, and need to move, all inhibition of action, resulted from depressing parts of the central nervous system. With increased knowledge of the differential effects of drugs in specific areas of the brain, the results of these tests suggested a slightly different mode of action in diazepam and chlordiazepoxide (Librium) compared with existing tranquilizers. Reduction in avoidance response, and changes in creation or extinction of learned patterns of behavior, went hand in hand with studies of aggression. All studied different forms of altering the link between stimulus and response. No matter whether you studied the effects in complex behaviors or near mechanistic responses, they were part and parcel of studying a drug used in treating psychosomatic disorders.

⁶¹⁸ Randall, *Pharmacological and Clinical Studies on Valium*, 415; this method of identifying similarities between tranquilizers, based on EEG patterns can also be seen in P. B. Bradley, "Effects of Drugs on the Electrical Activity of the Brain and Behavior," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 291-92.

⁶¹⁹ Randall, *Pharmacological and Clinical Studies on Valium*, 406-07, 413.

Randall's battery of tests did not evaluate simple CNS depressant properties; contemporary theories suggested existing tranquilizers depressed different parts of the CNS, possibly through localized effects, selective repression, or action in areas of the brain associated with more or less complex mental processes. Dominant medical theory suggested chlorpromazine (Thorazine) and reserpine had a wide scope of physical actions in the brain, as a result "simply an increasing stupor[.]"⁶²⁰ Alcohol affected a constellation of behaviors, disinhibiting some (reducing repression), inhibiting conditioned behaviors, and usually decreasing tension.⁶²¹ Meprobamate appeared to normalize behavior; it did not alter feeding behavior, yet reduced anxiety caused by conflict situations or environmental alteration, but without producing sluggishness or stupor.⁶²²

In the late 1950s, focus on the central brain stem was a hot new topic.⁶²³ Researchers previously thought it only had effects on basic bodily processes. However, researchers such as S. Margolin now "identified [it] as the seat of the principal integrating system of the brain, which by virtue of its manifold functions and widely dispersed ramifications, has come to be known as the 'unspecific' Reticular Activating System (RAS)."⁶²⁴ The concept of an

⁶²⁰ Erik Jacobsen, "The Effect of Psychotropic Drugs Under Psychic Stress," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 119-24, 120.

⁶²¹ Jacobsen, *Effect of Psychotropic Drugs Under Psychic Stress*, 122.

⁶²² Jacobsen, *Effect of Psychotropic Drugs Under Psychic Stress*, 121.

⁶²³ For example see Harold E. Himwich, "Psychopharmacologic Drugs," *Science* n.s. 127, no. 3289 (1958): 59-72.

⁶²⁴ J. D. French, "Psychopharmacology," *Annual Reviews of Medicine* 9 (1958):

ascending level of integration from perception of stimuli to understanding, knowledge, or thinking, helped explain the range of behavioral effects found in tranquilizers. Published articles associated chlorpromazine use with a constellation of side effects, usually termed extrapyramidal, explicable by assuming the drug acted on the brain stem, and therefore affected more systems than the more physically and behaviorally targeted minor tranquilizers. Association of the RAS with arousal, (sleep to fully awake), sorting of sensory stimuli (possibility of overstimulation, stress responses) and emotional regulation (anxiety), proved a mechanism for explaining the hypnotic/sedative/tranquilizer spectrum of action.

The mouse roll test was similar to established methods for assessing effects on complex and interacting systems of mental and muscle coordination by testing reaction speed and coordination in escape from painful stimuli.⁶²⁵ Randall and his associates took three groups of rats and gave each a different dose of diazepam. Roche labs had previously used this test in studies of chlorpromazine, meprobamate (Miltown), and other existing

334.

⁶²⁵ E. J. Fellows and L. Cook refer to the “complex mechanisms” involved in tests of motor coordination, such as climbing a pole. E. J. Fellows and L. Cook, “The comparative Pharmacology of a Number of Phenothiazine Derivatives,” in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 397-404, 398; G. L. Gatti and M. Frank, “The Technique of the ‘Pole Climbing Response’. Effect of Various Types of Drugs on the Latency-Period and Flight Reaction of the Rat,” in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 147-50; Leonard Cook and Roger T. Kelleher, “The Interaction of Drugs and Behavior,” *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 77-92.

tranquilizers; preexisting information paved the way for comparison of results.⁶²⁶ The pharmacologists lowered dosed mice onto a thirty degree inclined screen. Whether a mouse rolled off or kept his footing produced the discrete data necessary to identify one of three doses as the ED₅₀. When the mouse rolled, it suggested the pharmaceutical dose interfered with rapid adjustment of muscle response.

The ED₅₀, identified by the mouse roll test, was a combination of ingenious methods and quantitative reduction forced by exigencies of experimental conditions. In a simple laboratory test, Randall and his colleagues produced a quick and dirty assessment of potential tranquilizers. Ideally, a drug showed an effective dose substantially below the lethal dose; if the effective dose was significantly smaller than the lethal, the drug was worth further assessment because it could produce muscle relaxation or incoordination without risk of death. The LD₅₀ of diazepam was over 700 mg/kg, but it took only 25 mg/kg to make half the mice roll. It took 100 mg/kg of Librium to produce the same results (ED₅₀). Yet, because they examined only three dosages of diazepam, the investigators could only show an effective dose within a broad range. With sample groups of six mice, individual variation could easily change the result; one mouse more or less shifted a dosage from the ED₅₀ to the ED₃₄. One mouse-sized toenail, stuck in a screen, would significantly change the results.

⁶²⁶ L. O. Randall, "Pharmacology of Methaminodiazepoxide," *Diseases of the Nervous System* 21, section 2, suppl. 3(1960): 7-10; Research at other laboratories, using nearly identical methods allowed comparison with mephenesin. Thomas B. O'Dell, Loretta R. Wilson, Martha D. Napoli, Harold D. White and Joseph H. Mirsky, "Pharmacology of a Series of New 2-substituted Pyridine Derivatives With Emphasis on Their Analgesic and Interneuronal Blocking Properties," *Journal of Pharmacology and Experimental Therapeutics* 128, no. 1 (1960): 65-74.

Reporting the results in quantitative form, without suggesting a range, gave an air of certainty far beyond the actual results.

Sternbach's recollections suggest results of the mouse roll was the most important test in showing his compounds were promising.⁶²⁷ The reason is simple. Excluding the barbiturates, meprobamates (Miltown, Equanil) were the main existing competition. The mouse roll test illustrated a major difference between Sternbach's compounds and Miltown. Mice on meprobamate, wanting to escape an electrified floor by climbing a rod, did not have sufficient muscle control. Changed response to punishment appeared to occur at the same or a higher dose as that causing lack of muscle control.⁶²⁸ Pharmacologic testing for diazepam's sister, chlordiazepoxide (Librium),⁶²⁹ showed it reduced muscle tension enough to cause a mouse to roll, while allowing the rodent enough dignity to walk away from the embarrassing situation, at least when prodded.⁶³⁰ Chlordiazepoxide (Librium) and diazepam's actions were more selective.

For a more direct link showing diazepam's muscle relaxant properties, Randall and

⁶²⁷ This test is consistently mentioned by Randall and Sternbach as one of the first and more telling procedures.

⁶²⁸ Leonard Cook and Edwin Weidley, "Behavioral Effects of Some Psychopharmacological Agents," *Annals of the New York Academy of Sciences* 66, no. 3 (1957): 740-52, 746.

⁶²⁹ Early research on chlordiazepoxide (Librium) also referred to the compound as methaminodiazepoxide or Ro 5-0690.

⁶³⁰ Randall, *Pharmacology of Methaminodiazepoxide*, 7-10; at the time the 'rotorod' provided a more common test of incoordination in mice. Quantification occurred by counting the number of mice falling off a rod rotating along a horizontal axis at a regulated speed.

his laboratory colleagues turned to more controlled studies in cats; they tested reduction of decerebrated cats' muscle rigidity up to four hours after ingesting diazepam. Knowing removal of a cat's cerebral cortex resulted in rigidity of limbs, spine, and tail, the pharmacologists could more directly study the relationship between drug and body; they isolated a portion of the brain, and removed the intervening variables of personality, social and environmental interactions. The researchers scored cats on a scale from zero to three for each joint of the limbs, spine, and tail, with 0 identifying "complete relaxation[.]"⁶³¹ Tellingly, these pharmacologists recorded the range within the study group, again suggesting they expected individual variation even with an animal's learned responses surgically excised. Yet, ultimately, it was the maximum change they sought to identify. They graphed maximum reduction in rigidity at various dosages, and interpolated to identify a dose reducing rigidity by half. That was the identified ED₅₀. Even more than with the mouse roll test, quantitative result covered assumptions with a veneer of statistical objectivity.

A similar set of experiments studied aggression with or without the possibility of behavior forming an intervening variable. In general, these tests used numerical scores to quantify observations of qualitatively different behavior. Naturally aggressive animals became tame, violently competitive mice learned to live together in semi-harmony, and surgically induced nastiness was mitigated.

⁶³¹ Randall, *Pharmacological and Clinical Studies on Valium*, 406; similar tests, with inconclusive results, were performed at other labs in order to establish muscle relaxant properties of mephenesin and other muscle relaxants. Adolph P. Roszkowski, "A Pharmacological Comparison of Therapeutically Useful Centrally Acting Muscle Relaxants," *Journal of Pharmacology and Experimental Therapy* 129 (1960): 75-81.

Using “[c]onsistently vicious”⁶³² Macaque monkeys, members of the laboratory created a measurement called the “Depressant M.E.D.” or median effective dose, which they considered a measure of the drug’s potency as a CNS depressant.⁶³³ Randall’s statement that “A blind procedure was not used” in this portion of the testing, is an understatement considering that, as well as observing activity through a one-way mirror, members of the laboratory team assessed aggression in terms of “behaviors specifically directed at the experimenter, such as forward lunge, baring teeth, attacking handler’s glove.”⁶³⁴ They sought to find the minimum dose reducing activity and aggression to seventy-five percent of the baseline score. Comparing dose necessary to reduce aggression by seventy-five percent, to that producing a similarly large decrease in activity, provided a quick and tidy numerical measurement of dosage range between effectiveness as a tranquilizer and as a sedative.

Determining an appropriate level of aggression mitigation for tranquilizers was subjective but relatively obvious for experimenters at risk of primate-created punctures. When the aggression to activity ratio was roughly 1:2 these primates behaved like tame creatures, they “failed to retaliate when handled or poked,” but at the same time were “not appreciably sluggish or ataxic.”⁶³⁵ Diazepam proved an improvement over chlordiazepoxide

⁶³² Randall, *Pharmacological and Clinical Studies on Valium*, 410.

⁶³³ Randall, *Pharmacological and Clinical Studies on Valium*, 410.

⁶³⁴ Randall, *Pharmacological and Clinical Studies on Valium*, 410.

⁶³⁵ Randall, *Pharmacological and Clinical Studies on Valium*, 410; The second edition *Van Nostrand’s Scientific Encyclopedia* defines ataxia as “Lack of muscular coordination due to disease of the brain, particularly the cerebellum, or spinal cord.” Leo A. Aroian, Howard C. Colton, Charles W. Cunningham, Richard M. Field, Warren

(Librium) in this situation, which in turn worked more effectively than meprobamate, chlorpromazine, or phenobarbital; “Monkeys...did not fight back when teased; under the other drugs they continued to retaliate until motor depression rendered them incapable[.]”⁶³⁶

To study aggressive social behavior, the researchers required more than one situation and species; extant publications illustrated differences in behavioral responses to drugs. On methamphetamine, cats became both aggressively and defensively hostile; hamsters were only defensively hostile. In contrast, hamsters on LSD tended towards contentment, whereas cats definitely did not.⁶³⁷ To test diazepam, Randall and his team used well established methods. They placed pairs of mice in conditions designed to make them fight, then attempted to find the dose of a drug which ‘tamed’ half of the pairs. Traditionally, scientists induced aggression through previous conditions of isolation (lack of social stimulus) or electrical shock (adverse environment).⁶³⁸ The goal was identification of a drug dose that

K. Green, Herman C. Hesse, Robert H. Heyer, Dorothy M. Horstmann, Peter W. Lindsey, D. E. Mack, Bernard S. Meyer, Frederick T. Morse, R. Sterling Mueller, C. B. Neblette, L. R. Quarles, Lloyd L. Smail, Edward S. C. Smith, Ralph K. Strong, Silas M. Thronson, LeRoy D. Weld and R. M. Whelden, contributing editors, *Van Nostrand's Scientific Encyclopedia*, second edition (New York: D. Van Nostrand Company, Inc., 1947), 122.

⁶³⁶ Randall, *Pharmacology of Methaminodiazepoxide*, 8; Randall used a less quantified test of taming in cats. Librium, he discovered “causes muscular relaxation and quieting. At a dose of 10 mg/kg orally, the cat hangs limply and without struggling when held by the scruff of the neck.... (mean cats became amenable to handling and became contented, sociable and playful.” *Ibid*, 9.

⁶³⁷ Stata Norton, “Behavioral Patterns as a Technique for Studying Psychotropic Drugs,” in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 81-82, 81.

⁶³⁸ The isolation induced fighting method was associated with P. Janssen, the

produced lack of fighting, a more appropriate social behavior.⁶³⁹ Again, this was an effort to identify doses of diazepam and other drugs improving capacity to interact with others. By studying patterns of social or antisocial behavior, Randall and his colleagues could quantify behavior in ‘natural’ settings because, as Stata Norton of Wellcome’s Research Laboratories explained “It is axiomatic that behavior occurs in patterns[.]”⁶⁴⁰ By examining changes in overall behavior, they could identify ‘tame’ or positive social behaviors.

To test physically caused aggression, arguably more definitively separate from personality, Randall’s team surgically created lesions in the septal region of rats’ brains, modifying the physical brain to create rodents prone to violence with little prodding. As with the cat-rigidity experiment, they created behavior through localized destruction of the physical brain. The test examined the extent to which tranquilizers, including diazepam, brought the animal closer to normal patterns of environmental interaction. Surgically created vicious rodents responded aggressively to pesky interactions with the fascinated scientists. Using a scale that rated response from zero to four, with higher numbers denoting more

electric shock method with R. E. Tedeschi. P. A. J. Janssen, A. U. Jageneau and C. J. E. Niemegeers, “Effects of Various Drugs on Isolation Induced Fighting Behavior of Male Mice,” *Journal of Pharmacology and Experimental Therapeutics* 129 (1960): 471-75; R. E. Tedeschi, D. U. Tedeschi, A. Mucha, I. Cook, P. A. Maltis and E. J. Fellows, “Effects of Various Centrally Acting Drugs on Fighting Behavior of Mice,” *Journal of Pharmacology and Experimental Therapeutics* 125 (1959): 28-34; Other experimenters tried to quantify the effects of drugs by studying duration of fighting. A. Scriabine and M. Blake, “Evaluation of Centrally Acting Drugs in mice with Fighting Behavior Induced by Isolation,” *Psychopharmacologia* 3 (1962): 224-26.

⁶³⁹ Randall, *Pharmacological and Clinical Studies on Valium*, 406.

⁶⁴⁰ Norton, *Behavioral Patterns*, 73.

violent reaction, laboratory technicians examined response under a fixed series of situations including, “blowing air on back...touching whiskers with stick...prodding back with stick...picking up tail with forceps and lifting rat off the floor.”⁶⁴¹ Drug evaluation involved comparing baseline measures with those at three to five other dosage levels. Once the team established baseline responses, the reactive rodents were dosed and retested half an hour, one hour, and two hours later. They tallied the numerical scores rating each rat’s response at these periods, and used the mean for all rats used to compare dosage levels to response when dosed with saline (rat placebo). Connecting the dots, the five points represented a decrease in aggression at ascending dosages of diazepam; Randall and his colleagues extrapolated to find an ED₅₀, “the dose reducing the score to half the value following saline injection.”⁶⁴²

Using these two experiments, the fighting mouse test and aggression in septal rats, the team at Roche’s pharmacological laboratory produced numerical evidence of diazepam’s capacity to reduce violent antisocial behavior. They could compare results for multiple drugs, establishing how diazepam was different from, and hopefully an improvement on, previously marketed compounds. They could compare results in numerical format, which to positivist scientists appeared more objective and trustworthy than descriptive evidence.

