

Barry Blackwell: Pioneers and Controversies in Psychopharmacology

Chapter 10: Early optimism & ambiguity

Frank Berger review of A Man of Understanding; Chemistry and affect

Jose Delgado biography; Brain stimulation

John Smythies biography; Trans-methylation hypothesis

As Psychopharmacology evolved from mid-century to the early 1960s contemporary attitudes and beliefs about the state of the field were often divergent. For some, hopes of solving the mysteries of the brain and its function were optimistic, sometimes lapsing into ambiguity while others began and remained cautious and skeptical. Chapter 10 offers three examples of the former followed by Chapter 11, expressing the latter viewpoint.

Frank Berger, the chemist who discovered meprobamate, Miltown, the first of the minor tranquilizers, was also an amateur philosopher by nature. His earliest scientific thoughts about meprobamate for anxiety were optimistic but restrained compared to the enthusiasm with which physicians and patients later prescribed and consumed them (See Chapter 14). After his death Frank's widow posthumously published his lifetime philosophical musings in book form. As time progressed Frank's view and those of some, but not all others, moderated. Most, if not all the use of minor tranquilizers was to stifle anxiety associated with existential predicaments which returned as soon as the drugs were stopped unless psychotherapy or insight helped the person "deal more successfully with life's vexing problems." The fact that medication was always cheaper than psychotherapy, a fact insurance companies knew well, hampered more widespread acceptance or adoption of Frank Berger's philosophy.

Jose Delgado, a Spanish neuroscientist, became Professor of Physiology and Psychiatry at Yale and Director of Research. Jose staked his claim to fame on innovative research using

implanted electrodes in the brain of mobile animals to produce changes in affect and behavior. Encouraged, he extended research into patients with chronic epilepsy and schizophrenia. Jose, like Frank Berger, was also an amateur philosopher whose scientific reputation earned an invitation to contribute a volume to a highly respected series on *World Perspectives* designed to have leading philosophers, scientists and thinkers speculate on the social implication of their work and ideas. Jose chose the provocative title, *Physical Control of the Mind: Towards a Psychocivilized Society*. Unfortunately, his philosophical ideas outstripped his research findings. This aroused controversy at a time in the early 70's when scientologists were lobbying Congress to ban surgery on the brain. The public was also outraged by the CIA's covert mind control research funded by the Federal Government.

Faced with lack of funding, widespread animosity, declining interest and relevance of surgery compared to medications Jose resigned and returned to Spain where he remained active in research and writing on scientific and philosophical topics until his 90's when he retired and returned to America.

John Smythies, was among the first pioneers in psychopharmacology, born in 1922, a contemporary of Joel Elkes (Chapter 3), now retired but still active at 96.

John is the scion of a distinguished aristocratic ancestry going back three centuries in England, "marked by the sturdy values of Puritan theology and the Enlightenment."

Born of disinterested and remote parents with long periods of separation John endured childhood in a bleak boarding school where he learned his brain liked biology better than mathematics leading to the dynastic tradition of a degree from Cambridge, during the equally bleak time of the Second World War. John distinguished himself in pre-med studies by winning a scholarship.

Uncertain of his calling, during his last week at Cambridge, facing an uncertain future and recently jilted by a girlfriend, he experienced an existential crisis leading to a religious conversion that ushered in the determination to model his life after Albert Schweitzer. This required he devote himself to seeking the best education available for whatever branch of medicine he found

enticing in order to provide service to others; a not uncommon motivation, kindled by a deprived childhood and known as the “wounded healer” syndrome.

After graduating from University College Hospital in London as the war ended he spent the two-year draft as a ships doctor in the Royal Navy before trying his hand at surgery for which he was temperamentally unsuited and without talent. Marking time and still uncertain of what kind of doctor he wanted to be he took a temporary house officer job with which one of the benefits was evening dances to which nurses from other hospitals were invited.

Here he met his future wife, Vanna and “fell in love at first sight ... still fizzing slightly from my religious experience ... deeply in love and loved in turn.”

Vanna was born and raised in Trieste occupied by the Nazis in World War 2. She shared childhood experiences similar to John, characterized by abuse and emotional deprivation in a dysfunctional family and confined to a boarding school run by nuns. Migrating to Britain after the war ended like John she chose a profession where she thrived on helping others.

John’s choice of career was clarified in dramatic fashion within six weeks of starting as a registrar (resident) in psychiatry at St. George’s Hospital in London where he quickly formed an alliance with his talented senior registrar, Humphrey Osmond. Intrigued by the hallucinations of patients with schizophrenia he read the French book describing visions from peyote, chemically related to adrenaline. Together Osmond and Smythies hypothesized that this might account for the illness and its symptoms submitting a paper to the *Journal of Mental Science* in April 1952 – one month before John Delay and his team published the effects of chlorpromazine in France. Instantaneously they attracted an international audience and the topic became the lynchpin of John’s scientific endeavors as it morphed into several theoretical frameworks focusing on adrenochrome, trans-methylation and DMPEA, a pink spot in the chromatogram of the patient’s urine. John’s memoir traces the idea through these different iterations as he and other scientists sought to confirm the hypothesis.

With John’s choice of specialty firmly identified, John and Vanna were married, ages 28 and 22, in December 1950 at the end of his first year as a psychiatric resident with a promising career looming ahead. Kindred spirits, they quickly adapted to one another and Vanna spent her

life in multiple enterprises that accommodated to John's itinerant search for the perfect education and the ways to put that to good use.

The nature of their idyllic marriage is revealed in the title of their joint memoir and readers who would like to read Vanna's side of the coin can do so on the INHN website in Biographies.

Although John had identified a defining interest in his career he was not distracted from his commitment to obtain an outstanding psychiatric education which he pursued with vigor, first in Canada, then America, for a brief period in Australia and finally back to Britain where he spent two years as a senior registrar (1960-1962) at the Maudsley Hospital. John left the month I arrived there to begin as a junior registrar while he took up the post of Reader in Psychiatry in Edinburgh University at age 40 where he became a talented teacher and author of several textbooks.

John Smythies had also developed two other lifelong interests. Working in an emergency room as a resident he had treated a hypnotist and clairvoyant who impressed him so much that he began a lifelong interest in psychic phenomena. Perhaps this and his religious conversion also explain his third major interest in the mind- brain controversy, a topic as old as Descartes, largely impervious to scientific scrutiny.

John's involvement in these three major preoccupations and many other interests are dealt with in his memoir during a 14-year stint in the US as a named Chair of Psychiatry at the University of Alabama in Birmingham, then a brief attempt at retirement in the UK after retirement that lasted only two years before he returned to his final sojourn and renewed productivity at the University of California at San Diego where he has been since the age of 70.

Two factors contributed to the eventual demise of attempts to incriminate metabolic congeners of mescaline in the etiology of schizophrenia during the 1960s.