Having tested effects on muscle tension and aggression, Randall and co-workers moved on to study anxiety and learning. Physicians interested in somatic treatments generally accepted tranquilizers’ usefulness for treating abnormalities of behavior

⁶⁴¹ Randall, *Pharmacological and Clinical Studies on Valium*, 407.

⁶⁴² Randall, *Pharmacological and Clinical Studies on Valium*, 408.

(sometimes manifest through somatic problems), possibly because the drugs influenced mediation of the mind's response to internal stressors or the organism's environment. Therefore part of the test battery focused on fear or anticipation of, and response to, noxious stimuli. Avoidance experiments looked at how an individual, in this case of the rodent variety, behaved when faced with events which were stress producing because they were unpleasant or unpredictable (noxious stimuli). In other words, they tested the conditions under which rats avoided electric shocks. This provided a means to create 'psychic stress.'⁶⁴³ They carried out avoidance experiments on small numbers of rodents, studied individually. Randall chose a sequence of three experiments, each in turn expected to identify more targeted characteristics of CNS depressant drugs, in order to find improvements or differences between diazepam and similar compounds.

The avoidance experiments' form relates to behaviorist techniques of the Pavlovian school as well as later operant conditioning techniques.⁶⁴⁴ Classical conditioning – capacity to learn stimulus-response pairs – played an important role in Randall's screening battery.

⁶⁴³ Erik Jacobsen, "The Effect of Psychotropic Drugs Under Psychic Stress," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 119-24, 119.

⁶⁴⁴ For discussion illustrating how self-professed Pavlovians saw conditioned-response drug experiments see W. Horsley Gantt, "Discussion Second Symposium, (a) Discussions by Invitation, W. Horsley Gantt," in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 124-25; see also Andrzej Jus, "Discussion Second Symposium, (a) Discussions by Invitation, Andrzej Jus," in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 125-31.

The more recent operant conditioning paradigm appears in implicit assumptions of variables – the animal’s thoughts, expectations, internal mental life – existing between stimulus and response. Use of Skinner-type boxes allowed establishment of regular conditions as well as numerical scoring of responses.⁶⁴⁵

The first test was one of “non-discriminated” avoidance,⁶⁴⁶ in which researchers shocked the feet of rats without any warning. This tested learning behavior because the shock came every 40 seconds, if the rat failed to press the correct lever during the intervening period. Rats needed to learn preemptive action based on previous experience. Then, with rats under influence of tranquilizers, the scientists reexamined changes in learned behaviors.

Published research already associated certain result patterns with tranquilizers; if rats responded less frequently, it theoretically indicated lesser preoccupation with impending pain.⁶⁴⁷ Tranquilizers typically mitigated or extinguished conditioned avoidance behavior before affecting the unconditioned response to pain. A good tranquilizer, therefore, altered responses such that they were to pain rather than to warnings. Theoretically, this was a test of motivational change, “that the drug affects responses motivated by fear more than it does

⁶⁴⁵ Miller, *Objective Techniques*, 87.

⁶⁴⁶ Randall, *Pharmacological and Clinical Studies on Valium*, 408.

⁶⁴⁷ The test used punishment as a penalty for inaction, making it a form of avoidance conditioning or a variant of variable-interval tests using reward. Miller, *Objective Techniques*, 87, 94.

those motivated by pain.”⁶⁴⁸

The second classical avoidance test, in which the rat heard a distinctive sound immediately preceding the shock, showed “more specific characterization of the distinctive actions of different types of depressant drugs[.]”⁶⁴⁹ Again, basic procedures were well established and therefore likely to be accepted by the community of pharmacologists as proof. In this second procedure, pairing a five-second warning sound with immediately subsequent shock, the researchers created predictive anxiety in rats. Rats avoided pain by associating the warning sound with need to press the lever quickly. An “avoidance response”⁶⁵⁰ referred to success. When rats failed in avoidance they received shock for up to five seconds, which they could terminate early by pressing the lever. If they failed to press the lever during this five seconds of shock it was a “response failure[.]”⁶⁵¹ Establishment of learned behavior, a baseline, involved establishing avoidance response in ninety percent of occurrences for each rat. One reason these tests produced predictive anxiety in the rats was because the warning noise or shock did not occur at regular, predictable, intervals. Ideally,

⁶⁴⁸ Miller, *Objective Techniques*, 95.

⁶⁴⁹ Randall, *Pharmacological and Clinical Studies on Valium*, 408; For an example of a similar type of test used to compare effects of multiple psychopharmaceuticals see William J. Kinnard, Mario D. G. Aceto, and Joseph P. Buckley, “The Effects of Certain Psychotropic Agents on the Conditioned Emotional Response Behavior Patterns of the Albino Rat,” *Psychopharmacologia* 3 (1962): 227-30. Kinnard and colleagues are trying to study drug effects on “conditioned emotional response[.]” 227.

⁶⁵⁰ Randall, *Pharmacological and Clinical Studies on Valium*, 409.

⁶⁵¹ Randall, *Pharmacological and Clinical Studies on Valium*, 409.

with a well-functioning tranquilizer, rats would react not during the interval between warning and shock, but only during the shock period.

To test the active drug, Randall and his colleagues put the trained rodents through their paces for one hour, after which the creatures received the drug and continued in the test conditions for one hour, approximately one-hundred and fifty potential jolts. Randall and his colleagues attempted to show that although diazepam increased failure to avoid shock, failure to respond quickly once shock had begun required a substantially higher dose. In theory, this illustrated the drugged rats were not anxious but remembered and responded quickly to terminate pain.

The experimenters tested a handful of doses and extrapolated results through graphs to find the dose creating avoidance failure in one quarter of trials, and a higher dose producing failure to respond quickly to shock (response failure) ten percent of the time. The pharmacologists assumed median results for all rats (for twenty-five percent avoidance failure) produced a relevant measure of drug potency in alleviating anxiety about future events; the ratio of median dose producing ten percent failure to respond with ten percent failure to avoid measured “the amount of escape responding”⁶⁵² to noxious external stimuli.

This test of ability to pair stimulus and response, with or without a drug in the system, provided means of showing difference between tranquilizing and hypnotic dosages and the drug’s effect on learned behavior, especially learned response to current danger or pain – ‘noxious stimuli’ – without preoccupation regarding potential dangers. The

⁶⁵² Randall, *Pharmacological and Clinical Studies on Valium*, 409.

experimenters found the ratio of response failure to avoidance failure was high in tranquilizers but lower in barbiturates and other hypnotics. This suggested tranquilizers were more suitable in treating nervous disorders because they allowed an organism to still respond to the external environment (including dangerous situations) while not remaining anxious, in a heightened state of apprehension. Those taking the drug could safely interact with their environment, and did not need the controlled conditions of a hospital or psychiatric institution. Learning remained unhindered, predictive stress reduced.

Similar experiments were performed at other laboratories. Irving Geller and his colleagues at Wyeth laboratories, which marketed meprobamate (Miltown), looked at the effect of tranquilizers, including chlordiazepoxide (Librium), on willingness to accept punishment in return for food.⁶⁵³ They interpreted the results, that Librium “attenuates the punishment discrimination”⁶⁵⁴ while chlorpromazine caused rats to give up food in order to avoid shocks, as showing clinically important differences between minor (Librium) and major (chlorpromazine) tranquilizers. Essentially, the tests at Roche and Wyeth looked at extinction of learned or conditioned responses to impending, but not currently existing noxious stimuli.

Testing diazepam, Randall showed the drug produced a response not in anticipation of pain, but only after experience of pain. The rats were not as anxious, yet still responded to

⁶⁵³ Irving Geller, John T. Kulak, jr., and Joseph Seifter, “The Effects of Chlordiazepoxide and Chlorpromazine on a Punishment Discrimination,” *Psychopharmacologia* 3 (1962): 374-85.

⁶⁵⁴ Geller et al, Effects of Chlordiazepoxide, 376.

pain; they retained beneficial but not stress-causing learned reactions. These tests helped place diazepam within the spectrum of available tranquilizers; effects were similar, but not the same as other compounds.

Once pharmacologists at Roche studied the drug's effects on a rat's capacity to predict and prevent problems, and ability for heightened alertness to produce fast reactions, they moved on to assess ability to associate a conditioned stimulus (initial five seconds warning sound) with shock following an intermediate delay. This was once again a test of learning in the Pavlovian sense; it looked at extinction and creation of new patterns, pairing and re-pairing conditioned stimulus to conditioned response. Yet, it also fit with newer operant conditioning theories, because the longer temporal period between stimulus and response implied reaction might not be automatic, it reflected learning. As in previous tests the initial training involved learning, proven by a high rate of association, in this case ensuring that a rat responded to the initial sound by pressing a lever to avoid shock in ninety percent of trials. Rats needed to respond during the initial warning noise, rather than the silent gap; this was a test of both predicting results (acting ahead of time to avoid pain) and effects of five seconds of apprehension as rats waited for the shock.

Results refined the scientist's knowledge of diazepam's behavioral relation to major tranquilizers. The pharmacologists extrapolated from a small number of dosages to find that producing failure to respond during the stimulus (warning noise) in, on average, a quarter of situations; the failure of proactive response. They also identified the dose at which one-quarter of all rodents, on average, failed to respond during the gap between noise and shock;

the failure to respond predictively. A ratio of the two measurements above, one-quarter failure to avoid shock over one quarter failure to respond to the noise, differentiated minor tranquilizers and related drugs, in this case chlorpromazine and other phenothiazines.

Although based on established methods, Randall and his team modified existing techniques to further focus studies on identifying desirable properties which could establish diazepam as an improvement over existing compounds. They modified tests of learning to examine the anxiety component of learning and behavior rather than willingness to accept an adverse environment. At Smith, Kline & French, Leonard Cook and Edwin Weidley developed a technique “to evaluate the CNS active pharmaceutical agents for specific effects on a conditioned response developed in rats.”⁶⁵⁵ Yet because “the buzz and the shock [were] delivered simultaneously” they had no means of differentiating between ongoing apprehension and temporary anxiety.⁶⁵⁶ Randall’s use of experiments where the conditioned stimulus preceded pain, allowed his team to differentiate between changes in failure to respond to the stimulus (sound) and failure to respond to the adverse event itself (electric shock). As a result, the laboratory tests provided ammunition for marketing; diazepam affected tension and anxiety at low doses, but required a much higher dose to cause sedation and lack of response to dangerous stimuli. In comparison to the competition, there was a much safer dose range, or at least a wider one. Comparing doses required to achieve an ED₅₀ illustrated quantitative differences from Librium.

⁶⁵⁵ Cook and Weidley, Behavioral Effects, 750.

⁶⁵⁶ Cook and Weidley, Behavioral Effects, 750.

If diazepam was to be marketed it needed to be either more effective, differently effective, or as effective as existing compounds. As long as tests could be cited to compare only specific drugs for specific effects, diazepam appeared ideal. Across-the-board comparisons, however, were not so clear-cut. Diazepam's competition included chlorpromazine, meprobamate (Miltown and Equanil), barbiturates, and Roche's own chlordiazepoxide (Librium). The pharmacologic profile Randall and his associates published, based almost exclusively on laboratory research in animals, showed diazepam superior to each of these alternatives in at least one aspect. Gram for gram, diazepam was more potent than chlordiazepoxide (Librium) in muscle relaxant, calming, and anticonvulsant properties. This could be a marketing feature, but the overall human dosage forms simply needed more or less inert filler; in either case the quantity of active drug required remained small. Diazepam had greater capacity to reduce physiological muscle rigidity in decerebrated cats than any of its potential competitors, however the extent to which a decerebrated cat needs to relax is questionable. It kept rats more active than those on chlordiazepoxide (Librium) or chlorpromazine (Thorazine), although sedated them as much as pentobarbital and more than meprobamate. A broad range of dosages could be used without toxic effects; barbiturate dosage needed closer monitoring to prevent intoxication or potentially lethal effects on breathing. Taming actions, seen in behavior of violent Macaques, fighting mice, and septal rats, were better overall with diazepam, although results showed significant variation. The naturally violent Macaques were most pleasant to associate with when on diazepam or chlordiazepoxide (Librium); none of the other drugs

tested made them even moderately amiable companions. Other tests showed interspecies differences with chlorpromazine (Thorazine); monkeys became less hostile on the drug, while cats became more so.⁶⁵⁷ Randall and associates reported diazepam (Valium) “4 times as active as a calming agent in the fighting mouse test[,]”⁶⁵⁸ but did not publish comparisons with other drugs; in septal rats, diazepam was less effective than chlordiazepoxide (Librium) or chlorpromazine (Thorazine), on the same level as pentobarbital, and only showed more effectiveness than meprobamate (Miltown, Equanil).

Interpreting results of the learned avoidance experiments posed problems. In nondiscriminated avoidance, Valium showed a wide range of doses between that reducing avoidance and that producing failure to escape. Compared to meprobamate (Miltown, Equanil) and pentobarbital, the results were wonderful; compared to chlordiazepoxide (Librium) and chlorpromazine (Thorazine) the results were only good. Efficacy was similar for all the drugs in experiments involving warning noise immediately followed by shock, all worked poorly. In the final avoidance test, which Randall explained “provided more sensitive and specific measures[,]”⁶⁵⁹ differences were more pronounced. Chlordiazepoxide (Librium) and diazepam had a wide effective dose compared to the others.

Overall, the results established that diazepam fit the profile of existing minor tranquilizers and was similar to chlordiazepoxide (Librium), but did not establish benefits

⁶⁵⁷ Norton, *Behavioral Patterns*, 80.

⁶⁵⁸ Randall, *Pharmacological and Clinical Studies on Valium*, 412; this measure was often repeated in reports of clinical studies by outside researchers.

⁶⁵⁹ Randall, *Pharmacological and Clinical Studies on Valium*, 416.

above and beyond all competitors. Across-the-board improvements were neither expected nor necessary to justify moving to more extensive and expansive tests in humans. Existing psychotropics used as tranquilizers, sedatives, or hypnotics (those treating “hyperactive states”⁶⁶⁰) had known problems, they produced initial excitation, sleepiness, addiction (potentially), and a wide variety of unwanted effects. Randall concluded diazepam deserved further research and Roche needed more information before they could position diazepam as a marketable compound, as Valium. It appeared to be an effective tranquilizer and muscle relaxant which reduced anxiety while keeping an individual alert enough to respond appropriately to its environment.

In hindsight, barbiturates appear to provide little competition for benzodiazepines such as diazepam (Valium). Barbiturates carried risk of addiction, intoxication, or death. It is easy to categorize barbiturates as sedatives or hypnotics (sleeping pills) and diazepam (Valium) as a milder antianxiety agent. But looking at the battery of tests Randall’s laboratory used to decide if diazepam was worth further study, whether it might be profitable to market, shows that researchers focused many tests on diazepam’s performance in comparison to the risks and benefits of the barbiturates.

Given existing knowledge, and the limits imposed by use of small animals, reporting methods, and the ill-defined mechanisms of tranquilizers, Randall and his colleagues developed a solid and workable battery of tests. The underlying action of tranquilizers was

⁶⁶⁰ J. Kleh, W. Ehrmantraut and J. F. Fazekas, “The Choice of Psychotropic Drugs in the Treatment of Neuropsychiatric Disorders,” in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 515-26, 515.

unknown. Existing theories were controversial and possibly contradictory. The Roche pharmacologists took a practical approach, identifying properties commonly seen in existing tranquilizers and studying how diazepam compared to its competitors. They sought to identify a drug of potential clinical utility, to suggest what further tests might be profitable and useful. Small laboratory animals were expensive enough when studying drugs whose use was only potential.

The scientific subcommunity of pharmacology had a pool of existing tests; the fact pharmacologists used these tests did not necessarily establish they tested the properties purported, but it vetted them for reliability and variability. Moreover, it provided a means for members of one laboratory to talk to others, to publish results in a common language. By 1961 that language was increasingly physiological, behavioral, and quantitative. By using a battery of tests, Lowell Randall and his colleagues attacked the problem from a variety of angles.⁶⁶¹ Muscle relaxation and sedation existed in all existing tranquilizers, so it made sense to identify compounds with this property. Changes in development and extinction of conditioned responses were also established measures. Mitigating aggression was seen in existing tranquilizers; it was a characteristic of major tranquilizers that helped convince staff at psychiatric institutions to use chlorpromazine in the 1950s. Anticonvulsant properties were associated with certain barbiturates, drugs used as tranquilizers. Changes in EEG suggested relationships to other CNS depressants, so they were also studied. Valium was a

⁶⁶¹ An example of how batteries of tests were justified and approached for uncovering information relating to untestable psychological factors can be seen in Miller, *Objective Techniques*, *passim*.

tranquilizer. It worked on animals. It was time to find out how this tranquilizer was useful in humans.

Clinical Trials

Pharmacological tests suggested the effects of Valium in humans, but whether studies using animal models translated into useful results in humans required clinical testing. That Librium, a closely related compound, was already on the market probably influenced Valium's testing. Writing in the journal *Science*, Walter Modell of Cornell University Medical College noted that although laboratory trials provided important information, the effects in animals "may differ qualitatively as well as quantitatively from that of man."⁶² Medical professionals only learned the complete risks and benefits of a drug once the public used it for a few years. Similar molecular structures suggested Valium was simply a variant of Librium; major risks should already be apparent. With Librium already on the market for two years, the post-marketing test pool, namely everyone who took it, was testimony to the pharmaceutical's safety and, by proxy, the safety of Valium.

Early clinical trials helped define what actual illnesses or symptoms Valium mitigated; in general the focus was affecting one or more target symptoms associated with an illness. Many of these trials sought to identify the psychiatric categories for which Valium appeared effective. Others compared it with potential competitors. But a significant group,

⁶² Walter Modell, "Hazards of New Drugs: The Scientific Approach is Necessary for the Safest and Most Effective Use of New Drugs," *Science* 139 (22 March 1963): 1180-85, 1180.

based on contemporary medical theory, studied either psychosomatic or somatic illnesses, conditions entirely outside the boundaries of psychiatry before World War II.

It is important to consider that the scientists involved might not have understood Valium as a substance acting directly on symptoms. Neal Miller, a psychologist at Yale, argued symptoms were external manifestations of something more central, motivations. Drugs such as Valium might effect changes in motivation, and “if the underlying motivation is relieved, a whole constellation of symptoms may permanently disappear.”⁶⁶³ Tests on conditioned avoidance behavior suggested the drug selectively altered motivations. Perhaps Valium treated the root of a constellation of mental and physical symptoms, treated psychosomatic illnesses, did something greater than simply mitigating specific symptoms.

Publication of clinical trials occurred alongside planning for the Roche marketing campaign. By the time of Valium’s introduction into the American market in late 1963, journal articles suggested it was safe and useful as a muscle relaxant or anticonvulsant, for neurotic anxiety and other illnesses with an anxiety, tension, or agitation component. A flood of articles in 1963 and 1964 argued Valium was useful in diverse areas of psychosomatic and somatic illness.

Only one early clinical trial directly applied Randall’s pharmacologic research under similar conditions. S. Elamrousi and M. K. Soliman applied taming of animals to larger beasts. In “Some Haematological and Biochemical Studies Following Administration of the

⁶⁶³ Miller, *Objective Techniques*, 83.

Tranquilizer RO-5-2807 in Egyptian Buffaloes.”⁶⁶⁴ the scientists utilized diazepam to tame the normally ornery Egyptian Buffalo, an important farm animal. Most studies, however, concerned use by the more economically important group, homo sapiens.

Testing Valium: The Thalidomide Crisis and Reform of Drug Laws

Initial clinical tests on human beings took place in 1961 and 1962. At the time, Americans were aware of the need and dangers of clinical testing to an extent not seen since the 1930s. The 1938 Federal Food, Drug, and Cosmetic Act passed into law in the wake of the ‘Elixir Sulfanilamide’ disaster. In September 1937, Massengill Company placed a liquid form of sulfanilamide, an early sulfa drug, on the market. Unfortunately the company examined the liquid base, diethylene glycol, for “appearance and taste[,]”⁶⁶⁵ but not for toxicity. More than one-hundred deaths later, the company and the FDA were far more aware how tough it proved to remove a drug from the market. The company could only be prosecuted by the FDA for mislabeling. The 1938 reform of FDA powers introduced premarketing safety approval requirements from the FDA.⁶⁶⁶

In 1960, a small group of physicians began identifying the common factor underlying a rash of children born with deformed limbs; mothers of these children took the sleeping pill

⁶⁶⁴ S. Elamrousi and M. K. Soliman, “Some Haematological and Biochemical Studies Following Administration of the Tranquilizer RO-5-2807 in Egyptian Buffaloes,” *Indian Veterinary Medicine* 42 (May 1965): 301-09.

⁶⁶⁵ Peter Temin, “The Origin of Compulsory Drug Prescriptions,” *Journal of Law and Economics* 22, no.1 (1979): 94-98.

⁶⁶⁶ Temin, Origin of Compulsory Drug Prescriptions, 94-98.

thalidomide early in pregnancy. Thalidomide was a popular drug in Germany and England, where it was first offered to the public in 1958 as a cure for insomnia. Unlike other sleeping potions, such as barbiturates, thalidomide was effective at inducing sleep but did not leave users drowsy in the morning. While useful for the purpose intended, when pregnant women took the drug some of their children came into the world deformed.

Thalidomide was a teratogen with a very specific effect. When taken between the thirty-first and forty-fourth days of pregnancy it caused phocomelia.⁶⁶⁷ This deformity of the limbs did occur naturally, but only rarely. After introduction of thalidomide, the number of afflicted children increased dramatically. One West German clinic saw only seven cases between 1948 and 1958, before thalidomide entered the market. By 1960 the same clinic saw twenty-seven cases, and one year later the number had climbed to sixty-five.⁶⁶⁸ Doctor Helen Taussig, who toured hospitals in England and Germany during March and April of 1962, reported the result was “the most ghastly thing you have ever seen.” Phocomelia created deformed limbs; the name derived from the Greek for seal (phoke) and limbs (melos).⁶⁶⁹ Arm and leg bones failed to grow, sometimes leaving hands and feet growing from the shoulders and hips, and sometimes creating lack of arms or legs altogether. Mental capacities were most often unaffected, creating children with “great abilities as well

⁶⁶⁷ William L. Lawrence, “Thalidomide: Account of Drive to Unmask Drug Reads Like Detective Story,” *New York Times* August 5, 1962; Anon, “Reaction of Thalidomide on Embryo is Described,” *New York Times* October 11, 1962.

⁶⁶⁸ Howard A. Rusk, “Thalidomide Tragedy-1: Surge in Congenital Defects Poses Questions on Precautions and Care,” *New York Times* August 5, 1962.

⁶⁶⁹ Rusk, *Thalidomide Tragedy-1*.

as...severe disabilities.”⁶⁷⁰

Frighteningly, pharmacologists had tested thalidomide in the laboratory, and there had been no signs of teratogenicity in offspring. Apparently, serious side effects might not show until a drug was on the market. Animal tests could not definitively prove a drug’s safety. The fact Valium’s pharmacologic safety profile appeared excellent did not obviate the need for clinical trials, trials with human beings.

In the early 1960s, physicians did not require Federal government approval before beginning human subject tests with investigational drugs. All a pharmaceutical company need do was keep records of shipments, and label the drug packages with the statement “caution, new drug limited by Federal law to investigational use.”⁶⁷¹ Officially the FDA did not deal with clinical or animal testing until they received a New Drug Application. It was therefore possible for companies to proceed with human trials before completing animal trials.⁶⁷² Doctors receiving investigational drugs had to sign a form attesting to their qualifications. After that point the physician could give the drug to patients. He need not tell them the drug was investigational.⁶⁷³ If he wished, the doctor could even charge the

⁶⁷⁰ Howard A. Rusk, “Thalidomide Tragedy-II: 3 Basic Steps Are Followed to Aid Victims and to Preclude a Recurrence,” *New York Times* August 12, 1962.

⁶⁷¹ Anon, “1,229 U.S. Doctors Got Thalidomide: Distribution Given by States—A.M.A. to Study Drug,” *New York Times* July 31, 1962.

⁶⁷² Marjorie Hunter, “U. S. Will Tighten Test Drug Rules: Celebrezze Will Issue Curbs on Companies ‘Very Soon’,” *New York Times* August 3, 1962.

⁶⁷³ The American Medical Code of Ethics did require physicians to obtain verbal consent before giving patients experimental drugs. Anon, “Association to Make Survey,” *New York Times* July 31, 1962.

human guinea pig. As an FDA official explained, doctors rightfully decided whether to inform the patient, because the information could influence experimental outcome and therefore the validity of the results.⁶⁷⁴ Doctor Helen Taussig, in a *Scientific American* article entitled “The Thalidomide Syndrome,” explained that the FDA “exercises no control until the drug is ready for sale.”⁶⁷⁵ Doctor Kelsey, the FDA inspector who prevented thalidomide from reaching the U.S. market, pointed out the need to test experimental drugs on human subjects was a necessary step in proving them safe for sale to the public. “Animals don’t answer all the questions,” she explained.

In 1961 and 1962, politicians of all flavors and ideologies tried channeling public concern into legislation. Estes Kefauver continued his prolonged hearings on drug prices, safety, monopolistic behavior, and other alleged abuses by the pharmaceutical manufacturing industry.⁶⁷⁶ President Kennedy continued his calls for passage of a law providing consumer drug protection. In mid-March he set out his program to increase consumer protection from

⁶⁷⁴ Anon, “U.S. Considering Regulations to Reduce Peril of New Drugs: Move by Food and Drug Administration Spurred by Thalidomide Birth Defects—Controls Are Limited at Present,” *New York Times* July 29, 1962..

⁶⁷⁵ Anon, “Industry is Criticized,” *New York Times* July 29, 1962; Marjorie Hunter, “How Drugs Reach the Public—A Q. & A.: Thalidomide Case Points Up Role Government Plays in Testing and Certifying New Products,” *New York Times* August 5, 1962.

⁶⁷⁶ Kefauver’s hearings, much publicized, ran from 1959 to 1961. Early topics included tranquilizers and brand name drugs. Senate Subcommittee on Antitrust and Monopoly of the Committee of the Judiciary, *Part 16. Tranquilizers*. 86th Cong., 2rd sess., January 21, 22, 26-29, 1960; Senate Subcommittee on Antitrust and Monopoly of the Committee of the Judiciary, *Part 21. Administered Prices in the Drug Industry (General: Generic and Brand Names)*, 86th Cong., 2nd sess., May 10-13, 1960.

high prices, low quality, and fraud. The consumer had certain rights, the president asserted. The public had a “right to safety,” “The right to be informed,” “The right to choose,” and “The right to be heard.”⁶⁷⁷

The problem, as Kennedy framed it, was that the wonder drugs introduced in the past twenty years were more powerful than anything in the past. They therefore held both promise and danger on a level never before seen. In his message to Congress the President spoke of “The successful development of more than 9,000 new drugs in the last twenty five years[.]”⁶⁷⁸ These novelties had the capacity to save lives but were “placed on the market with no requirement that there will be either advance proof that they will be effective in treating the diseases and conditions for which they are recommended or the prompt reporting of adverse reactions;”⁶⁷⁹ if Congress was concerned about the public well-being it should pass a law to protect Americans. After all, Congress already offered this level of protection to medication for animals; “It is time to give American men, women and children the same protection we have been giving hogs, sheep and cattle since 1913 under an act forbidding the marketing of worthless serums and other drugs for the treatment of these animals[.]”⁶⁸⁰

⁶⁷⁷ John F. Kennedy, “Special Message to the Congress on Protecting Consumer Interest,” March 15, 1962, John T. Woolley and Gerhard Peters, *The American Presidency Project* [online]. Santa Barbara, CA: University of California (hosted), Gerhard Peters (database). <http://www.presidency.ucsb.edu/ws/?pid=9108>.

⁶⁷⁸ Kennedy, “Special Message to the Congress on Protecting Consumer Interest.”

⁶⁷⁹ Kennedy, “Special Message to the Congress on Protecting Consumer Interest.”

⁶⁸⁰ Joseph A. Loftis, “Kennedy Submits a Broad Program to Aid Consumer:

Kennedy explained.

To accomplish his goals, Kennedy suggested changing the existing Food and Drug Act to make drugs “better, safer and less expensive.” Specifically, he argued the updated law should require that companies offer proof new drugs were both safe and effective “for their intended use” before marketing. Kennedy called for listing generic names on labels, to promote competition between older brand-name pharmaceuticals and generic versions of the drugs. He called for all drug manufacturing facilities to follow industry-standard Good Manufacturing Practices (GMP), to ensure quality and reliability in their products. To guarantee they were up to snuff, the FDA should inspect factories regularly. The government should require that companies report to the FDA any incoming evidence pointing to problems in already marketed drugs. When the FDA doubted safety of a drug, it should be able to withdraw it from the market immediately. In general, Kennedy’s consumer protection program was compatible with Kefauver’s bill. It was silent, however, on the issue of patient notification.⁶⁸¹

By the second week in April 1962, when the thalidomide scare broke, the Drug Reform Bill was struggling for life. Rather than appearing on the Senate calendar to be debated, it had been referred to the Committee on Patents. In all likelihood that committee would not disgorge it during the 87th Congress. The thalidomide scare resuscitated the

Calls for Greater Protection of Buyers of Drugs, Food, Cosmetics and TV Sets,” *New York Times* March 16, 1962; Anon, “Text of Kennedy’s Message to Congress on Protection for Consumers,” *New York Times* March 16, 1962.

⁶⁸¹ Loftis, Kennedy Submits a Broad Program, 16; Text of Kennedy’s Message to Congress on Protection for Consumers.

Kefauver drug reform bill. Public demand pushed Congress to pass the bill, or a bill, into law.

A *New York Times* editorial titled “The Control of Pharmaceuticals,” indicates how people reacted to the news of thalidomide’s effects. The editor, horrified by the events in Europe, wrote about the moral of the situation, “even more stringent tests of drug safety are needed[,]” he warned. The editor associated this need with passage of the Kefauver drug reform plan, which he considered important “regulatory legislation.” The FDA discovered formidable difficulties in recalling thalidomide and identifying all doctors given the drug. Therefore, to prevent a similar occurrence in the U.S.A., regulation should allow the government “immediately to ban the drug in question and submit it to further tests rather than wait to see if enough reports of damage to human beings come in to prove the lack of safety.”⁶⁸² Unfortunately, the bill ultimately passed into law was shaped by political, administrative, legislative, legal, and corporate concerns.

The Kefauver-Harris bills proceeded quickly through Congress. The Senate Judiciary Committee released the bill on 20 August 1962, with two final amendments requiring ‘substantial’ proof of efficacy and authorizing government inspection of factories. Senate bill 1552 did not include provisions demanding informed consent by human subjects of experiments or a mandatory arsenal of animal tests before human trials. The bill moved to discussion on the Senate floor within the week and by mid-October went over the final

⁶⁸² Anon, “The Control of Pharmaceuticals,” *New York Times* April 13, 1962.

hurdles into law.⁶⁸³ The Kefauver-Harris bill proceeded to the White House where President Kennedy signed it on 10 October 1962, in the presence of Senator Kefauver, Representative Harris, FDA Commissioner Larrick, and Dr. Frances Kelsey.⁶⁸⁴

Before passage of the 1962 Act, government agencies could remove unsafe or ineffective drugs from the market, but existing regulations were little help. Ineffectual pharmaceuticals could go on the market as long as proven safe. After they were in the hands of the public, the FDA could gather its own information on how well they worked. They had control over labeling, which provided an indirect means for requiring that manufacturers sell drugs with a medical purpose. Lack of efficacy was not enough to justify removing a drug from the market. In order to recall a drug, the FDA had to prove that the manufacturer was engaging in false advertising to doctors. If companies advertised and sold directly to the public, the Federal Trade Commission regulated advertising. Therefore, when the makers of Rybutol told the public their drug would treat “tiredness, loss of a sense of well-being, loss of happiness and appearing and feeling older than one should,” the FDA believed they deceived the public, but it was the FTC that charged the makers, Lanolin Plus, with false advertising. The FDA governed pharmaceutical companies’ literature sent to doctors; on a single day the FDA seized two types of antibiotics because the literature sent with them to

⁶⁸³ Marjorie Hunter, “Drug Safety Bill Cleared by Panel For Senate Vote: Curbs Sought by President Approved—Hearings are Reopened in House,” *New York Times* August 21, 1962.