In 1966 Connie Charalampous showed that C14 labelled DMPEA given to volunteers in oral doses twice those of mescaline that caused hallucinations were inert even after prior treatment with an MAO inhibitor. It is unclear whether John Smythies knew of this work since he continued his own experiments (See Chapter15, Part 2). Or it might be yet another example of

one scientist's work going unremarked by another (See Chapter, 11, Part 2). In addition, public concern and outrage at the recreational use of hallucinogens also stifled research on them. More recently concerns have suggested that the effect of hallucinogens on the human brain is too important not to resume research.

A MAN OF UNDERSTANDING: A NOTED SCIENTIST'S GUIDE TO HAPPINESS AND SUCCESS

By FRANK M. BERGER, M.D.

ACB Publishing LLC, New York, 2013

Reviewed by Barry Blackwell M.A., M.D. (Cantab), M.Phil, FRCPsych.

Frank Berger's posthumously assembled book of short writings, *A Man of Understanding* is a lifetime's treasure trove of wisdom; of truth in action. As he states in its "Personal Views" section, "I have only one prejudice: that there is nothing beyond the inquiry of science. The notion that there is any truth we are not allowed to know is abhorrent to me."

Readers should realize the who, how and why of the way in which this unusual and unexpected book came to exist. Frank was an eminent member of the half-dozen or so true pioneers who made the break-through discoveries in psychopharmacology in the mid-twentieth century. The drugs they discovered released thousands of patients from asylums into more humane (but still inadequate) community care. Frank Berger's particular contribution was to develop, beginning with research in animals, the first effective drug for the treatment of anxiety: Meprobamate or "Miltown." This and other so-called "minor tranquilizers" rapidly became among the most widely used drugs in America, prescribed by physicians of all stripes including family physicians and psychiatrists. In one short year, 1995-1996, Frank's discovery increased Wallace Laboratories' annual revenue from \$80,000 to \$200 million.

The milestones of Frank's scientific career spelled out at the beginning of his book appear in more detail in *The Oral History of Neuropsychopharmacology* (ACNP 2011).

Frank's entry into medical school in Prague was pre-determined by an interest in research and he made his first discovery at age 22 while still a student, a drug treatment for cystitis he sold to a pharmaceutical company. Frank's long and productive life ended at age 94 in 2008. Throughout this time, he kept detailed notes that reflected his philosophical views on life, quite separate from his scientific work. In "Why Write the Book?" he says, "What I have learned is much more important than what I have contributed... (it) is not original and has been taken over intentionally and unintentionally from others. And: "In my immodesty I want to offer a recipe for happiness and success."

Dr. Berger clearly intended to eventually publish his material with a working title borrowed from Maimonides, Judaism's medieval physician-philosopher: *A Guide for the Perplexed*, which is retained as the title of his introduction. After his death that task fell to his widow, Christine Berger who brought the book to press with its current title and Dr. Berger as author.

Why Frank Berger's only book for the general public should be about his philosophy of life and not his scientific discovery is revealed by the only allusion he makes to this paradox, quoted on the back cover, "*There are misunderstandings about tranquilizers, about what they can do, who should use them, when and how to use them. They may make you feel normal again, able to cope again, but are no substitute for philosophy.*"

This honest appraisal is striking and key to understanding Frank's purpose for his book. In 1970, three years before he retired from industry (but not research); Frank was honored with an award and presented the story of his discovery at a conference in Baltimore that I helped convene with Frank Ayd. The lecture was published in the book we co-edited, *Discoveries in Biological Psychiatry* (1970). By that time Miltown had been overtaken by the benzodiazepines, Librium and Valium, and controversy was raging in Europe and America over the appropriate and inappropriate use of minor tranquilizers; whether they were panaceas for the vicissitudes of daily life or were more effective treatments for a biological brain disorder. Frank Berger's position was

crystal clear; following a scholarly review of anxiety and its treatment he concluded they were useful for the latter and not the former. With the passage of time his reason for this became clearer and more widely acknowledged: drugs can stifle anxious thoughts, feelings and behaviors but cannot change them; they re-emerge once treatment ends. New improved responses to anxiety-provoking stimuli only arise when learning occurs, based on life experiences and sometimes facilitated by talk therapy.

This is made explicit in the Introduction where Frank describes the book as “an attempt to share some of the things life has taught me.” Further, that they “are not concerned with medicine or science but with “an approach to day-to-day living that has helped me deal more successfully with life’s most vexing problems.” A life-changing experience produced one of those lessons: escaping from his Czech homeland two days after Hitler invaded, being denied passage to America at the last minute and crossing to Britain instead with his wife, no money and unable to find work or speak the language. “There was good reason, one might say, for me to be depressed or downhearted.” So, Frank’s response was to “set about doing the best I could in the face of great difficulties”.

This epiphany is translated into four cardinal components of his philosophy that liberate action: tolerating uncertainty and being content with small victories; accepting life’s cultural and spiritual realities while rejecting comforting but ineffectual religious, scientific or philosophical dogma; letting go of unconscious beliefs or fallacies and establishing new beliefs. This last point is driven home by a quotation from Buddha; “The man of understanding makes for himself an island that no flood can overwhelm.” This is prelude to Frank’s benediction: “May this book help you see that it is possible to build such an island without leaving the mainland.”

In the main body of the book Frank Berger’s insights, merged with those of independent philosophers, scientist, authors, politicians and others are stockpiled in alphabetical order in 60 categories the reader can delve among.

Finally, Frank the scientist and empiricist might pose the question, “To what end?” As a philosopher he would be wise enough to know that the answer is beyond the reach of our often crude and error-prone “outcome measures.” It will be up to the reader to seek whatever insights

fit their existential predicaments or angst, testing them in real life and sharing them with friends, family, lovers or fellow workers and, perhaps, with a therapist or two. It remains only to quote Anglo-Saxon folk wisdom: *“The proof of the pudding will be in the eating thereof.”*

A Distinguished but Controversial Career

Jose Manuel Rodriguez Delgado

By Barry Blackwell

Sometimes the personality of a scientist, his chosen field of enquiry and a changing social or scientific zeitgeist can collude to create unanticipated and career changing controversy. There may be no better example of this than what befell Jose Delgado during the half century of a distinguished career. I first learned of this while writing his obituary for *Neuropsychopharmacology* (Blackwell 2012a) but became so intrigued that my research eventually produced a brief 10,000-word biography published in my memoir titled, *“Science, Hubris, Nemesis and Redemption”* (Blackwell 2012b).

Jose Delgado was born in Ronda Spain in 1915, a founding member of the ACNP and lifelong Fellow he died at age 96, three months before our organization celebrated its fiftieth anniversary.

Jose intended to emulate his father, an ophthalmologist, but fell under the spell of Santiago Ramon y Cajal often considered the “Father of Neuroscience,” Nobel Laureate in 1906.

Jose enrolled in Madrid Medical School in 1933 to study both medicine and physiology. In 1936 the Spanish civil war erupted, his mentor Juan Negri fled the country and Jose joined the Republican side as a medical corpsman. After the fascist victory he spent five months in a concentration camp before obtaining his M.D. and Doctorate of Science, both *cum laude*.

From 1942 to 1950 he began research in neurophysiology on selective brain ablation and electrical stimulation in animals, published 14 articles and won several prizes. In 2005, at age 90,

he was interviewed for the ACNP's Oral History of Neuropsychopharmacology where he tells how he went to Africa to buy primates for research, bonded with a gorilla and, unable to operate on his "new friend," donated the animal to a zoo.

In 1950 Delgado won a scholarship to Yale University in the Department of Physiology under the direction of John Fulton whose pioneer work on pre-frontal lobotomy in chimpanzees encouraged the Portuguese psychiatrist Egas Moniz to perform the operation in schizophrenic patients, for which he received the Noble Prize in 1949.

Delgado flourished at Yale; rising to Professor of both Physiology and Psychiatry he eventually succeeded Fulton as Director of Research. Described as "a technological wizard" he invented the "stimoceiver"; implanted electrodes which established two-way communications with the brain in mobile animals allowing Jose to stimulate different regions, producing changes in affect and behavior. Encouraged by these results, and Moniz example, Delgado extended his research to patients with chronic refractory epilepsy and schizophrenia.

This ground-breaking research was published in 1952 anticipating similar work by Bob Heath at Tulane University. 1952 was a watershed year in neuroscience, when chlorpromazine was being given to patients with schizophrenia, spawning the neuropsychopharmacology revolution.

Delgado positioned himself between growing disapproval of mutilating brain surgery and his own belief that electrical stimulation of specific brain areas was scientifically superior to oral administration of drugs whose effects were mitigated by liver metabolism, the blood brain barrier and uncertain distribution.

Events proved Jose wrong; the effects of electrical stimulation were imprecise, poorly replicated and yielded no useful therapeutic outcomes. Conversely neuropsychopharmacology thrived. Drugs were developed for every type of psychiatric disorder, deinstitutionalization occurred and, in 1970, the Nobel Prize went to Julius Axelrod and colleagues for discoveries about humoral transmitters at nerve endings that led to the catecholamine hypothesis of depression.

Nevertheless, in two decades (1950-1970) Delgado authored 134 scientific publications on electrical stimulation in cats, monkeys and patients, psychotic and non-psychotic. In 1963 he performed an experiment that attracted worldwide attention, including a front-page article in the New York Times. After implanting his stimulator in the caudate nucleus of a fighting bull Jose stood facing the bull waving a red cape before stopping the animal in its tracks by activating the electrodes.

Soon after this Delgado was invited to contribute a volume to a series on *“World Perspectives.”* Its editorial board comprised twelve of the world’s most distinguished leaders in ethics, sociology, economics, spirituality and science, including three Nobel Laureates. The series editor was a renowned philosopher whose life was devoted to inviting leading scientists and thinkers to speculate on the societal and philosophical implications of their narrow fields; to “extrapolate an idea in relation to life.”

Jose chose a provocative title for his volume, *“Physical Control of the Mind: Towards a Psychocivilized Society.”* The text and tone were equally challenging. While Jose’s discussion of his scientific findings was modest and objective the philosophical speculations were grandiose and went beyond the data. None the less his intent was benevolent; to encourage the development of “a future psychocivilized human being; a less cruel, happier and better man.” In essence he was proposing that science might accomplish what two millennia of religion failed to do!

Unfortunately, this rhetoric and hyperbole clashed with a changing scientific, political and social Zeitgeist, engulfing Delgado in controversy that would end his career in America. Without distinguishing between science and philosophy Jose’s research and ideas were attacked and denigrated on two fronts.

In 1972 Congress held hearings in response to efforts to end funding for this type of brain surgery. Testimony was given by a libertarian psychiatrist, a scientologist at the time, who disparaged drugs, ECT and biological psychiatry. This included a collage of selective, out of context, quotations from Delgado and other neuropsychiatrists.

Coincidentally public and political outrage surfaced over covert CIA “mind control” experiments, designed to combat communism, initiated in the McCarthy era and extending into the mid-1960s (MK-ULTRA).

These twin forces manifested a plethora of websites fed by conspiracy theorists and alleged victims of psychosurgery that disseminated innuendo and largely unsubstantiated accusations for four decades. Delgado’s name and book figure prominently along with other well-known psychiatrists from among 43 Universities and Colleges alleged to have been involved.

Mired in controversy Delgado accepted an offer to become Chair of Physiological Science at a new medical School in Madrid and moved there in 1974.

For the next quarter century Jose continued to publish his research and philosophical ideas, achieving a lifetime total of over 500 articles and six books. His final book, in 1989, was titled “Happiness” and went through 14 editions.

In the last years of his life Jose and his wife returned to America and lived in San Diego where he died unheralded. Unjustly treated and harshly judged by segments of the public and his profession Jose Delgado’s ground-breaking research, benevolent philosophy and memory deserved better. His career trajectory may provide budding scientists with a cautionary note about the pitfalls of mingling science with philosophy and the perils inherent in a changing social, political and scientific landscape.

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TWO COINS IN THE FOUNTAIN: A Love Story

By

John and Vanna Smythies

Self-published 2005, Available on Amazon

REVIEWED by Barry Blackwell

It is a pleasure and privilege to review this memoir. Its 113 pages are divided between John's life story and that of Vanna, his wife of 65 years. While their stories and styles differ, they share a talent for colorful prose tinged with humor that portrays people, places, culture and life's predicaments in what is also a travelogue of International work and play in England, Canada, Australia, Scotland, Bermuda, Italy and throughout the rest of Europe.

There are now six memoirs of distinguished neuroscientists on the INHN website in the Bibliography Program which I edit. They vary in length, style and format but all convey a lifelong passion for the clinical and scientific rewards of careers in neuropsychopharmacology enabled by strong supportive partners and domestic tranquility. Reviewing them has been easy and enviable task with the sole caveat that this occasionally requires me to rescue the authors from overly modest reticence about their own accomplishments. Such is the case here.

John Smythies' scientific oeuvre extends from 1952 till the present (at age 92), created in several of the world's leading academic environments and many published in major journals. This body of work includes the first modern neurochemical theory of schizophrenia (the transmethylation hypothesis), a balanced approach to the role of vitamins in prevention and treatment of disease (orthomolecular theory) and philosophical speculation concerning the ancient enigma of putative mind-brain relationships. The book includes a Bibliography of the 16 books he has published and a modest selection of 25 scientific papers (from more than 200 published).

John begins the story with an exploration of his genealogy. Like many ancient English stock the family name is toponomic; derived from the Yorkshire moors where small pits (Smythies) contained iron ore, limestone and charcoal from which blacksmiths smelt and fashioned tools. Henry VIII hung six subjects of that name for treason in 1528! John's direct male lineage traces back to forbears who graduated from Cambridge University in unbroken

succession through nine generations from 1617 until John matriculated in 1940. Sifting through the occupations and accomplishments of his genome there is much to admire and live up to. John's father won philately's highest award, his brother was a leading ornithologist and more distant cousins included the ethologist Richard Dawkins and the author Graham Greene. He describes his ancient ancestors; "the family portraits of the Divines, all dressed in black with their little white puritan collars, all display the well-fed confidence of pillars of the Establishment ... they were mainly friendly but cool, reserved rather than affable, and devoted to the concept of duty. My father's last words were to ask if he had done his duty." John sums up the ethos of his ancestors as, "thus the Smythies family for over three centuries have been marked by the sturdy values of Puritan theology and the Enlightenment."