⁶⁸⁴ Anon, “Drug Control Bill is Passed by Senate,” *New York Times* October 4, 1962; Marjorie Hunter, “Congress Votes Drug-Curb Plan: House, 347-0, Sends Stiff Control Bill to Kennedy,” *New York Times* October 5, 1962.

doctors stated usefulness in treating “tonsillitis, bronchitis, lobar pneumonia, influenza and a number of other conditions.” The safety clearance granted for those drugs was only for use in treating the common cold and preventing secondary infections.⁶⁸⁵

One of the strangest aspects of the assumption that thalidomide caused passage of the Kefauver bill was that the bill dealt with drug control in general, but did little to assure teratogens never again reached the public. Proponents referred to Kefauver’s reform plan using terms such as “tighter control over drugs,” but apart from allowing the FDA to withdraw a drug from the market before holding hearings, few of Kefauver’s provisions could be formulated as thalidomide preventatives. The same editor who referred to the Kefauver bill’s “tighter control over drugs” also made a point of explaining the need for additional legislation to prevent a recurrence of the thalidomide scare in the future. “[I]t is clear that other action is needed too if the full implications of this epidemic of deformed babies are to be dealt with[,]” he wrote, “[c]ertainly the regulations governing experimental distribution of drugs need to be tightened up.”⁶⁸⁶ Another editorial referred to the reform plan as “an important step toward preventing such tragedies as followed the use of thalidomide,” yet noted that even provisions for testing drugs on animals could not have shown the dangers of thalidomide; “Tests on animals had found thalidomide to be safe when

⁶⁸⁵ Anon, “False Advertizing Laid to Rybutol,” *New York Times* February 14, 1962; Anon, “Antibiotics Are Seized: Leaflets to Doctors Said to Differ from Labels,” *New York Times* February 14, 1962.

⁶⁸⁶ Anon, “Better Drug Control,” *New York Times* August 7, 1962.

given to normal adults.”⁶⁸⁷

The issue of informed consent amply illustrates the oversimplification inherent in considering the thalidomide scare as cause for passage of the Drug Reform Act. That thousands of Americans acted unknowingly as human guinea pigs to test thalidomide terrified them. Yet both the new FDA regulations on use of investigational drugs and the 1962 Drug Reform Act were silent on this issue. Dr. Frances Kelsey, who prevented market approval of thalidomide in the United States, believed doctors should retain the right to decide whether to inform patients that they were taking an experimental drug, or to remain silent. “There may well be times in which it would not be desirable for the patient to know,” she told a television interviewer.⁶⁸⁸

The concept of volunteer test subjects proved illusory. In May, Doctors Mary and Ira Gabrielson, commenting on the need for better premarket testing, complained that pregnant women were involuntarily turned into test subjects every time they filled a prescription. True human volunteers, those involved in premarket testing of experimental drugs, “incur risks willingly,” they wrote in the *New York Times*, “and know that their hazard is of known dimension.”⁶⁸⁹

Scientists, doctors, and pharmaceutical companies were less than thrilled by the

⁶⁸⁷ Anon, “Safer Drugs,” *New York Times* August 25, 1962.

⁶⁸⁸ Anon, “Dr. Kelsey Says Physician Should Decide on Test Drug,” *New York Times* August 13, 1962.

⁶⁸⁹ Mary O. Gabrielson and Ira W. Gabrielson, “Testing New Drugs: Physicians Cite Mutilated Infants in Urging Safeguards,” *New York Times* May 18, 1962.

changes. Pharmaceutical companies discovered many doctors were wary of participating in clinical trials, “afraid lest another ‘thalidomide’ crop up as unexpectedly as the real one did.”⁶⁹⁰ The prospect of new regulations did not assuage their fears, possibly because the Kefauver-Harris amendments did not include any provisions that would have stopped thalidomide reaching the public. Its manufacturer performed animal tests on rats before giving thalidomide to humans. As scientists were discovering, the teratogenic effects of this drug were hard to reproduce in animals, so even using larger mammals probably would not have revealed the drug’s dangers. The prospect of required animal tests for all drugs offended manufacturers and physicians for other reasons; although most ‘reputable’ manufacturers did animal tests before conducting human trials (experiments consumed an estimated nine million animals in 1961), some researchers feared the regulations, created for the entire industry, would be too strict. They warned that rigid requirements could “have a paralyzing effect on such programs as the national multi-clinic cooperative screening effort aimed at developing cures for cancer.”⁶⁹¹ Other authors explained the changes damaged physicians on a more personal level because they “eliminate the use of professional judgement, which is the basis for true investigations.” Doctors were used to using their own judgement in prescribing investigational drugs. Some, like Howard A. Rusk, considered the

⁶⁹⁰ John A. Osmundsen, “Scientists Fear New Laws May Curb Drug Research: They Are Concerned That Furor Over Thalidomide Will Lead to Restriction of Necessary Clinical Experiments,” *New York Times* August 26, 1962.

⁶⁹¹ John A. Osmundsen, “Scientists Fear New Laws May Curb Drug Research: They Are Concerned That Furor Over Thalidomide Will Lead to Restriction of Necessary Clinical Experiments,” *New York Times* August 26, 1962.

multiplication of regulations demeaning, reducing the physician to a technician “limited to confirming or denying a hypothesis.”⁶⁹² After receiving over three hundred letters from concerned physicians and researchers, FDA officials made a point of reassuring them the final regulations would be “flexible enough to encourage research.”⁶⁹³

Hoffmann-La Roche performed clinical tests on Valium before and during this turbulent time. Laboratory tests showed no obvious changes in fetal development,⁶⁹⁴ but the thalidomide crisis illustrated how pharmacological testing on animals was only the first step. Human trials were necessary before a pharmaceutical manufacturer could market a drug legally, ethically, and practically. The nature and expected uses of Valium raised further quandaries. What qualities were they testing for? Studying effects of a drug combating diseases with a specific pathogen was easy. Drugs worked if the pathogen became harmless and symptoms subsided. Psychopharmaceuticals were far more problematic. Neuroses tended to be self-limiting; left untreated, some patients would get better anyhow. Quantifying symptoms was not easy. And no one could definitively state what symptoms best illustrated Valium’s actions.

From Diazepam to Valium™: Testing Theories and Finding Uses

⁶⁹² Howard A. Rusk, “Drug-Test Regulations: U.S. Proposals Innocuous on Surface, But Lowering of Standards is Feared,” *New York Times* September 16, 1962.

⁶⁹³ Anon, “Drug-Test Rules Will Be Flexible: F.D.A. Assures Physicians of Modification in Revisions of Draft Regulations,” *New York Times* October 25, 1962.

⁶⁹⁴ Randall et al, *Pharmacological and Clinical Studies on Valium*, 417, 421.

The nature of clinical studies on Valium are a remarkable melange of techniques or choices probably influenced in part by the thalidomide crisis, and other aspects which suggest clinicians involved took entirely different lessons, if any, from the crisis. Clinical trials of Valium, mainly performed by physicians with few or no official links to Roche, occurred once extensive experiments with multiple species suggested toxicity risks were low. Randall and his associates conducted teratogenicity studies in the laboratory, but in light of the thalidomide crisis it is fascinating to note that women were not excluded from early trials. Researchers commonly noted what portion of their subject pool was female, but rarely separated out results by gender. The investigators excluded women from clinical trials only with studies carried out in all-male hospital wards.

Pharmacologic testing suggested Valium had an activity profile similar to meprobamates, phenobarbital, and chlorpromazine, as well as the expected similarities to its sister compound, Librium. Physicians mainly prescribed these drugs as tranquilizers. They reduced tension and dampened reaction to stress, they sedated mildly, and could battle insomnia through stress reduction, or more direct action on the physical brain. It made sense, therefore, to test Valium in clinical settings where meprobamate, phenobarbital, chlorpromazine, and Librium were in use.⁶⁹⁵ Physicians already prescribed existing tranquilizers for “practically every psychiatric condition with varying success.”⁶⁹⁶

⁶⁹⁵ It was well-established by this point that meprobamate was marketable as an antianxiety agent. H. Bauer, “Meprobamate in Neurological Disturbances,” in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 560.

⁶⁹⁶ Paul H. Hoch, “Problems Arising from the Generalized Use of Psychotropic

Although there are only thirteen clinical trials published before 1963 relating to Valium (also identified at the time as diazepam or Ro 5-2807), they illustrate remarkable similarities of approach and expectations.⁶⁹⁷ The authors treat Valium as both a muscle relaxant and a compound reducing psychic tension. Physicians Ruth Crossfield and Manuel

Drugs,” in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier Publishing Company, 1961), 9-16, 9.

⁶⁹⁷ The pre-1963 articles are: J. Collard and J. Kerf, “Le Traitement De L’Anxiété Néurotique par le Valium,” *Encéphale* 51 (November-December 1962): 571-73; R. J. Kerry and F. A. Jenner, “A Double Blind Crossover Comparison of Diazepam (Valium, Ro 5-2807) with Chlordiazepoxide (Librium) in the Treatment of Neurotic Anxiety,” *Psychopharmacologia* 3 (1962): 302-06; J. Whitney Kelley, “Management of Psychiatric Disorders with Diazepam,” *Clinical Medicine* 69, no.8 (1962): 1789-1802; Ruth M. Crossfield and Manuel E. Soria, “Parenteral Use of Diazepam,” *Diseases of the Nervous System* 23 (November 1962): 647-48; Eugene J. Chesrow, Sherman E. Kaplitz, John T. Breme, Joseph Musci and Raoul Sabatini, “Use of a New Benzodiazepine Derivative (Valium) in Chronically Ill and Disturbed Patients,” *Journal of the American Geriatrics Society* 10, no.8 (1962): 667-70; M. L. Towler, B. D. Beall and J. B. King, “Drug Effects on the Electroencephalographic Pattern, with Specific Consideration of Diazepam,” *Southern Medical Journal* 55 (August 1962): 832-38; Carl Ludvig Laane, “Erfaringer Fra Poliklinsk Behandling Med Librium og Librium analog, Valium, Spesielt Ved Svære Angst- og Tvangsneuroser,” *Tidsskrift For Den Norske Lægeforening; Tidsskrift For Praktisk Medicin Ny Række* 82 (1 August 1962): 960-62; J. Collard, “Clinical Experience with Diazepam in Neuroses,” *Journal of Neuropsychiatry* 3, suppl.1 (August 1962): S157-S158; M. I. Vilkin and J. B. Lomas, “Clinical Experience with Diazepam in General Psychiatric Practice,” *Journal of Neuropsychiatry* 3, suppl.1 (August 1962): S139-S144; M. L. Towler, “The Clinical Use of Diazepam in Anxiety States and Depressions,” *Journal of Neuropsychiatry* 3, suppl. 1 (August 1962): S68-S72; P. E. Feldman, “An Analysis of the Efficacy of Diazepam,” *Journal of Neuropsychiatry* 3, suppl 1 (August 1962): S62-S67; S. Merlis, W. J. Turner, and W. Krumholz, “A Double-Blind Comparison of Diazepam, Chlordiazepoxide and Chlorpromazine in Psychotic Patients,” *Journal of Neuropsychiatry* 3, suppl. 1 (August 1962): S133-S138; Lowell O. Randall, G. A. Heise, W. Shallek, R. E. Bagdon, R. Banziger, A. Boris, R. A. Moe and W. B. Abrams, “Pharmacological and Clinical Studies on Valium™ a New Psychotherapeutic Agent of the Benzodiazepine Class,” *Current Therapeutic Research* 3 (September 1961): 405-25.

Soria explained how the apparent complexity of mental illnesses provided opportunity for treating a specific symptom, which in turn could affect a wide variety of syndromes. Textbook explanations for symptoms of mental illness varied widely, these physicians argued, although “Their dynamics,... are well known – namely, that a vicious cycle of anxiety-guilt-depression (sometimes with aggression) is usually to be found.”⁶⁹⁸ J. Whitney Kelley, a physician publishing in the journal *Clinical Medicine*, prefaced discussion of his research with a brief description of psychopharmaceuticals recently introduced. “Although not curative,” he explained, “these drugs have been instrumental in reducing the symptoms of psychotic and psychoneurotic disorders[.]”⁶⁹⁹ Many of the authors had previous experience using chlordiazepoxide (Librium), and expected diazepam to behave similarly.⁷⁰⁰ Symptoms occupying their interest were reduction of anxiety and tension, nervous agitation, and sedation.

One possible theoretical framework for these trials is what Max Pollack and his colleagues in the Department of Experimental Psychiatry at Long Island’s Hillside Hospital termed the “neurophysiologic-adaptive hypothesis.”⁷⁰¹ This approach examined behavioral

⁶⁹⁸ Crossfield and Soria, Parenteral Use of Diazepam, 647-48.

⁶⁹⁹ Kelley, Management of Psychiatric Disorders, 1789.

⁷⁰⁰ Collard and Kerf, Traitment De L’Anxiété Néurotique, passim; Walter Pöldinger, “Klinische Erfahrungen mit dem Librium-Analagon Ro 5-2807 (Valium) bei Psychotischen Zustandsbildern,” *Zweite Wissenschaftliche Sitzung* (May 19-20, 1962): 510-14; Chesrow et al., Use of a New Benzodiazepine Derivative, 667-70.

⁷⁰¹ Max Pollack, Eric Karp, George Krauthamer, Donald F. Klein and Max Fink, “Neuropsychologic Response Patterns of Some Psychotropic Drugs,” in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium*

change resulting from both interaction of chemicals with the brain and an aspect of mind, personality. In clinical trials of Valium, the test subjects were not ‘normal’ people, investigators selected them based on existing medical problems. Perhaps this approach helped remove some personality variables from the trials; those in test and control groups already had personalities rendering them prone to mental or physical illness. Another explanation is simply that the drug was developed for treating ill individuals, and clinicians therefore saw no rationale for testing Valium’s effects on a ‘normal’ population.

The sweep of articles published in 1962 and 1963 show a breadth of interest within the academically-oriented medical community in use of pharmaceuticals for treatment of minor psychiatric illnesses. Although small in number, these research publications brought this prospective new drug to the attention of physicians in the United States, Belgium, Norway, Argentina, Mexico, England, and Germany.⁷⁰² Passing reference to other studies

Internationale Neuro-Psychopharmacologicum (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 381-84.