John's matriarchal heritage is more nuanced and laced with wry humor. His mother traced her descent from the "Celtic Princes of North Wales and the time of Owen Glendower" (1349-1415, date added). John's maternal grandfather Percy owned a fine manor house large enough to raise his seven children and directed the company that founded and dominated the marble exporting business in Carrara, Italy. Percy was rumored to be the illegitimate offspring of a "certain member of the nobility"; he came to an enigmatic and tragic end, dying from a penetrating knife wound which the family blamed on an accidental fall onto "an open pair of scissors." More probable is that, "he was stabbed by a jealous Italian husband." To deal with their social stigma the maternal side of John's family developed a myth that an ancestor was awarded a coat of arms by a medieval King for bravery. Later in life, on a visit to the College of Heralds in London, John learned the shield was bogus and that, "the story was typical of the attempts many Victorian families of dubious origin made to add a little glamour to their humdrum lives."

John Raymond Smythies was born on November 30, 1922 in the Indian Hill Station of Naini Tal. His father and grandfather broke from their clerical lineage to work as Forest Officers in the days of the British Raj; his mother described her own experiences in two memoirs, "*Tiger Lady*" and "*Ten Thousand Miles on Elephants*." John's early upbringing was typical of the time and place. The family owned thirty servants and his parents "spent all summer in a whirl of tennis parties, yacht races round the little lake, golf matches, fancy dress balls and so on." John saw little of them and was cared for by an Indian Ayah, a male bearer and a groom who looked after his pony.

“When I passed my seventh birthday this paradise abruptly vanished. I was taken back to England and deposited in a boarding school ... the shock was severe.” John contrasts the “warm colorful world of India where I had been the center of affectionate attention of my little Indian team” with the new environment he likens to, “a modern-day version of Dotheboy’s Hall.” He describes it as, “cold, grey, austere, impersonal, totally lacking in affection, sparkle, culture and wit, or any semblance of anything human except discipline, repression, Latin, compulsory games and compulsory chapel.”

After suffering for a year John was rescued and removed to live with a maternal aunt and her three children while he attended a day school where his English master was the famous poet, Cecil Day-Lewis. This influence blossomed late in John’s life when, at age 80, he published his own book of *“Poems from the Edge of Time.”*

How often and long John was separated from his parents in India is unclear but his need and appreciation for affection is everywhere apparent. During summer he spent time with his grandfather in Devon. After his spouse died he married the housekeeper, much to the dismay of the family. “Aunt Dorothy was warm and affectionate, unlike most of my own relations, who believed that discipline, not coddling was the thing. So, I much preferred her to them. I wept bitter tears on the country bus taking me back from Dolton to school. Every childhood deserves at least one place that one weeps on leaving.”

At age 13 John’s life took a predestined turn. Like his male ancestors for 200 years he had been enrolled since birth as a future pupil at Rugby, in the top echelon of archetypal English “Public Schools.” John describes his ambivalence to the new environment in elegant prose. It was a place of “Spartan discipline tempered by muscular Christianity ... They also provided a superb academic education. But they failed to focus on the need to develop the finer aspects of personality.” To his chagrin “the only way to achieve prestige was to be good at games ... The system was not designed for sensitive and imaginative Athenians, such as myself, who did not excel at sports.” He quotes Evelyn Waugh in *“Decline and Fall”* ... “anyone who has been to an English public school will always feel comparatively at home in prison.” How would an adolescent youth compensate for such a lack of affection and prestige? Certainly not in “muscular

Christianity.” John notes: “Their system of religious instruction was particularly disastrous ... based largely on compulsory chapel.” Hopefully, John took the matter into his own hands, “inspired by Darwin and modern science I told the Headmaster that I would prefer not to attend chapel.” More “in sorrow than anger” he was told, “Boys who refused to attend chapel were expelled.”

John struggles to rationalize the unhappiness inherent in his boarding school experience, noting that his school days “Coincided with the Great Depression ... At least we were not compelled to join the Hitler Youth or the Young Communist League.” The near impossibility of this task reveals itself; “We should have put up cheerfully with the enormous rats that lived under the floors in the School House, dormitories so cold that ice formed on the jugs of washing water left overnight, and food that even the rats found unpalatable ... we should have shown more understanding in our rejection of the continual attempt to make us fit for a world that a few years later ceased entirely to exist.”

Fortunately, the winter holidays provided a respite and a reward. They were spent in Switzerland where, “I became a competent skier, the only sport I was ever good at.” Occasionally (he does not say how often) he was joined by his parents from India. Summer vacations were spent in Cornwall where another aunt had discovered an idyllic sandy beach on the Lizard peninsula. Noteworthy and prescient John spent one spring holiday with an uncle in Carrara where he was entranced by a friendly Italian niece. “The way that the English girls I knew moved was honed by many hours playing hockey and by many hours astride the saddle – Italian girls did not play hockey. They flow and do not jerk. Every gesture seemed destined to end in a caress. I must have tucked that away in my unconscious mind.”

As John matures his thoughts and plans turn towards medicine. He does not attribute this to psychological influences but to a forced choice in the Rugby curriculum between mathematics and biology. After failing at the former he found “biology endlessly fascinating.” This led naturally to medical school and he was accepted at Christ’s College in Cambridge University in 1940. “Cambridge in wartime was a shadow of its former self. A skeleton staff, a meagre social life, very little fuel and not much food. However, I cared not a whit for these ... I found anatomy, physiology

and biochemistry endlessly fascinating.” The following year he did well enough in the exam to be elected an Exhibitioner of the College. “I was content to spend all my time in my rooms totally immersed in the marvels of science.” This was despite the icy Cambridge winters and a totally disinterested (though famous) tutor, C.P. Snow.

In 1942 Cambridge was followed by University College Hospital in London for clinical studies. Interestingly the focus switches abruptly from study to social life. John shares a flat in Soho with a Cambridge friend, next to the “best restaurant in London.” His room-mate’s father was a famous film actor and his mother a leading gynecologist both “steeped in the avant-garde culture of Bloomsbury ... familiar with the writings of Freud and Marx and close friends with Bertrand Russell.” John contrasts “The world of socialist politics, psychoanalysis, art, music and writers ... to my own world of Empire, the Army and Church.”

This convivial social atmosphere pervaded the medical school as well. “It was the tradition in those far off and distant days for medical student to live rakehell lives ... our language would have made a bargee blush. One was expected to get drunk at respectable intervals and girls were there merely to be chased.” One of John’s class mates wrote the famous *Doctor in the House* books under the pen name Richard Gordon. John joined in, “I discovered that glamorous young starlets can take innocent young men on a giddy ride.” John also did his bit as a firefighter when German rockets were pouring down on London during which he saved a Ward Sister “from a sticky end.”

There is little mention of the serious side of medical training, perhaps due in part to the fact that teaching was dilatory, “the Consultants were God Almighty and the whole system was run by them and for them.” Most made their money in Harley Street private practice and hospital work was for charity, a system that would change drastically when the National Health Service was introduced in 1948.

In 1943 all medical students were sent to hospitals in the Midlands to tend the D Day casualties from Normandy and John was among the first to use Penicillin. In 1945 he took and passed his final exams and “became a full-fledged Doctor of Medicine at the absurd age of 23.” Following graduation family connections with an Admiral secured John a plum draft posting as a

Temporary Acting Surgeon-Lieutenant assigned as a ship's doctor to a frigate of the West Indies Squadron based in Bermuda. John describes a convivial congenial life on board at a time when the island was, "literally a paradise on earth" and one of his daily jobs was to "supervise the issue of rum to the sailors" in the timeworn naval tradition. On shore he became familiar with wealthy American land owners and, again, his impression was prescient, "How pleasant I thought they were, how open and friendly, how free of so many layers of hidden and sarcastic meanings was their speech."

On completing his two-year draft and returning to England John "started in the wrong direction", taking a job as a trainee surgeon at Addenbrooke's Hospital in Cambridge where he discovered, "I have jumpy nerves, a vivid imagination, fingers that are all thumbs and my knots show a distressing tendency to become unraveled." John accepted an interim position at Charing Cross hospital in London and "started packing his bags."

During this last week in Cambridge John experienced two juxtaposed events that were life changing. At a time when he was "feeling very low" because his career had stalled and he had just been jilted he lay awake one night "ground between the millstones of regret and remorse." What then transpired was a transforming religious conversion of the kind described by William James in *Varieties of Religious Experience*. Immediately John awoke he visited a bookstore in Cambridge and "without hesitation went to a bookshelf and took down the first book I saw. It was Albert Schweitzer's *Civilization and Ethics*." Back home he spent the day reading and underlining key phrases, coming to the twofold conviction he had experienced an "instantaneous enlightenment and would model his future life on Schweitzer's example."

This revelatory experience bridges John Raymond Smythies' past with his future. John's brilliance as a Cambridge scholar echoed the promise of his forebear's talents and accomplishments but had not blossomed in Medical School or the British Navy, overshadowed by age related social preoccupations. It is likely that deeply felt *noblesse oblige* (privilege dictates responsibility) also helped trigger John's spiritual awakening and ensuing commitment to employ his intellect and energy in the service of others. From this point forward, his life trajectory becomes purpose driven and quickly bears fruit, fulfilling Pasteur's aphorism that "chance favors

the prepared mind.” He would soon discover his life’s theme and meet the person whose presence and persona would anchor their lives going forward.

In John’s own words he would emulate Schweitzer; “I would get a thorough professional grounding in medicine, philosophy and ethics as he did, as well as psychology and the science of the brain. I would also look for a branch of medicine for my practice more suited to my overall plan than surgery.” John would follow this commitment rigorously and faithfully for the remainder of his life.

Paradoxically, while he planned this course of action, the interim position he accepted required that he fulfill an obligation to “mainly taking out tonsils ... I got quite adept at it.” Meanwhile he spent his spare time at the public library reading voraciously on topics relevant to his real plans. On Christmas Eve he attended a hospital party crowded with house officers in white coats and imported Irish nurses. “I caught sight of a remarkably beautiful girl standing by herself.” The rest is described in elegant prose ending with, “I fell in love at first sight.” This was his future wife Vanna and the outcome of that epiphany is told by her in the second half of their memoir.

“Still fizzing slightly from my religious experience ... deeply in love and loved in return”, John took turns working in the hospital’s emergency room where he encountered psychiatric patients he worked up enthusiastically, following them to the psychiatric clinic. In this milieu he also treated a professional hypnotist and clairvoyant who so impressed John with his gift that he joined the Society for Psychical Research, beginning a lifelong interest and developing many friendships.

In April 1950 John Smythies’ future career began to crystallize when he started work as a psychiatric registrar (resident) at Saint George’s Hospital in central London. The three Consultants he worked under were all distinguished and competent Harley Street psychiatrists but none had any interest in research or transcendental metaphysics. However, the senior registrar, Humphrey Osmond, had a “keen intelligence and remarkable range of interests.” He also wrote plays.

Six weeks into his first psychiatric rotation events would unfold that forever linked the names of Osmond and Smythies in jointly proposing the first neurochemical theory of schizophrenia, attracting worldwide attention. In pursuing an interest in hallucinations John had come across a French book describing visions from eating peyote. The author, Rouhier, identified the active principle as mescaline and published the chemical formula. Working with John a medical student on the psychiatric rotation, Julian Redmill, identified it as adrenaline. “So perhaps schizophrenia was due to a defect in the metabolism of adrenaline, leading to the production in the body of a substance chemically akin to mescaline?”

Visiting a friend in Cambridge John was introduced to an organic chemist, John Harley-Mason, who worked out a possible metabolic route by which a methyl group could be added to adrenaline to produce a substance like mescaline (M- substance). The transmethylation theory of schizophrenia was published in the *Journal of Mental Science* – precursor to the *British Journal of Psychiatry* – in 1952 (Osmond and Smythies, 1952). This was the same year that Jean Delay and his team in France discovered chlorpromazine, the first effective treatment for schizophrenia. But “the Consultants at Saint George’s did not show any interest in our theories” and Humphrey Osmond soon left England to take up a position as Deputy Director of a psychiatric hospital in Saskatchewan, Canada where he continued work on his theory with Abram Hoffer.

In mid-1950, as John’s scientific career was about to flourish, he experienced a profound personal setback. He took Vanna to Ireland to meet his parents but the trip was not a success. “To marry a nurse was bad enough – to marry an Italian as well was insupportable.” His mother’s sights were set on an upper crust marriage to the British aristocracy. Temporarily derailed John began to have doubts of his own until Vanna was stricken and hospitalized with a mysterious fever; “I dashed to the hospital and proposed at once at her bedside. After that it was all plain sailing.” John’s appraisal of his parent’s opinions provides a stringent vignette of his own feelings, “they were racist beyond belief, snobbish beyond reason and xenophobic to a ridiculous degree.” As John and Vanna travelled the world, settling in different cultures, John’s comparative dislike for the English class system became a recurring theme.

The marriage of John and Vanna took place in December 1950 followed by an extended honeymoon in Europe visiting Vanna's relatives and friends, described in lyrical language. On return to London John continued to fulfill his career plans by an appointment in the EEG Department at Queen Square – the epicenter of European neurology and neurophysiology. Here he established significant contacts with leaders and mentors in the field as well as elaborating his own theories concerning the brain and consciousness.

After completing his appointment but finding that the British Medical Research Council showed no interest in the trans-methylation hypothesis John's thoughts turned to Canada and the prospect of joining Osmond and Hoffer who was both a psychiatrist and biochemist, Head of Psychiatric Research in Saskatchewan. Their interests had shifted from a theoretical M-substance to a known oxidation product of adrenaline, adrenochrome, which produced a florid psychosis when taken orally. John's research during this time is described more fully in the scientific literature (Smythies 1998).