⁷⁰² For example of the international span consider the place of publication of the following: Norway, Carl Ludvig Laane, Erfaringer Fra Poliklinsk Behandling, 960-62; Argentina, Alfredo Buzzi, Jose Cibera, and Emma Apolinario, “Valoracion Clinica E. Instrumental de un Nuevo Relajante Muscular: El Ro 5-2807,” *La Prensa M’edica Argentina* 49 (March 16, 1962): 625-29; France, Collard and Kerf, Traitment De L’Anxiéte Néurotique, 571-73; Mexico, J. R. Monroy, “Resultados Con el Uso Clinico Del Ro 5-2807,” *Archivos Del Instituto de Cardiologia De Mexico* 32 (September-October 1962): 553-58; Germany, Pöldinger, Klinische Erfahrungen mit dem Librium-Analagon Ro 5-2807 (Valium), 510-14; Italy, L. Molinego, “Modifcazioni Provocate da Alcuni Depressori del SNC nel Ratto Valutate per Mezzo Dell’Inhibizione Operativa,” *Archivo Italiano di Scienze Farmacologiche* 13 (July 1963): 224-27; Canada, Lucien LaRue and Jean-Yves Gosselin, “L’Apport du Diazepam (Valium) à la Psychiatrie Moderne,” *Laval Médical* 34 (December 1963): 1208-20; and Belgium, J. Van Herck, “Essai D’Évaluation Clinique D’Un Nouvel Anxiolytique du Groupe Des Benzodiazepines,” *Bruxelles-Médical: Revue Belge Des Sciences Médico-Chirurgicales*

suggest a large number of small investigations and evaluations, before or during 1962, remained unpublished; Crossfield and Soria mention “preliminary investigations and pilot clinical evaluations” involving “183 investigators” and “almost 3000 patients with different psychiatric disorders.”⁷⁰³

These early articles generally focused on neuropsychiatry and show atheoretical approaches to psychiatry.⁷⁰⁴ The test populations were rarely uniform, more often consisting of those with “both psychiatric and neuropsychiatric disorders[.]”⁷⁰⁵ Even when an aspect of theory testing appeared, as with Walter Pöldinger’s report on effects in psychotic patients, it focused more on differentiating between types of tranquilizers rather than attempting to understand how any of these compounds interacted with the brain or caused specific effects in the body.⁷⁰⁶

43, no.37 (September 15, 1963): 933-46.

⁷⁰³ Crossfield and Soria, Parenteral Use of Diazepam, 648.

⁷⁰⁴ An exception are the two articles continuing laboratory pharmacological work. Towler, Beall and King, Drug Effects on the Electroencephalographic Pattern, 832-38; William J. Kinnard, Mario D. G. Aceto, and Joseph P. Buckley, “The Effects of Certain Agents on the Conditioned Emotional Response Behavior Pattern of the Albino Rat,” *Psychopharmacologia* 3 (1962): 227-30.

⁷⁰⁵ Kelley, Management of Psychiatric Disorders, 1791; Walter Pöldinger’s study also included patients with a wide variety of diagnoses. Pöldinger, Klinische Erfahrungen mit dem Librium-Analagon Ro 5-2807 (Valium), 510-14.

⁷⁰⁶ Pöldinger was interested in classification of psychiatric drugs. Part of the reason for his interest in the behavior of Librium and Valium was because the third World Congress of Psychiatry, held in Montréal in 1961, included debates whether the major tranquilizers should be reclassified as neuroleptics, with meprobamate representing tranquilizers, and the role of Librium, at that time the only marketed benzodiazepine, positioned either between the two, or even more differentiated from

Most early work attempted to establish appropriate diagnostic categories for prescribing Valium. The 1962 studies focused on neuropsychiatry, both inside and outside institutions. Articles encompassed a broad spectrum from psychoses including schizophrenia, to neuroses, personality disorders, and neuropsychiatric disorders associated with senility. As a group, the investigators concluded Valium effectively treated anxiety and tension, reduced agitation, and had relatively mild side effects.

Research publications based on clinical studies of Valium, published soon after Roche obtained a New Drug Application in December 1963, illustrate how Valium's utility expanded out from a starting point as treatment for neurotic anxiety and towards popular promotion as a substance useful in a broader variety of psychosomatic conditions. Researchers tested the potential application of Valium's antispasmodic properties to preventing miscarriage or premature labor⁷⁰⁷ and as an anticonvulsant.⁷⁰⁸ They examined its utility as an adjunct for nonpharmaceutical treatments.⁷⁰⁹ Researchers also noted the

neuroleptics. Pöldinger, *Klinische Erfahrungen mit dem Librium-Analogen Ro 5-2807 (Valium)*, 510-14.

⁷⁰⁷ K. W. Schultze and V. Patt, "Zur Behandlung des Abortus Imminens mit Valium, Einem Benzodiazepinpräparate," *Geburtshilfe und Frauenheilkunde* 23 (November 1963): 1003-09.

⁷⁰⁸ Joseph T. Brock and Mark Dyken, "The Anticonvulsant Activity of Chlordiazepoxide and Ro 5-2807," *Neurology* 13, no.1 (1963): 59-65; Ayerbe, *Ensayo Terepéutico Con El Ro 5-2807*, 899-900.

⁷⁰⁹ Don L. Winfield, "The Use of Diazepam in Clinical Electroencephalography," *Diseases of the Nervous System* 24 (September 1963): 542-47; use in psychotherapy was assessed in Harry H. Farb, "Intravenous Diazepam as a Pre-Interview Medication (A Clinical Note)," *Diseases of the Nervous System*, 24 (April 1963): 233-36.

relevance of this new drug to nonpsychiatrists, the class of physicians who would later write the vast majority of Valium prescriptions.⁷¹⁰

The clinical trials reported in the early 1960s typify some of the most problematic aspects of testing psychiatric drugs. Practitioners planning clinical trials chose between two types of test populations, inpatient or outpatient. Each group had advantages and disadvantages. In the larger picture, multiple trials (some involving inpatients, others outpatients) provided greater knowledge of Valium's potential use in psychiatry.

Inpatients resided day and night in either a psychiatric ward, an institution entirely devoted to psychiatric patients, or a general hospital. One benefit of tests involving inpatients was the capacity to control outside issues; physicians could accurately study and take into account concomitant drug use. Patients were more likely to remain in the study group, whether because they had few viable alternatives or by virtue of a climate conditioning patients to obey staff rules and regulations. Another benefit to using inpatient populations was that most suffered from long-term illnesses. The paths of their illnesses were predictable, and remission unlikely. Because many of the ill-defined psychiatric conditions were often self-limiting, investigators faced problems in separating improved condition due to drug effects from improvements resulting from the natural course of illness.

⁷¹⁰ Henry A. Cromwell, "Controlled Evaluation of Psychotherapeutic Drug in Internal Medicine," *Clinical Medicine* (December 1963): 2239-44; Robert Rathbone, "The Role of a Therapeutic Drug in Internal Medicine," *Medical Times* 91 (December 1963): 1186-91.

By 1957, ambulatory treatment of neuroses was the norm.⁷¹¹ Most potential Valium users, including those with mental health or psychosomatic problems, saw general practitioners in their offices. Doctors treating these outpatients (ambulatory patients) were Roche's target market. But a trial population in this setting was less controllable as the patient "decides how long the therapy is continued."⁷¹² The likelihood these patients considered themselves in need of treatment by tranquilizers differed greatly depending on diagnosis; those who interpreted their symptoms as somatic problems were unlikely to "accept the idea of a psychogenic origin of their disease,"⁷¹³ and therefore likely resistant to treatment with Valium.

The disadvantages of using an inpatient population for clinical trials were twofold: the spectrum of diagnoses seen was less similar to that of Valium's expected target market, and this spectrum generally involved more severe mental illnesses. The major pharmacologic breakthrough in treatment of severe mental illness, mostly seen in psychiatric institutions whose role had degenerated largely into custodial care, was discovery, development, and use of the major tranquilizers. The already known profile of Valium suggested its usefulness in less severe cases, because among its benefits was a relatively mild

⁷¹¹ Armo Hormia, "The Patient's Subjective Need of Treatment as a Cause of Success or Failure in the Ambulatory Treatment With Psychotropic Drugs," in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 251-54, 252.

⁷¹² Hormia, *The Patient's Subjective Need of Treatment*, 251.

⁷¹³ Hormia, *The Patient's Subjective Need of Treatment*, 252.

side effect profile which allowed use in clients who did not see physicians on a day-to-day basis.

The second major disadvantage to studying outpatient populations was that the illnesses seen were less severe than those seen within psychiatric care institutions. Outpatients had the symptoms Roche was most interested in, but it was tougher for researchers to show change in moderate symptoms. One consequence of the post-World War II conceptualization of mental health and mental illness as a spectrum, was an implicit assumption that drugs mitigating symptoms in the severely mentally ill provided proof of efficacy in less severe mental illnesses. If there was a spectrum of mental illness, with untreated neuroses potentially becoming more chronic psychoses, any pharmaceutical capable of mitigating severe conditions would also have benefit for milder cases. Valium's efficacy, in theory, would be less noticeable in outpatient populations; although the eventual users would be outpatients, proving Valium's usefulness was easier using severely mentally ill patients.

Choosing use of an outpatient population in clinical trials reflected similarly weighing advantages and disadvantages. Among the advantages, outpatients were more likely similar to Valium's ultimate users. Patients seen in private practice might have long-term illnesses, but doctors saw them intermittently; prescription drugs needed a moderate and mild side effect profile. Whether general physicians, neuropsychiatrists, or those with a greater deal of specialization in psychiatry – somatic or psyche based – the clientele was more likely to include a large variety of patients suffering from reactive neuroses, neurotic

personalities, situational stresses, insomnia, agitation or obsessional behavior. Underlying these diagnoses, which physicians usually based on assumptions of causal factors, were certain common symptoms thought highly suitable for treatment with Valium: physical or mental tension, psychic stresses causing insomnia or agitation, and general anxiety.

The disadvantages of using an outpatient population, included having less control over drug taking behavior. Published reports of clinical trials among outpatients suggest that when Valium did not have an expected effect, physicians began investigating concomitant drug use. Outpatients could easily hide alcoholism, or concurrent use of other drugs without the physicians' knowledge. Assessing Valium's side effect profile was more problematic when using a population who, when experiencing disturbing side effects, could easily drop out of the pool of test subjects, perhaps seeing little personal advantage in the substance, and possibly even switching to another physician.

Today, double-blind placebo trials are an accepted ideal. In the early 1960s, however, the medical profession was divided on the benefits of this trial design type. Use of double-blind placebo trials for psychopharmaceuticals was rare.⁷¹⁴ Investigators used this research design for investigations into which of two or more drugs performed better. In the 1950s and early 1960s medical professionals did not consider double-blind placebo trials the gold standard for objective proof of the drug's efficacy; many physicians considered them especially unsuitable for psychiatric, and psychosomatic illness-affecting drugs. In these

⁷¹⁴ The small group of these trials include Merlis, Turner, and Krumholz, Double-Blind Comparison of Diazepam, Chlordiazepoxide and Chlorpromazine, S133-S138, and Kerry and Jenner, Double Blind Crossover Comparison, 302-06.

cases many of the conditions were self-limiting; therefore, patients taking placebos were likely to respond beneficially in large numbers simply because of the nature of their illnesses. Recent research suggested some people, possibly with characteristic personality types, were prone to respond to any substance, including placebos.⁷¹⁵ The role of doctor-patient interaction, highlighted by well-established techniques such as psychoanalysis, psychotherapy, and group therapy, suggested expectations of medical personnel who knew or guessed which drug was active, or patients discussing experiences among themselves, biased and altered placebo based trials. An additional problem was that many patients in studies had experience with a broad variety of psychopharmaceuticals. This experience, or knowledge gleaned from others, meant patients often knew the side effect profiles of existing tranquilizers, and therefore could distinguish inactive placebos. Patients anticipated certain side effects and they likely expected any substance which did not cause problems such as mental sedation, inability to sleep, nausea, changes in blood pressure, or other common side effects, to be a placebo. Matching the shape, color, smell, taste, or size of pills was far easier to accomplish than finding a placebo with a similar side effect profile. Because of these concerns, investigators mainly used double-blind placebo trials only for studies comparing the effects of more than one active substance as well as the placebo.

⁷¹⁵ Gerald L. Klerman, "Discussion Fourth Symposium," in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 319-22, 320; placebos were used sporadically in early clinical trials of Valium. For an example see Henry P. Hare, "Comparison of Diazepam, Chlorpromazine and A Placebo in Psychiatric Practice," *Journal of New Drugs* 41(July-August 1963): 233-40.

Reporting trial results was far more complex for Valium than in cases where a specific drug attacked an identifiable specific pathogen, as with antibiotics. The illness typologies used in psychiatry were becoming standardized by the 1960s, but continued including categories based on unobservable presumed causes, overlapping groups of symptoms, and no absolute method of consistently defining the extent to which a drug affected specific symptoms. Overall, cleanly comparative data was impossible, given the “lack of a solidly established methodology of test procedures for the observation and measurement of action of psychotropic drugs on the human organism.”⁷¹⁶ There was no expectation that tranquilizers cured mental illness; they mitigated symptoms which in turn might promote cure. Later, physicians interested in psychosomatics might interpret Valium as a cure, but the way psychiatrists defined mild to moderate mental illnesses, produced conditions in which it was hard to consider any patient permanently cured; positive mental health was a goal, something constantly at risk.

In general, the clinical trials on Valium reported results separately for each diagnosis, and assessed efficacy on how completely it reduced or removed symptoms. The boundaries between categories such as mild or moderate improvement were essentially subjective, even when based on a combination of observation by one or more trained medical professionals, use of self-assessments by patients or their relatives, and use of standardized inventories

⁷¹⁶ H. E. Lehmann and D. A. Knight, “Measurement of Changes in Human Behaviour Under the Effects of Psychotropic Drugs,” in *Neuro-Psychopharmacology: Proceedings of the Second Meeting of the Collegium Internationale Neuro-Psychopharmacologicum* (Basle, Switzerland, July 1960), ed. E. Rothlin (New York: Elsevier, 1961), 291-303, 292.

such as the MMPI (the Minnesota Multiphasic Personality Inventory). Journal articles suggest many researchers believed structured psychological tests offered the most reliable results possible.⁷¹⁷

In 1963 and 1964 the majority of published reports of clinical trials with Valium continued to focus on mental health and illness, but construed psychiatric illnesses more broadly. They began including study of psychoneurotic personalities prone to somaticize anxiety, and psychosomatic disorders.⁷¹⁸ By reducing tension, patients stopped obsessing

⁷¹⁷ Lehmann and Knight, *Measurement of Changes*, 292.

⁷¹⁸ Examples of this focus is evident in the following reports: LaRue and Gosselin, *L'Apport du Diazepam (Valium) à la Psychiatrie Moderne*, " 1208-20; Molinego, *Modificazioni Provocate da Alcuni Depressori*, 224-27; V. E. Gscherlacht, "Ambulante Behandlung Psychisch Kranker Mit Dem Neuen Psychopharmakon Valium (Roche)," *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie* 92 (1963): 193-203; William B. Cline, Jr., "Treatment of Emotional Disorders with Amobarbital, Diazepam, and Psychotherapy," *Texas State Journal of Medicine* 59 (June 1963): 512-17; Armand DiFrancesco, "Diazepam, A New Tranquilizer," *American Journal of Psychiatry* (April 1963): 989-90; George A. Constant and Frank A. Gruver, Jr., "Preliminary Evaluation of Diazepam in Psychiatric Disorders," *Psychosomatics* 4 (March-April 1963): 80-84; Antonio M. Ayerbe, "Ensayo Terapéutico Con el Ro 5-2807 en Clínica Psiquiátrica: Nota Preliminar," *La Semana Me'Dica* 122 (9 May 1963): 899-900; Einar Geert-Jørgensen, "Treatment of Anxiety Neuroses and Psychosomatic Syndromes by a New Librium-Metabolite: Valium," *Acta Psychiatrica Scandinavica* 39, suppl. 169 (1963): 218-22; Georges Boittelle, Claudine Boittelle-Lentulo, Jeanine Cophignon, Gérard Blotnikas and Jacques Thomas, "Indications du Ro. 5-2807 Dans les États D'Excitation et D'Anxiété," *Annales Me'dico Psychologiques* 2 (June 1963): 83-86; W. Meusert, "Erfahrungen mit einem neuen Psychotropen Präparat Aus Der Librium-Reihe (Ro 5-2807- Valium)," *Medizinische Welt* 34 (24 August 1963): 1680-83; Harry F. Darling, "A Comparative Study of Diazepam and Chlordiazepoxide in Psychoneurotic Patients," *Diseases of the Nervous System* 24 (August 1963): 501-03; Benjamin Blackman, "The Adjunctive Role of Diazepam in the Treatment of Depression," *Clinical Medicine* (August 1963): 1495-1500; Irving Hirshleifer and William Kroger, "Benzodiazepines in the Differentiation and Treatment of Anxieties," *Clinical Medicine* (September 1963): 1673-78; Leo E. Hollister, J. L. Bennett, Isham Kimbell, Charles Savage and John E. Overall, "Diazepam in Newly Admitted

about their symptoms.⁷¹⁹ In theory, Valium reduced adrenal feedback interfering with, prolonging, or producing psychosomatic illnesses. Increasingly, these publications began to show interest in use of Valium to treat, or as an adjunctive treatment, for psychosomatic illness. Actions earlier identified as side effects interested more and more researchers, who looked at how Roche's Valium might be more widely useful. By late 1963, the core activity profile of Valium was settled; it reduced mental and physical agitation, had mild if any sedation effects, and reduced both mental and muscle tension. Yet clinical research continued expanding the sweep of conditions Valium was suitable to treat.

Conclusion

The breadth of laboratory tests and clinical trials published or started before Roche placed Valium on the U.S. market is remarkable, not only as a sign of the interrelated complexity of symptoms and conditions for which doctors prescribed the drug, but also as a touch point for examining later changes in drug testing. In the 1950s and early 1960s it was possible to bring drugs onto the American market for symptomatic treatment of nebulous

Schizophrenics," *Diseases of the Nervous System* 24 (December 1963): 746-50; Van Herck, *Essai D'Évaluation Clinique D'Un Nouvel Anxiolytique*, 933-46; J. Collard and J. Kerf, "Un Nouvel Anxiolytique: Le Ro 5-2807 ou Diazepam," *Acta Neurologica Belgica* 63 (December 1963): 1004-10; Cromwell, *Controlled Evaluation of Psychotherapeutic Drug*, 2239-44; Hare, *Comparison of Diazepam, Chlorpromazine and A Placebo*, 233-40; and Julian Love, "Diazepam in Treatment of Emotional Disorders," *Diseases of the Nervous System* 24 (November 1963): 674-77.

⁷¹⁹ F. J. Ayd, Jr. "A Critique of Tranquilizing Drugs," in *Psychotropic Drugs*, eds. S. Garattini and V. Ghetti (New York: Elsevier Publishing Company, 1957), 548-55, 549.

conditions, such as neuroses, and to market compounds variously termed tranquilizers, minor tranquilizers, antineurotics, or ataractics. They could treat motivations, symptoms, clusters of reactions. By 1980, the therapeutic landscape differed dramatically; pharmaceutical firms needed to prove a drug efficacious for a specific condition, and strong formal and informal guidelines shaped the types of tests and scale of populations used.

Following the thalidomide scare, legislators in Congress were able to push through the Kefauver-Harris amendments, legislation that would eventually dramatically alter the role of the FDA in drug testing, approval, and monitoring. Although thalidomide never made it past the experimental stage in the United States – theoretically, doctors only prescribed it in the United States as an investigational drug – changes went far beyond improving controls over the use of investigational drugs. Manufacturers needed to perform premarket testing to prove the usefulness of pharmaceuticals, a caveat of the legislation which effectively required drugs be proven useful for symptoms and conditions with more narrow and measurable definitions. Once a pharmaceutical manufacturer submitted a New Drug Application (NDA) and test results, the FDA had to act to permit marketing. Previously, unless the FDA denied the application, in 180 days the compound had been automatically approved for sale. The FDA could pull drugs from the market more readily, although threat of litigation promoted hesitance to use this option. Increasingly wary researchers shied away from using ‘possibly pregnant’ women in their clinical investigation of new drugs, especially after 1974, when the Supreme Court declared the distinction

between pregnant and nonpregnant persons nondiscriminatory.⁷²⁰

The thalidomide crisis highlighted awareness of the potential effects of pharmaceuticals on embryonic development. Reminders of the physical differences between men and women brought unintended consequences; for the remainder of the twentieth-century drug testers excluded women from most drug trials. They argued women's hormonal cycles brought too many variables into play, as well as that women were essentially the same as men, and therefore they were represented sufficiently, when their gender was not represented at all. The category of 'possibly pregnant' effectively excluded all women between the ages of 14 and 60 from clinical testing of pharmaceuticals. The pre-Kefauver-Harris days, when investigators tested Valium for antineurotic potential, would be hard to replicate after 1977;⁷²¹ most outpatients treated by psychiatrists for neuroses were women, who were over-represented in clinical trials of Valium.⁷²²

⁷²⁰ *Geduldig v. Aiello*, 417 U.S. 484 (1974).

⁷²¹ In this year the F.D.A. published *Guidelines for the Clinical Evaluation of Antianxiety Drugs* (Washington, D.C.: U.S. Government Printing Office, 1977). Based on the now typical series of clinical trials grouped in three stages, the guidelines stated it unethical to include "women of childbearing potential" (3) in Stage 1 trials, which were those establishing effects of the pharmaceutical in humans and thereby the potential uses of the substance.

⁷²² 129 women and 54 men were in the study group reported in Constant and Gruver, Preliminary Evaluation of Diazepam, 80-84; 74 women and 32 men were included in Hirshleifer and Kroger, Benzodiazepines in the Differentiation and Treatment of Anxieties, 1673-78; 21 women and 11 men in Collard and Kerf, Un Nouvel Anxiolytique, 1004-10; 32 women and 17 men in Hare, comparison of Diazepam, Chlorpromazine and A Placebo, 233-40; 46 women and 26 men in Love, Diazepam in Treatment of Emotional Disorders, 674-77; overall a relatively steady proportion of two women per man is apparent in studies of psychiatric disorders when schizophrenia is not a dominant diagnosis, and neuroses are the major disorder group

Valium was studied, tested, and introduced during a nexus of change. Drug regulations were in flux. The first generation of psychopharmaceuticals – major tranquilizers, antihistaminergic anxiolytics, and MAOI antidepressants – were replaced by a second generation which targeted more narrow groups of symptoms and attempted to retain therapeutic efficacy with fewer side effects. Concepts of mental health were also in flux, moving from a focus on mitigating internal response to the external environment, towards selective modification of central nervous system activity through enzymes, and increasingly based on sites of transmission and reception of chemical compounds within the brain. Pharmaceutical regulation was shifting from an era of trust in the personal observation of physicians, to formalized rules limiting what companies could market and how.

Valium slipped into the market during this period of flux. Roche tested and marketed it as a minor tranquilizer, a drug with more selective action and fewer side effects than earlier compounds. Doctors studied and used it to mitigate the body's reaction to anxiety, overstimulation, and perception of pain. They used it to treat psychosomatic conditions and the feedback loop of anxiety and adrenalin. Physicians also prescribed Valium as a general CNS depressant, a minor tranquilizer with more selective effects on the brain and therefore fewer side effects. Hoffmann-La Roche started marketing Valium just after passage of the Kefauver-Harris amendments. At the time, the FDA did not have new regulations in place; it was trying to cope with the backlog of drugs already on the market, figuring out ways to assess thousands of existing drugs for their efficacy. Roche could present Valium as a

under study.

compound closely related to Librium, and therefore effectively an existing drug. It was an in-between drug, not existing on the market before 1962, nor being a truly new drug undergoing the rigors of a new FDA.

CHAPTER 7. THE SOMATIC MASK: MARKETING VALIUM™

In December 1963, Hoffman-La Roche applied to the Food and Drug Administration for acceptance of their New Drug Application (NDA).⁷²³ Soon after, Roche placed Valium on the market. So by early 1964 Americans, and more so their doctors, became aware of a new tranquilizer, called Valium. The NDA occurred before the Kefauver-Harris Amendments, passed earlier in 1962, came into effect. Therefore, technically, all Roche had to prove was the new compound was safe. Realistically, more extensive tests showing usefulness were still necessary. By 1963, clinical testing in North America and Europe prepared Valium for the market. Tests suggested use for psychiatric disorders, especially neuroses, as well as muscle related and psychosomatic conditions. Roche developed more extensive evidence of Valium's utility through clinical trials in humans. This was essential to prove it nontoxic. As long as the evidence Roche gathered explained Valium's use within the general profile of a tranquilizer, they could use this new information to promote the drug without triggering FDA efforts to prevent wrongful labeling in doctor-oriented marketing.⁷²⁴

⁷²³ "Sternbach Inserts (Originals)," Oral History Files, Beckman Center for the History of Chemistry, file no.0043, Sternbach, Leo H. Chemical Heritage Foundation, Philadelphia, PA.

⁷²⁴ Before the 1962 amendments came into effect, the Federal Trade Commission controlled advertising of drugs and the FDA controlled labeling. Information available solely to physicians fell into a grey area based on the doctors forming an educated audience, presumably less susceptible to marketers' trickery. Pharmaceutical companies trod a thin line when they presented educational and semi-educational information to doctors. They could run afoul of rules for labeling or advertising. In practice, the legal system made it nearly impossible to efficiently

Valium rapidly rose in use, becoming the most widely prescribed brand-name pharmaceutical in history. Its success in the market grew from a combination of its benefits over other drugs and skillful marketing. Roche promoted Valium use for psychosomatic conditions, psychological components introducing problems with treatment of chiefly somatic disorders, as well as conditions already associated with other tranquilizers. The Roche campaign also skillfully played on doctors' concerns about the quality of evidence provided by pharmaceutical companies, and whether widespread prescription of tranquilizers fit with their beliefs of what it meant to be a doctor.

It is important to consider that few of Valium's major competitors were falling out of use because of existing and recognized problems. Valium did not step into an empty market; doctors prescribed similar drugs in large numbers, and known profiles of action suggested how these drugs would be used and what side effects to expect. Presumably the Roche marketing department focused its concerns on the obvious competition: chlorpromazine and its derivatives, meprobamates, barbiturates, and chlordiazepoxide (Librium).

Tranquilizer Advertising

Whether doctors should prescribe major tranquilizers – chlorpromazine (Thorazine), and to a smaller extent reserpine derivatives – for treating mild and moderate neuroses was already debated in medical literature. Smith, Kline & French laboratories (SKF) marketed Thorazine in the 1950s and 1960s, as a substance suited for hospitalized patients once

prosecute companies.

returned to society. A 1964 advertisement, in the *Journal of the American Medical Association* shows the back of a man fishing, the epitome of calmness of action and environment. Presumably SKF intended to illustrate the state of tranquility experienced by patients on Thorazine. The text focuses on marketing to family physicians who “must often assume responsibility for the discharged mental patient.”⁷²⁵ The benefits of Thorazine, its makers explain, are experienced by the patient, the physician, and his family. Turning the sedating properties into a benefit, Smith, Kline & French argue the drug “helps prevent relapses by insulating him [the patient] from the impact of stressful experiences.”⁷²⁶ Physicians concerned about continuing the high dosages of Thorazine used in mental institutions could be tempted, the advertisement warns, to reduce dosages. Reassuring readers that high dosages for long periods of time were justified and appropriate treatment, the advertisement suggests side effects are less of a concern to the general physician than practitioners coping with psychotic inpatients. The makers do not argue Thorazine has a mild side effect profile. Instead, the advertisement focuses attention on the idea that hospital doctors would notice serious side effects early in a patient’s treatment. Therefore, family physicians treating outpatients could use high dosages in long-term therapy with little risk. “Continuing therapy is almost always well tolerated, and it is central to most patients continued well-being[,]” assures the text.⁷²⁷

⁷²⁵ Smith, Kline & French, “The Discharged Mental Patient...and Thorazine,” *Journal of the American Medical Association* 187, no. 1 (January 1964): 18.

⁷²⁶ Smith, Kline & French, The Discharged Mental Patient...and Thorazine, 18.

⁷²⁷ Smith, Kline & French, The Discharged Mental Patient...and Thorazine 18.

Although the Thorazine advertisement suggests it is a safe and needed tranquilizer, the approach accepts that doctors are unlikely to prescribe it for the run-of-the-mill neurotic without prodding. Doctors were well aware of side effects and the association of Thorazine with institutional treatment, hence the ad needed to reassure physicians that dangerous side effects would already have been experienced during hospitalization. The major tranquilizers were mentally sedating and tended to induce sleep, acting as hypnotics. They insulated individuals from stressful experiences. The side effects, life threatening in a small number of patients, frequently often involved drops in blood pressure; they required supervision by a physician for at least the early weeks during which a patient began taking the drug, and necessitated frequent returns to the doctor by any outpatient. This led to many physicians assuming major tranquilizers were inappropriate for treating the vast majority of American neurotics, when an important goal of treatment was to prevent hospitalization. Furthermore, because medical literature often described neuroses as less severe versions of the psychoses, it was hard to sell the idea that an individual needed a powerful, and potentially dangerous, medicine. Smith, Kline & French still tried positioning chlorpromazine (Thorazine) for this use.

After World War II introduced broader concepts of mental health, a spectrum between absolute mental health and complete mental illness, the major tranquilizers were suited to those falling close to the extreme of mental illness. The majority of Americans now thought to need assistance in promoting mental health, preventing mental ill-health, or treating neuroses and neurotic personalities, were theoretically better served by a mild form

of tranquilizer, less sedating to the mind, not inducing sleep inappropriately, and safe for everyday use in outpatients because it had an excellent safety profile. The new interpretation of mental health and mental illness expanded the market for tranquilizers, but required greater effort on part of pharmaceutical manufacturers in establishing an apt, and expansive, niche for their product. Major tranquilizers suited inpatient use and continuing treatment for schizophrenia and major thinking disorders. Conceptually, small doses of a major tranquilizer appeared rational treatment for mild mental illnesses, but pharmaceutical manufacturers faced growing competition from the new, 'minor' tranquilizers.

The more recently introduced meprobamates met some concerns about using major tranquilizers in the outpatient population and treatment of neuroses. They had a broader spectrum of action, fewer side effects, were better tolerated and safer than major tranquilizers. How Roche positioned and marketed Valium was in part their attempt to differentiate the benzodiazepines and meprobamates; to take part of the market share from the most successful antineurotic (minor tranquilizer) of the early 1960s, meprobamate. In the popular press, meprobamate marketed under the trade name, Miltown, was better known than the same molecule marketed as Equanil. By the mid-1960s, generic meprobamate and combination drugs also competed in the psychopharmaceutical marketplace.

Pharmaceutical manufacturers marketed meprobamate compounds for treatment of anxiety, emotional components of somatic illness, and psychosomatic illnesses; Roche promoted Valium for a similar spectrum of medical conditions. In the 1965 issues of *GP: General Practitioner*, Lederle Laboratories touted Pathibamate (combination tridihexyl

chloride and meprobamate) for treatment of “organic and functional disorders of the gastrointestinal tract, including ulcer – real or potential – especially when accompanied by anxiety, neurosis or tension.”⁷²⁸ Wallace Laboratories pushed Miltown “[f]or treatment of emotional factors in cardiovascular disease[.]”⁷²⁹ They referred to meprobamate as “The one tranquilizer that belongs in every practice[.]”⁷³⁰

Because of its name brand recognition as Miltown or Equanil, and widespread use by 1963, the meprobamates were important competitors to Valium. Having been on the market for years, doctors already prescribed these pills, they knew the benefits and dangers more thoroughly, simply because large numbers of people had used the compounds for years. Some writers questioned the addictiveness of meprobamates, but they were less addictive than the earlier alternative, barbiturates. Meprobamates produced drowsiness, but less dramatically than the major tranquilizers. Like Valium they improved regular sleep but had little impact on patients maintaining an active day.

Librium, although also sold by Hoffmann-La Roche, was competition to Valium. In published clinical trials, doctors regularly referred to Librium either as a parent compound to Valium, a sister compound, both closely related benzodiazepines, or as Valium as a derivative of Librium. This link to a molecule already on the market benefitted Roche;

⁷²⁸ Lederle Laboratories, “Ulcerogenic Index: High,” *GP; General Practitioner* 31, no. 1(1965): 67.

⁷²⁹ Wallace Laboratories, “For Treatment of Emotional Factors in Cardiovascular Disease,” *GP; General Practitioner* 31, no. 1 (1965): 214-15.