Before John moved to Canada he visited Carl Jung in Zurich where they shared their common interest in the observation that mescaline visions were unrelated to the personality of the subject experiencing them but, instead, induced scenes "all of a transcendental beauty and depth of meaning ... Jung and I agreed that the collective unconscious must indeed be a strange and marvelous place – similar to the Bardo so clearly described in Tibetan Buddhist tradition."

John joined Osmond at Weyburn Hospital after he had assumed the role of Director and began transforming the asylum from a snake pit into the most improved hospital in North America. John describes one "horrific ward" he helped oversee before this improvement occurred. "It housed some eighty severely retarded male patients ... There was no furniture in the ward and the patients had no clothes. There were no toilet facilities other than a hole in the floor that led to the drains. Every morning the attendants would hose down the patients and the floor with powerful jets of water."

After a year John was invited to join the Neurological Research Team at the University of British Columbia (UBC) in Vancouver where he spent a highly productive two-year period. This included mapping the intricate pattern of brain synapses under the microscope, work that earned

him a Doctoral degree from Cambridge University. Simultaneously he took a second degree from UBC in philosophy and cultural anthropology to help fulfill his “Schweitzerian program.”

While all this was going on interest in the adrenochrome theory attracted the attention of the Rockefeller Foundation, granting Hoffer and Osmond six years of support after the Foundation had grown weary of supporting “Ivy League universities to establish Chairs of psychoanalysis ... money that had been wasted” (Hoffer 1998).

John took a different tack, continuing to broaden his interests and knowledge base. Throughout his career he was committed to remaining a generalist to “make sense of the whole picture ... in an era of ever increasing specialization and the accumulation of enormous amounts of information” (Smythies 1998). To pursue this goal, he sought further training in neurophysiology and was attracted to the work of Sir John Eccles, a Nobel laureate in Canberra, Australia, who, like John, was a modern-day mind-body dualist committed “to the older tradition that people have minds or souls as well as bodies.” To accomplish this, he needed financial support. His work on mescaline had attracted the interest of Heinrich Kluver the German scientist, now working in Chicago, who used his influence with Sir Aubrey Lewis, “the king of British Psychiatry” in obtaining support for a two-year Nuffield Fellowship in Medicine. Sir Aubrey may well have been influenced by his Australian origins as an anthropologist and similar support he received from the Rockefeller Foundation to broaden his own training that helped him become a quintessential generalist in the field of psychiatry (Goldberg and Blackwell 2015).

Sadly, these well laid plans were dashed. Six months before the Smythies left Vancouver for Canberra their daughter Nicola was born. From birth she was increasingly fretful with problems in motor development. On the ship to Australia her symptoms worsened and on arrival in Sydney a neurologist diagnosed severe cerebral palsy with total paralysis of voluntary movements. It became clear they would have to return to England where Nicola died two years later.

John’s fellowship was transferred to work in the Psychological laboratory at Cambridge University under Oliver Zangwill. Here he spent two productive years on research into the hallucinations generated by flickering light (stroboscopic patterns). As usual this research was

connected to his broader interests. “I thought this might offer a way of tackling the unsolved problem of how brain processes generated conscious experiences.” The research resulted in three long papers in the *British Journal of Psychology* and also contributed to his first book, *The Analysis of Perception* (Smythies 1956). Simultaneously John continued his philosophical enquiries by joining the Moral Sciences Club “where Wittgenstein had once terrorized his opponents” and where he presented a paper of his own.

After completing the fellowship in Cambridge there were no attractive openings congruent with John’s career plans in Britain so he decided to spend almost two years in America (1958-1959) dividing his time between two centers of excellence. During this epoch of psychoanalytic dominance both these biological enterprises were located in the State Hospital system. First was the Galesburg Laboratory at the State Hospital in Illinois where the research space was named Thudichum after the “Father of Neurochemistry.” Harold Himwich was the head of research involving basic animal and human experiments across a broad spectrum of neurochemical and neurophysiological projects. (Vanna later tells the story of how Himwich served the colleagues and guests at his party’s cocktails spiked with raw alcohol!).

Research was supplemented by weekly seminars in clinical and basic topics by invited experts from America and round the world. Its reputation was further advanced when the team was joined by Ermino Costa who arrived “like a cyclone” in 1956 (White 1998). John’s involvement was relatively modest. He completed work on stroboscopic patterns and participated in ongoing clinical trials with the new antidepressant, imipramine. His principal learning must have come from immersion in a vibrant epicenter of innovative research conducted by world leaders in their fields.

Following this John spent a second year at the Worcester Foundation in Shrewsbury, Massachusetts transformed from one of the earliest asylums in America into a distinguished center of biological research under Hudson Hoagland (Calloway 2013). Here John worked with a Swiss scientist studying the effects of serotonin on reflexes and mescaline on the electrical activity of the brain.

As was his custom John also spent time in America pursuing contacts with the Parapsychology Foundation and its Irish President, who garnered her fame from predicting the disaster of the British airship R101. Reminiscent of John's time in Bermuda the Smythies fell in love with America and its people. "Here the people accepted us for what we were. They were not in the least arrogant, condescending or infatuated with their own self-importance. They were direct, generous, friendly and kind. We loved it."

John's sojourn in America ended, perhaps for two reasons. However impressive his degrees and credentials, to practice medicine in America would require him to repeat his clinical training and pass the requisite exams. In addition, outside the centers of excellence he visited, academic psychiatry was in the stranglehold of psychoanalysis. Psychopharmacology was still in its infancy and located largely in the V.A. and asylums. The American College of Neuropsychopharmacology (ACNP) was not founded until 1961 and John would not become a member until 1981.

Nevertheless, John promised Vanna they would one day return to live in America when "I have reached the top of the tree." And so, they did!

The Smythies return to England in 1959 coincided with John's realization that to move up the academic ladder in Britain, "it was time to complete my training in clinical psychiatry; and the only place to do that was the Maudsley Hospital which was the center of the web of influence and patronage." John's impressive career path, research accomplishments and publications as well as the advocacy of powerful supporters like Heinrich Kluver and Lord Brain assured his appointment as a senior registrar at the Maudsley, beginning in October 1959. John's impressions of the training environment under the eye of Aubrey Lewis are cited in a recent biography (Goldberg, Blackwell and Taylor 2015) and John Smythies' contributions to psychopharmacology are mentioned in a commentary on Aubrey Lewis' generative contributions to that field, (Blackwell and Goldberg 2015).

As John's time at the Maudsley drew to a close in 1962 (the same year I began as a registrar), the Smythies' fourth child, a son Robert, was born with the same disorder as Nicola

(after two normal boys). He died six months later and John describes a two-year period of grief and mourning that clouded their lives.

Perhaps it was attenuated to some degree for John by accepting a new job as Senior Lecturer and later Reader in Psychiatry at the University of Edinburgh. The family also took an idyllic trip through Europe in the hiatus between jobs. John and Vanna enjoyed Scotland's wild countryside and welcoming folks. "We found the Scots to be refreshingly free from the class conscious that sours life in England. All Scots people, like the Americans and the Irish, have an inbound sense of their own worth, not conceit but derived from a firm grip on old-fashioned values."

The new job involved giving lectures, running a small clinic and doing research funded by a grant from the Medical Research Council to continue work on mescaline. Collaborating with chemists the team synthesized congeners and tested them in a rat model of psychosis. During his twelve years in Edinburgh (1962-1974) John's teaching activities are reflected in the publication of four textbooks dealing with the biochemistry of schizophrenia, the neurological basis of psychiatry and biological psychiatry, all cited in the memoirs Bibliography (Smythies 2015).

John's literary account of life in Scotland is evocative and colorful with interesting characters and enjoyable pastimes. He developed an interest in lapidary and Vanna turned the agates he found into fashionable jewelry. Leisure included summer camping trips throughout Europe and Arctic skiing adventures in the Cairngorms.

Meanwhile John's academic career and reputation prospered. He was elected President of the International Society of Psychoneuroendocrinology and a Fellow of the Royal College of Physicians. In 1968 he spent six months as a Fellow in Neuroscience at MIT, including time with Seymour Kety. For several years John was a Consultant in psychopharmacology to the World Health Organization, attending WHO sponsored meetings around the globe. In the penultimate year of his time in Edinburgh he spent a sabbatical year in Alabama at the University that opened the door to the future and the remainder of his long career.

But between Edinburgh and Alabama John's memoir includes three pages, titled "Storm Clouds" that tell a story of the vicissitudes that can influence and afflict a scientific career. In his

words, “A new and sinister development took place.” But these were events kindled years before that burned with a slow fuse. John’s account is in agreement with and supplemented by the updated Wikipedia Encyclopedia entry that includes 81 citations from scientific, philosophical and religious sources. (Wikipedia 2014).

In 1952 when Osmond and Smythies published their ground-breaking paper, “Schizophrenia a New Approach” their work with mescaline immediately attracted the attention of the American author Aldous Huxley who offered himself as an experimental subject. Soon afterwards Osmond and Huxley met in Los Angeles at the annual meeting of the American Psychiatric Association after which Osmond visited Huxley in his home and administered mescaline, producing an eight-hour psychedelic experience. Huxley and his wife then took a 5,000-mile car tour of all the American National Parks following which Huxley wrote “*The Doors of Perception*” composed in a month and published in 1954. The title is taken from William Blake’s poem, “*The Marriage of Heaven and Hell*.”

“If the doors of perception were cleaned everything would appear to man as it is, Infinite.

For man has closed himself up, till he sees all things thro’ narrow chinks of his cavern.”

Huxley’s public tone concerning hallucinogens was restrained and discrete. For the next decade Osmond and Huxley restricted their experiments to a “carefully selected group of academics – psychologists and philosophers.” (Wikipedia 2014). John did likewise, all three sharing the view that mescaline’s purpose was to acquaint professionals with “something they needed to know about their subject – i.e. the theory of mind.” The initial psychiatric response in 1954 was constrained and consistent with this. William Sargent reviewed “*The Doors of Perception*” for the British Medical Journal hoping it would stimulate “physiological rather than psychological” enquiries – consistent with his strongly held biological views (Sargent 1954). Despite the centuries long history of the use of hallucinogens in faith based rituals the philosophical and religious opinions tended to be ambivalent viewing it as a “flight from reality” (Buber 1965) or “an artificial interference with consciousness” and nothing to do with the Christian “Beatific Vision” (Richards 2005).

Perhaps inevitably, in the 1960's, the tide began to turn from psychiatric and philosophical speculation to the popular use of hallucinogens as part of the emerging hippie drug culture abetted by misguided advocacy from the likes of the Harvard psychologist Timothy Leary (Leary 1968). As John Smythies notes, "the lid was off Pandora's Box" with deleterious effects on psychiatric research and its funding. "Mescaline from being a possible key to unlock the secrets of schizophrenia became a pest that had to be stamped out at any cost."

During John's tenure in Edinburgh there were additional setbacks affecting his chosen areas of interest. Abram Hoffer had continued his work on adrenochrome but ran afoul of Julius Axelrod's Nobel Prize winning catecholamine research, backed by Seymour Kety's influence that failed to confirm the role of adrenochrome in the metabolism of schizophrenia. Meanwhile Hoffer and Osmond's research led to conclusions that supported Linus Pauling's controversial orthomolecular theories concerning the prevention and treatment of various diseases and the role of vitamins in maintenance of optimal body function. These provoked allegations from the medical establishment of quackery due to failure to confirm the claims in traditional double blind studies.

John's final paragraph rightly asserts these storm clouds would eventually dissipate when more modern findings cast them in a better light but in 1971 the future for his ideas, research and funding in Britain must have seemed bleak and he might rationally have been seeking greener pastures.

Ron Bradley, John's friend, colleague and fellow Journal editor had already quit Edinburgh to settle at the University of Alabama in Birmingham (UAB) as Director of a new Neuroscience Program. Here John accepted an invitation to spend his sabbatical year and, after returning to Edinburgh, the philanthropic Ireland family offered to endow a named Chair for him at UAB - *The Charles Byron Ireland Chair of Psychiatric Research*. He accepted and would remain in that post for the next 16 years until mandatory retirement.

In Birmingham the Smythies adjusted rapidly to a congenial antebellum environment that included many families of Anglo-Saxon ancestry. John's research and writing prospered, backed by tenured security and the resources of an endowed chair in a parent Department of Psychiatry

with a supportive Chair, “a slot that often attracts the power hungry, cunning and unscrupulous – at least in England.”

During this epoch John’s team identified two enzymes in the brain defective in schizophrenia, MAT and SHMT. He was able to continue research on mescaline and he facilitated the recruitment of Humphrey Osmond from Canada to work at the State Psychiatric Hospital in Tuscaloosa. John’s imaginative and inventive brain also lured him into a novel enterprise; stimulated by Linus Pauling’s CPK plastic models of neurotransmitters, “My subconscious, tuned to my work in anatomy immediately took to these examples of microanatomy. I wondered if it might be possible to use them to build up models of receptor molecules in the brain on which neurotransmitters act.” John spent several years on the Research Advisory Board of a California research and development company seeking for novel drugs capitalizing on this new paradigm but with little success. “Like many scientific hypotheses my model did not turn out to be right in detail, but it was useful.”

This honest and modest observation may reflect insight derived from the painful experience of witnessing three of his major contributions mired in controversy that prefaced his migration from Britain to America. It might also underpin what, for such a fertile mind, was a relatively fallow period during which he chose to use his talents in different arenas. A bibliography of books and selected scientific papers at the end of the memoir reveals a hiatus in publications during his sixteen years at UAB (1972-1988). He cites no scientific papers between 1969 and 1994 and only three books (two authored, one edited) all in the early years (1973-1978).