⁷³⁰ Wallace Laboratories, “For Treatment of Emotional Factors in Cardiovascular Disease,” *GP; General Practitioner* 31, no. 1 (1965): 214-15.

existing tests and extensive market use suggested to the FDA, physicians, and the patient population that Valium was also safe and useful. But similarities between Valium and Librium also necessitated Roche creating a marketing campaign differentiating the two compounds.

Roche's overall campaign focused on Valium having a broader spectrum of action than Librium and being more potent. They used less openly emotional advertising than for Librium. Roche played up the fact smaller quantities of Valium produced similar effects, but the quantities in question were small and it is likely patients interpreted Valium as a stronger drug than Librium because of differences in their delivery systems. Librium tablets were coated, Valium not. As a result patients experienced the effects of Valium more quickly, giving the impression of a stronger drug.

Unfortunately a common property among addictive drugs is also the ability to gain a sense of euphoria or relief quickly enough for an individual to make a strong association between consuming the drug and pleasure or relief. No matter how similar these compounds, Valium and Librium, were at a molecular level, Valium's delivery system endowed it with greater potential for psychological addiction. Yet, in 1963 when Roche introduced Valium to the market, its elder sister was at a stage of maturity when widespread use resulted in published reports of less common, but potentially dangerous, side effects.

By 1960, reports were already surfacing about side effects of Librium. In a letter to the editor, I. M. Ingham and Gerald C. Tilbury, of the Southern General Hospital in Glasgow, reported side effects in over half of their patients treated with Librium. Most were

drowsy, dizzy, listless, or otherwise bothered by side effects to the extent some patients stopped work. They note Librium was already commercially available and “widely advertised in terms of taming effect on wild animals and ... value in controlling phobic and obsessional symptoms in psychoneuroses although the published evidence for this is slight.”⁷³¹ The authors advised doctors be wary prescribing Librium and remain skeptical of its usefulness “until the results of controlled trials are available.”⁷³²

As Roche planned its marketing campaign for Valium, they tried to deal with the types of concerns doctors such as Ingham and Tilbury expressed. Roche marketed Valium based on images of good science, rational clinical medicine, controlled trials, objective evidence, and proven efficacy. The resulting advertisements may look insulting in how they portray patients, but Roche did not intend these advertisements for general public consumption. They placed them in medical magazines for physicians, who were usually male, affluent, and socially conservative. Roche tried to sell Valium as part of good science-based medicine. The written and visual aspects of these ads are part of an interaction between the pharmaceutical marketing company and a physician, without the patient as a central part of the equation.

One outstanding question is why Roche marketed Valium alongside Librium. The company sunk substantial monies into introducing and marketing Librium; why not build on success? If Valium offered a longer monopoly, why not drop Librium and focus on the

⁷³¹ “Side Effects of Librium,” Ingram, 1960, 766.

⁷³² “Side effects of Librium,” Ingram, 1960, 766.

newer drug? Why did Roche promote both substances? They chose to market both and it turned out well. By 1972, Valium was the most commonly prescribed brand-name drug, and Librium was the third or fourth. Obviously both pharmaceuticals could compete successfully for essentially the same market.

Advertising strategy differentiated the substances. In the 1960s and early 1970s, Librium marketing focused more strongly on treatment of psychiatric disorders and responses to environmental or social stress. Valium marketing mainly promoted its use in psychosomatic disorders, or somatic conditions where stress allegedly interfered with successful treatment. A major Valium marketing campaign, entitled the ‘Somatic Mask,’ will be discussed later in this chapter.

The barbiturates are less commonly recognized as competitor compounds, but their popularity declined as Valium’s rose, and they were prescribed for overlapping groups of symptoms. By 1963, medical journals treated barbiturate addiction as fact, but often treated it as an affliction of deficient personalities, affecting mainly those already prone to addiction. Assessing public awareness of barbiturates’ dangers is harder; newspaper and magazine articles made information on addiction and suicide available, but do not appear related to any major decrease in barbiturate prescription or refill rates.

Barbiturates had a marked effect as mental and physical relaxants. They relaxed muscles including the diaphragm, and therefore at least in large doses, created risk of unplanned death as the body became unaware or unable to breathe. Perhaps Roche could have used this problem to promote Valium’s benefits over the barbiturates, but it is not clear

to what extent the average doctor interpreted widespread barbiturate use as increasing suicide rates. As noted previously, people usually obtained barbiturates by doctor's prescription. They required doctor approval before buying refills. A wide variety of legal pharmaceuticals included small doses of barbiturates; some of the drug's risks declined alongside the quantities consumed in composite pharmaceutical products. Prescription and usage rates of barbiturates and barbiturate compounds remained high in the 1960s.

Rates of new and refill prescriptions suggest continuing widespread use of barbiturates as solitary compounds. In the mid-1960s, McNeil laboratories ran ads in *JAMA* (the *Journal of the American Medical Association*) for Butisol, a barbiturate compound which differed from the more widely used phenobarbital because "it does not tend to produce cumulative toxicity." The photograph used in the advertisement is typical of what we would expect Valium ads to be in the 1960s based on government hearings and publications of the 1970s and 1980s. Talking on the phone, hair in curlers, pictures of famous men attached to her wall, is a teenager obviously ignoring her mother. The daughter is not the only problem, the picture suggests, looming over her is a mother, shaking her finger and obviously telling the young woman how inappropriate is her behavior. An apron over her clothes, hair tied back with a scarf, mop in hand, mom is the one whose "nervous tension augments family problems[.]" Evidently, even in the mid-1960s, pharmaceutical corporations promoted barbiturates for treating women suffering from the stresses of everyday life, running a home, being a wife and mother, or balancing career and family. Even these doctors, concerned with the barbiturate intoxication associated with long-acting

compounds such as phenobarbital – itself the most prescribed generic drug until 1967 – had well marketed alternative barbiturates at their fingertips.⁷³³

That barbiturates sedated the mind or induced sleep when taken in larger quantities was less of a concern by 1960, because most barbiturate compounds incorporated only small doses of barbiturates, which made their suppression of autonomic functions less of a problem. As an example, Burroughs Wellcome & Company marketed Cardilate-P, a compound including phenobarbital, for treatment of angina. They justified inclusion of phenobarbital by arguing it “allays the anxiety and tension which often trigger anginal attacks.”⁷³⁴ McNeil Laboratories promoted a similar compound as Butiserpazide, described as a “combination of the smooth, not cumulative ‘daytime sedative’ *Butistol* butabarbital with established ‘background therapy’ of hypertension[.]” In this case, the graphic shows an angry looking middle-aged matron staring outward, evidently toward the physician who is taking her blood pressure. Her gaze appears both angry and apprehensive. Alongside the graphic is a caption “Normalize both her blood pressure and emotional state with BUTISERPAZIDE.”⁷³⁵

⁷³³ McNeil Laboratories, “When Nervous Tension Augments Family Problems,” *Journal of the American Medical Association* 187, no. 2 (January 11, 1964): 228.

⁷³⁴ Burroughs Wellcome & Company, “For Angina: ‘Cardilate-P’, Erythrityl Tetranitrate With Phenobarbital,” *Journal of the American Medical Association*, 187, no. 1(January 1964): 16.

⁷³⁵ McNeil Laboratories, “Normalize Both Her Blood Pressure and Her Emotional State With BUTISERPAZIDE,” *GP; General Physician* 31, no. 1 (1965): 24-25.

The dominant explanations for decline in barbiturate use are: that increased regulation reduced prescribing and increased awareness of long term use; that physicians and the public became more aware of these drugs' dangers, therefore prescribing and using them less often; or, that introduction of newer drugs displaced barbiturates from the market.⁷³⁶ Prescription requirements introduced by the Humphrey Act impacted barbiturate use little. Whether or not the public was more aware in the 1960s than the late 1950s that barbiturates were addictive and potentially lethal, usage rates remain high through to the late-1960s. Arguably, reduced rate of use relates to introduction of benzodiazepines, but whether this is a matter of chronological chance or obvious improvements and merits is disturbingly hard to establish.

Perhaps how physicians learned to understand barbiturates' actions undercut the rationale for prescribing them. The effects of barbiturates were a combination of agitation and sedation. Within developing concepts of tranquilizer action, this created an awkward situation for explaining proper conditions for prescribing barbiturates as hypnotics, sedatives, or tranquilizers. In the 1950s medical literature discussed tranquilizers as central nervous system depressants. A tranquilizer should, therefore, be a compound causing sedation, whether mentally mild, sedating, or in large enough doses, sleep. Because barbiturates had a combined action of agitation soon after dosing, followed later by sedation, they did not fit with contemporary understandings of how tranquilizers acted; they fell

⁷³⁶ For example see "Tranquilizer Prescription Drop Sharply," *The New York Times* September 9, 1980; Liz Hodgkinson, "Costs of Tranquillity – The 'Happy Pill' is a Horror Story," *The Times (London)* February 18, 1988.

outside the parameters defining tranquilizers. Advertisements for Miltown pointed out that unlike barbiturates, their drug “does not cause paradoxical excitation[,]”⁷³⁷ suggesting Wallace Laboratories’ marketing staff were conscious that contemporary ways of explaining drug actions poorly explained barbiturates effects.

Although barbiturates were virtually the only safe and effective substance reducing occurrence and severity of epileptic episodes, Valium’s profile as a tranquilizer in general made it more logically consistent to use for anti-epileptic properties. Valium fit better within the boundaries of existing medical knowledge because its presumed mode of action fit expectations. An underlying theme in History of Science speaks to this issue; results fitting expectation are less strongly questioned than those going against the existing models and accepted knowledge.

Marketing Valium

Roche’s marketing strategy took the competition into account. Valium was not uniformly better than every alternative. Roche competed for a portion of an existing market. Although Valium critics in the 1970s and 80s remembered it expanding boundaries of tranquilizer use, this largely results from their tendency to use the term ‘Valium’ when referring to tranquilizers in general.⁷³⁸ The post-World War II understandings of mental

⁷³⁷ Wallace Laboratories, “For Treatment of Emotional Factors in Cardiovascular Disease,” *GP; General Practitioner* 31 (1965): 214-15.

⁷³⁸ Mickey C. Smith, *A Social History of the Minor Tranquilizers: The Quest for Small Comfort in the Age of Anxiety* (New York: Pharmaceutical Products Press, 1991),

health and mental illness expanded the boundaries within which doctors could justifiably prescribe minor tranquilizers well before Valium's 1963 debut. In the 1960s, physicians wrote tranquilizer prescriptions for an assortment of ills it is hard to imagine in early twenty-first century terms as having any justification. However, seen within the boundaries of normal science at the time, it's questionable whether Valium or any other tranquilizer expanded boundaries of correct treatment for mental illness or social problems. Valium marketing made physicians aware of this specific pharmaceutical, and tried to explain why they should choose to prescribe it rather than alternatives, through promotion of psychosomatic concepts and its use in problematic diagnoses.

Roche's marketing strategy promoted use of Valium in a wide variety of conditions, not just as a tranquilizer for anxiety or stress alone. Mickey Smith gives a broad outline of the campaign in the eminently readable *A Social History of the Minor Tranquilizers: The Quest for Small Comfort in the Age of Anxiety*. He gives only a single visual example of Valium advertising. The picture shows an unhappy housewife sitting in an armchair, the magazine on her lap remaining unread as she stirs her tea and smokes cigarettes. The caption "Psychic support for the 'always weary'"⁷³⁹ easily gives an impression Roche approached doctors by promoting Valium as a way to re-create or restore the perfect housewife, but it is not established as typical of Roche advertising to physicians. This visually oriented advertisement does include what the FDA required as minimal information,

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⁷³⁹ Smith, *A Social History*, 177.

indications and warnings, something administration leaders and FDA critics considered inadequate and misleading in all psychotropic drug ads. In all likelihood, it is this minimal information which resulted in Smith including the unhappy housewife advertisement. The large print text reads “When psychic tension is the reason for chronic fatigue, Valium (diazepam) can help provide the right kind of support. That’s because, in proper dosage Valium calms the tense, tired patient while seldom dulling the senses or interfering with function.”⁷⁴⁰ In a part of the book where doctor Smith focuses less on treatments of mild situational anxiety, his analysis of tranquilizer advertising in the journal *Medical Economics* fits the advertising profile I found in *Clinical Medicine*, *Journal of the American Medical Association*, *Image*, and the detailman’s book *Aspects of Anxiety*.

The Roche marketing campaign plays into how physicians saw their role as medical professionals. Beginning in 1964, Roche promoted the idea that animal and clinical studies already proved Valium safe and useful. Presumably the fact that a very similar drug, Librium, was already vetted by the market and its safety extensively tested in this post-marketing forum, made severe problems with Valium unlikely. Yet, in marketing a drug just after the thalidomide crisis, Roche needed to exert extra effort to reassure physicians of drug safety. The Valium campaign focused on promoting the drug as a product of extensive scientific testing and vetting. Roche’s advertisements reassured physicians using images of ‘objective’ science. In an issue including a series of four nonadvertising pages discussing a

⁷⁴⁰ Smith, *a Social History*, 177.

recent symposium called “Man Under Stress,”⁷⁴¹ an advertisement for Valium lays out information on the ‘new’ medicine, with no pictures, drawings, or catchy slogans. A chart shows results of diazepam use in forty-four psychoneurotic patients with various diagnoses. Tight hand column includes, in smaller text, apparently detailed information on appropriate dosages, warnings, available forms, and the citations for ten different articles in well-known journals. The titles on two columns are understated, almost dry; one reads “Excellent Response in Emotional Tension With Somatic Components,” the other “Valuable for Muscle Relaxation in Cerebral Palsy and Atheoid Patients.”⁷⁴²

The major campaign series, called the Somatic Mask, promoted Valium use in psychosomatic disorders and somatic conditions with psychological complications. This campaign ran in the mid- to late-1960s, parallel with Valium’s rise to the most prescribed brand-name drug in the United States. In 1965, advertisements focused on use in a specific psychosomatic condition; the somatic mask in which patients experienced anxiety and tension, whether mental or physical, as chest pain. Advertisements inside the cover of *Clinical Medicine* show a stoic man looking down, waiting for a verdict from the physician whose face appears over his shoulder. These respectable men are anxious about the medical condition.

In 1967, Roche added heartburn to its list of conditions which might be somatically

⁷⁴¹ “Stress,” *Journal of the American Medical Association*, 187 (January-February 1964): 26-29.

⁷⁴² Roche, “New Valium (Diazepam),” *Journal of the American Medical Association* 187 (January-February 1964): 51.

masked. These physically experienced conditions, Roche argued, were often rooted in anxiety and tension. Doctors could never be sure if the condition was somatic or psychosomatic, unless they tried prescribing Valium. The ‘Somatic Mask’ advertisements suggested physicians needed a way to differentiate causes of chest pain; “heart disease or psychic tension?” is the question.⁷⁴³ In 1968, advertisements focused on treating somatic conditions in general, the idea being that anxiety associated with somatic illness complicated a patient’s path to recovery. In the early-1970s, Roche continued to market Valium based on psychosomatic symptoms, and reduction of anxiety associated with conditions such as heart attacks, of which no physician could deny the reality. It is only in the mid-1970s that Roche marketing campaigns begin turning to a general concept of psychic tension in journal advertisements for physicians.⁷⁴⁴

Roche’s general marketing approach for Valium differs from marketing and use of tranquilizers in general. Valium becomes a symbol of differential diagnosis to women, marketing campaigns focusing on tranquilizers for psychological tensions, drugs treating problems of living. Perhaps the fact Valium competed within a field filled with minor tranquilizers marketed as antianxiety or antineurotic drugs removed the need for Roche to market their own drug’s potential in this sphere. Valium was a minor tranquilizer, so it followed necessarily that doctors could prescribe it for worried and neurotic patients.

⁷⁴³ Roche Laboratories, “The Somatic Mask: Chest Pain. Heart Disease or Psychic Tension?” *Clinical Medicine* 72 (February 1965): inside front cover; Roche Laboratories, “The Somatic Mask: Epigastric Pain. Peptic Ulcer or Psychic Tension?” *Clinical Medicine* 72 (July 1965): inside front cover.

⁷⁴⁴ Smith, *A Social History*, 115-17.

Instead, Roche spent its marketing dollars explaining to physicians how they could view themselves standing at the forefront of medical science, while running a successful practice with efficient and appropriate diagnosis, unhindered by the psychological problems of their patients.

The actual marketing of Valium, before 1967, focused primarily on psychosomatic conditions and how anxiety or tension components problematised treatment of somatic conditions. This focus on interplay between psyche and soma takes a particular shape during the 1950s and 1960s, one which places emphasis on the role of stress. Because the dominant concept of psychosomatic illness at that time focused on the intimate interactions between body and mind, flowing in both directions, and producing ‘real’ physical illnesses, it differs from early twenty-first century divisions between physical and mental illnesses.

It is hard for us simply to accept their broad concept of psychosomatic illness as part of legitimate medicine. It fits our own training to assume widespread use of tranquilizers in the 1960s and 1970s was and should have been viewed as a problem. The idea that these drugs were responsible for improperly expanding the boundaries of mental illness, that they were lifestyle drugs, is an easier concept for us to accept. Yet numerous articles in medical journals highlighted the role of stress in creating and perpetuating somatic illness, and as a complicating factor in cure.

Promoting use of Valium for somatically experienced ills took it out of the realm of psychiatry and into the general practitioners’ domain. General practitioners, whether referred to as family or primary physicians, saw most patients with nervous complaints.

Psychiatrists' clients already identified their ills as mental. General practitioners faced clients repeatedly returning with nebulous complaints – conditions where diagnosis was difficult – as well as middle class and less affluent clients who were more comfortable with physical diagnosis of psychosomatic ills. Roche advertising suggested Valium eased general practitioners' treatment of problem patients, no matter whether these people created problems by taking up time, returning repeatedly, or by perversely refusing to have a constellation of problems fitting a clear diagnosis and cure.

One of the most pervasive trends developing alongside, and probably influencing, the development of Valium, is blurring philosophical boundaries between mind and body in the mid-twentieth century. Post-1940 behaviorists normally considered physiology related to behavior, whether or not they were willing to extrapolate mental processes from behavioral evidence. Jules Masserman and Horsley Gantt created experimental neuroses in animals through psychological stresses, and assessed changes in behavior and measurable physical effects. Pharmacologists, including Lowell Randall, measured physical responses – righting reflex, heart rate, blood pressure, muscle flexibility – in efforts to identify, distinguish, and characterize psychoactive drugs suitable for affecting anxiety and stress, conditions noticeable only through internal experience.

The existence of compounds understood as psychopharmaceuticals implied many Americans – scientists and medical professionals as well as everyday people – could accept (perhaps by ignoring the issue) a physical compound had effect on behaviors associated with the psyche. Sedatives were physical calming compounds; accepting their existence did not

require belief in an interaction of drug and mind. Tranquilizers, as developed and used, were compounds changing behavior, feelings, the very pattern of interaction with the world understood as personality. Whether aware of the tension or not, accepting that tranquilizers worked required acknowledging they could modify the very things identified as self: emotions, patterns of interaction, goals, aspirations, dreams, anger, and an emotion-bound perception of the world tightly bound to our past experiences. Whether used to treat neuroses, personality disorders, psychosomatic conditions, or the emotional and anxiety complications preventing efficient somatic medical treatment, Valium was effectively a psychosomatic drug. Understanding how scientists and the medical profession, and through them the public, understood psychosomatics helps explain the rationale that made widespread prescription and use of Valium reasonable.

The roots of North American psychosomatic theory lay largely in ideas of figures discussed earlier in this dissertation: Walter Cannon's focus on homeostasis, Hans Selye's General-Adaptation-Syndrome, channeling or blocking the flow of energies within Freudian theory, the work of Flanders Dunbar, Roy Grinker's neuropsychiatric work during and after World War II, and S. Margolin's focus on the ascending reticular activating system as locus of interaction between psyche and soma.⁷⁴⁵ Overall, North American psychosomatic theory characteristically privileged the role of interaction between emotion, stress and glands on development of higher thinking from sensation. This focus played an important role in use of tranquilizers, because it suggested an expanded role for stress by conceptualizing it as

⁷⁴⁵ E. D. Wittkower, "Twenty Years of North American Psychosomatic Medicine," *Psychosomatic Medicine*, 22, no. 4: 308-16.

bodily change derived from interaction with the internal or external environment. Stress itself could be a pathogen, underlying a wide variety of illnesses which could manifest long after the originating events. Tranquilizers acted on the reticular activating system, offering the possibility of influencing experience of stress at a level of integration from sensation to thought, allowing experience of tranquility without preventing the body from restoring itself to balance.

Consequently, Roche positioned Valium both as a competitor to existing pharmaceuticals and a more broadly useful drug. Valium could break the psychosomatic feedback loop of anxiety – bursts of adrenalin, apprehension, overreaction to stressors leading to bursts of adrenalin, and so on. Existing medical theory associated this feedback circle with psychosomatic disorders as well as short-circuiting physical treatment of diseases and dysfunctions considered entirely somatic. Valium treated the underlying condition according to this interpretation; it was a cure rather than a palliative medicine.

Selling Scientific Medicine

During and after World War II, the United States pharmaceutical industry moved out of its infancy, becoming a troublesome teen. Hard on the heels of large-scale production and sale of antibiotics during the war, came a series of important discoveries. Within a generation, sulfa drugs, antihistamines, hormones, analgesics, antispasmodics, antidiabetics, diuretics, vaccines, antiseptics, dermatologicals, treatments affecting cancer, blood anticoagulants, and psychotropics brought physicians an armamentarium to fight common

illnesses. In 1939, the pharmaceutical industry sold roughly 149 million dollars worth of prescription drugs; in 1958 the figure was 2 billion.⁷⁴⁶

With swelling sales and efficacious drugs came greater public concern about the ethical implications and dangers of prescription drugs. Senate hearings raised public awareness of situations of ethically problematic practices. Hearings highlighted cases in which pharmaceutical manufacturers funded trials with friendly physicians, arranged publication of positive results in respected medical journals, or promoted detailmen bringing selective, unprofessional, or misapplied research reports to physicians.⁷⁴⁷ Hearings and newspaper reports exposed illegal or unethical practices of pharmaceutical industry members, to physicians as well as the lay public. Roche's campaign took into account existing physician concerns that pharmaceutical manufacturers provided nonobjective evidence, results from small-scale surveys, tended to selectively report only positive results, and over all tended to market drugs in a manner insulting to their perceived professional abilities and status.

Physicians might read medical journals such as *JAMA* (the *Journal of the American Medical Association*), *General Practitioner*, *American Journal of Psychiatry*, or the *New*

⁷⁴⁶ Austin Smith, "Statement of Austin Smith, M. D., President, Pharmaceutical Manufacturers Association, Before the Subcommittee on Anti-Trust and Monopoly of the Senate Committee on the Judiciary, February 23, 1960," reprinted as pages 115-183 in Pharmaceutical Manufacturers Association, *Year Book, 1960-1961* (Baltimore, MD: The Lord Baltimore Press, Inc., 1961), 154.

⁷⁴⁷ Senate Committee on Antitrust and Monopoly of the Committee of the Judiciary, *Drug Industry Antitrust Act: Pursuant to S. Res. 52 on S. 1552*, 87th Cong., 1st sess., 1961; House Committee on Interstate and Foreign Commerce, *Drug Industry Act of 1962: Hearings on H.R. 11581 and H.R. 11582*, 87th Cong., 2nd sess., 1962.

England Journal of Medicine. However, many probably flipped through or past the advertisements. Roche could sponsor research which eventually produced articles in these journals, bringing their message to doctors reading those specific articles in the specific journals. Yet, there was another approach to advertising, one doctors found it harder to avoid, to escape from, detailmen. Detailmen were company representatives who visited doctors in person, telling them about the company's new drugs, their benefits, and often giving out perks (such as pens, cups, calendars, golf balls) with the company and drug name prominently displayed. These marketing agents also brought news of the latest research, especially that putting their company's products in a good light.

An example of the information approach to advertising used by detailmen in marketing Valium is the book *Aspects of Anxiety*. First published in 1965, it was released in a second, enlarged, edition in 1968. Although the publisher of record was J. B. Lippincott Company, there is little doubt it was a Roche publication. Printed inside the cover are the words "Presented to _____ With the Compliments of Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, N. J.," A copy in the author's possession was given to P. E. Lashburn, and a sticker on the same page identifies Powell Douglas as the Roche representative detailed to Doctor Lashburn. In format and style it is similar to other Roche publications such as *The Anatomy of Sleep*, published in 1966, and *Aspects of Alcoholism*, published in 1963.⁷⁴⁸ Clinching the fact that Roche produced this book for their detailmen to

⁷⁴⁸ Roche Laboratories, *The Anatomy of Sleep*, Hoffmann-La Roche, Inc.: Nutley, NJ, 1966; n.a. *Aspects of Alcoholism*, preface by Ebbe Curtis Hoff, (Philadelphia: J. B. Lippincott Company, 1963).

pass on to primary physicians is a statement in the preface that the information was “collated by Roche laboratories into a single volume.” and the book written “for the purpose of bringing these matters to the attention of the primary physicians[.]”⁷⁴⁹

Aspects of Anxiety exemplifies the soft sell; soothing physicians’ fears that the pharmaceutical manufacturers were attempting to hoodwink them. The framework of medicine Roche highlights, and ties to anxiety, broadens the realm under which it is rational to prescribe Valium. Physicians already associated tranquilizers such as the meprobamates, hydroxyzine (Atarax), and (chlordiazepoxide) Librium with treatment of neuroses. As long as Roche did not distance Valium too far from the broad tranquilizer profile, there was no need to highlight that it functioned as an antineurotic. *Aspects of Anxiety* wastes no pages showing a use for Valium that doctors would assume suitable. The way this book enlarges possible uses for Valium is by tying anxiety into psychosomatic medicine, and its utility as adjunctive treatment to prevent complications to somatic treatments.

Aspects of Anxiety tries to put forward three main points. First, the text argues that issues important in family practice medicine – termed primary medicine – could usually be treated with Valium. Second, Roche argues anxiety and neuroses lay at the root of most cases where it was hard to identify a somatic cause. Third, the book suggests that even in cases which had an easily identifiable somatic cause, alleviation of anxiety was a rational adjunctive treatment, because it reduced complications and augmented and improved

⁷⁴⁹ *Aspects of Anxiety*, 1968, 6.

somatic based treatments.⁷⁵⁰

Publishing and gifting doctors hardcover books that linked aspects of accepted medical knowledge in order to justify prescription of the company's drugs, was a brilliant tactic. It faced and passed through FDA and the American Medical Association concerns about abusive pharmaceutical advertising. Because *Aspects of Anxiety* does not mention any specific drug, and was direct marketing to physicians, there was almost no way the FDA could insist on changes to the text. Arguably the book was educational, not advertising. Failing to mention specific pharmaceuticals also helped Roche present an impression of objectivity. And because this book is a soft sell, relying on doctors to make the connection between the way Roche explains mainstream medicine and actually prescribing Valium to patients, it appears to respect the intelligence and autonomy of physicians.

Conclusion

Explaining development of Valium in the 1950s and widespread use in the 1960s, without reference to later events, ties to a tangle of related questions. How was the relationship between mind and body understood in ways explaining research and marketing of Valium? Why did Valium use make sense to physicians and the general public? There must be reasons, otherwise widespread use would not have occurred. Widespread prescription and use of Valium was reasonable at the time, for reasons outlined in this

⁷⁵⁰ n.a., *Aspects of Anxiety*, 2nd edition, Preface by C. H. Hardin Branch (Philadelphia: J. B. Lippincott Company, 1968).

dissertation.

The post-World War II conceptualization of mental health and illness as a spectrum, with the majority of Americans falling between the poles, and therefore either neurotic or at risk heightened interest in mechanisms and concepts of mental health. Increased availability of health insurance brought more Americans to their physicians. National programs – establishment of the National Institutes of Mental Health, passage of the Hill-Burton Act, and formation of a Joint Commission on Mental Illness and Health through the 1955 Mental Health Study Act – recognized widespread support for programs to increase the number of mental health practitioners and facilities focused on neuroses, personality disorders, and outpatients in general. Popular theories, including Walter Cannon's homeostasis and Hans Selye's General-Adaptation-Syndrome, promoted the idea that stress, and response to it, were among the most important aspects of health. The American public increased its demands for mental health services. Interplay between these conditions promoted use of psychopharmaceuticals. They were quick to prescribe and therefore allowed doctors to see more patients each day. They somaticized mental illness, bringing it within the boundaries of traditional medical insurance coverage. They did not cure an illness, they reduced symptoms and therefore either allowed the body to recover, or in an ongoing fashion prevented immature personalities from reaction to stresses in a manner leading to more serious medical problems.

In the 1950s, it became possible to search among chemicals for a tranquilizer. The expense of creating and treating experimental neuroses in animals to screen chemical

compounds was prohibitive. Yet these experiments informed pharmacologists; they could identify antineurotic or tranquilizing drugs through physical manifestations. With availability of antibiotics, pharmaceutical industries could keep fairly healthy populations of mice, rats, cats, and monkeys for testing. Chlorpromazine's discovery and introduction into institutional psychiatry, around 1953, set out the basic features defining a tranquilizer. By 1958, pharmacologists had the ability and expectations required to inject a mouse with diazepam, check if it rolled off an inclined screen and, observing the tumbling rodent, recognize the ingested molecule was a potentially marketable tranquilizer.

Valium's development and discovery took place when tranquilizers were new and held out the promise as mental health prophylactics, mild sedatives, and safe hypnotics. Mild mental illness needed rapid, effective, and fairly inexpensive treatment. Faced with a patient undergoing severe or ongoing stress, doctors logically turned to anxiety-reducing drugs in order to prevent psychosomatic mechanisms resulting in any of a dozen physical illnesses. Compared with earlier alternatives – barbiturates, alcohol, major tranquilizers – Valium was safe, nonaddicting, and had few if any dangerous side effects.

Valium became a drug of abuse in the final years of the 1960s, recognized as such by inclusion on the Schedule of Controlled Subclassification started in 1955 and fought step-by-step until 1973, by which time mental health had been substantially reconceptualized. When it first entered the market, it was medically justifiable to prescribe Valium widely. Prevention of mental illness was a pressing national need. Stress of everyday life produced physiological effects. Prolonged or extreme stress, or even everyday stresses experienced by

a neurotic personality, strained the body's resources, led to gastrointestinal, sexual, cardiac, circulatory, asthmatic or other dysfunctions of nervous system components. Valium was an important preventative treatment for nervous system illnesses. The anxiety associated with somatic illness interfered with normal treatments and the healing process. Valium was a useful adjunct to other treatments, preventing stress reactions interfering with recovery. And, like other tranquilizers, Valium could normalize behavior of neurotic personalities.

Although the statement remains trite, widespread Valium use was a product of its time. The ways of understanding mental health, medicine, and the interaction of body and mind, all play into justifying widespread use of minor tranquilizers, such as Valium. Why Valium, rather than alternatives, became the best-selling brand-name pharmaceutical – in 1972 retail pharmacies filled roughly 530 million prescriptions for Valium⁷⁵¹ – remains an unanswered question. Yet, understanding more about the context of Valium's development, up to the point when Roche placed it on the market, prepares the way for well-grounded and informed further investigation. Better understanding Valium as a construct, formed by interplay between a molecule and the assumptions and actions involved in identifying and defining it as a marketable and useful psychopharmaceutical, creates a touchstone for understanding how acceptable and unacceptable use of Valium changed over time.

⁷⁵¹ B. D. Colen, "America's Psychic Aspirin: Valium: Problems with America's 'Perfect Drug; Valium's Popularity Points Up Problems with Drug," *The Washington Post*, January 21, 1980

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