However, John remained an active participant in international neuroscience. During this entire period, he spent three months each year travelling to numerous scientific meetings often combined with family vacations in Europe and the West Indies, during which he regularly attended the annual December ACNP meetings in Puerto Rico or Hawaii. He describes the people he met and the places visited in elegant and occasionally astringent prose. In 1972, early in his time at UAB, he was one of only five scientists from the West invited by the Academy of Medical Sciences of the USSR to attend a conference on schizophrenia. “I was impressed by the warm and

genuine friendliness of our Russian hosts. I was also impressed by their complete inability to organize anything efficiently and by the dismally low standards of their research.” The Professor who organized the conference was chief architect of the “infamous policy of throwing dissidents into psychiatric hospitals with the diagnosis of a non-existent disease called ‘sluggish schizophrenia’ he had invented himself.” Not much had changed in Russia since Aubrey Lewis visited there in 1938 on his Rockefeller Foundation tour. (See Goldberg, Blackwell and Taylor 2015).

John Smythies dealt with retirement in 1988 in a manner to be expected from someone of his intellect and temperament. He sought an environment that was domestically tranquil but intellectually vibrant. So, the Smythies returned to England where John obtained an honorary appointment at Queen Square in the Psychiatry Department and the family moved to a country cottage on the Sussex-Hampshire border.

Whether John was intellectually satisfied is unmentioned but the domestic debacle is described in a colorful portrait of their dismal life in an uncomfortable rural setting plagued by English plumbing, weeks of wet weather and social ostracism. “You have to live in an English village for at least ten years before the locals will take any notice of you.” The only ameliorating aspect was proximity to the English Channel providing the opportunity for regular escapades to France with its attractive bed and breakfast “gites” where they were “welcomed into the inner life of the family.”

It took only two years to decide that “life in the country is strictly for the birds.” They sought refuge in the North Country, birth place of the Smythies dynasty, and purchased a Victorian terraced house next door to their son and daughter in law in York, “the best medieval city in Britain, one visit to the Minster charges one’s spiritual batteries for a month.” Meanwhile when a former friend at MIT described San Diego as the new center of gravity for neuroscience in America the Smythies decided to sample its ambience. Finding the atmosphere ‘gemutlich’ and the climate perfect they began a commuter life between the cities of York and La Jolla.

John’s intellectual pursuits began to flourish again at the University of California at San Diego (UCSD). He “spent the first few years at UCSD catching up with the great advances that had

taken place in neuroscience. I also learned to manage a computer.” Inevitably the domestic and intellectual charms of California won out. “Every year our visits to La Jolla grew longer and our time in England grew shorter.” Finally, the family relocated fulltime in America; their son and daughter in law in Alabama and the parents to La Jolla where they moved into an idyllic mansion looking out over the Pacific Ocean.

John Smythies’ memoir tells its own story of a remarkable renaissance in intellectual productivity beginning in the mid-1990s (at age 72) and continuing to the present (at age 93). This work has revisited and updated two of his lifelong interests in mind-brain dualism and antioxidants as well as a novel interest to integrate “the vast amounts of information being churned out about biochemical mechanisms involved in synaptic plasticity of the brain.” This late life burst of creativity also produced a volume of poetry (Smythies 2002).

Most impressive about John’s return to the adrenochrome (Smythies and Galzigna 1998; Smythies 2002) and megavitamin-antioxidant controversies (Smythies 1998) is that John sets the record straight with impeccable science devoid of hyperbole. His new views on synaptic plasticity are set forth in *The Dynamic Neuron* (Smythies 2002) with theories that may have significance in Alzheimer’s and Parkinson’s disease as well as schizophrenia. Perhaps John’s most controversial contributions are in mind-brain dualism both because of its spiritual implications as well as the highly sophisticated, complex conceptual relationship it theorizes between the physico-chemical structure and function of the anatomical brain and our sensations, images, feelings, memories, thoughts or experiences.

John first presented these ideas in his book *“The Walls of Plato’s Cave”* (Smythies 1994) and later elaborates on them in an article, *Brain Consciousness: The Ghost in the Machine*, (Smythies 2009). Whether or not mind is merely a function of the brain, possibly unique to humans, has been a central issue throughout the history of philosophy with three prevailing schools of thought, materialism (identical and interdependent functions), dualism (separate and independent functions) and idealism (mental functions only). The new school of thought proposed by John, “Substance Dualism” (Smythies 2009) and its significance may be difficult for most lay and many empirical scientific readers to grasp. The theory requires “a paradigm shift in

our concepts of time and space” in which we need to replace a four-dimensional model with a higher dimensional structure in which phenomenal space, with its contents, (mind or soul) and a physical space, with its contents, (brain) are different cross sections (branes) of a higher dimensional space (the bulk).

The abstract level of reasoning and semantics are a rarity but, John suggests, a comforting one, which can “explain the facts discovered by parapsychologists ... and it can present a plausible account of a human soul in ‘next world’.”

The final paragraph of John’s contribution to this shared memoir reminds the reader that his saga began with a commitment to emulate Albert Schweitzer. He makes the categorical statement, “I do not accept the current dogma that science has abolished the soul. Of course, neither has it been demonstrated by scientific methods that it exists. This question is still wide open.” John notes that to adopt such an ambivalent position is ethically sound based on “a rational religion such as the gentle faith of “Quakers, Buddhism and Hinduism shorn of minor polytheistic components.” In this he seems to be following in the footsteps of Thomas Jefferson.

The space between the male and distaff side of the Love Story is taken up by John’s tribute to his wife in the form of a poem. Vanna’s tale is told in fewer pages but with equal eloquence and colorful prose spiced with humor and psychological insights.

Vanna was born in Trieste in 1928, a city founded by the Romans, incorporated into the Austro- Hungarian Empire and rebuilt in the 18th century in Viennese style. The population is multi-ethnic and polyglot. All her family are fluent in Italian, German, French and English while her father, from an ancient line of ship owners, also spoke Rumanian, Spanish and Arabic.

Vanna grew up in “bitter-sweet culture” and lived in a large and beautiful house, bought by her grandfather when she was four, looking out over the old city and sea beyond. This served as the compound for a fragmented and dysfunctional family. It housed her father, “who always saw the end of the world around every corner” her uncle Alfredo, “a cheerful playboy” and her Aunt Titty, “a tyrannical monster of the blackest arrogance and malice” into whose care she was committed by parents who led a ‘marriage of convenience’ and a mother who “found her

pleasures elsewhere.” It was a time and culture where “children had to fit into the straight jacket that had been prepared for them and do what they were told – no matter what.”

This ideology set the framework for a bleak childhood as the victim of her aunt’s verbal and physical abuse. She was forced to eat foods she hated, received “stinging blows to the face” and was repeatedly locked in a dark coal cellar for hours on end due to minor infractions her aunt deemed “wicked resistance.” After years of such torment Vanna was labelled “incorrigible” and packed off to a nearby Convent boarding school to be cared for by nuns where her “heart would ache and long for home.”

While John and Vanna’s childhoods shared parental neglect and early banishment to boarding school their reaction and coping strategies differed. While John eventually found refuge sheltered in a prestigious all male public school Vanna responded with exuberant escapism, sustained by “a cheerful, resilient and optimistic nature.” Aided by a close friend, Beatrice, Vanna found ways to evade school and home, “so I limped along from childhood to youth sustained by my many friends ... Italian, Greek and Jewish of happily mixed parentage. I lived an intense, happy and varied life with all these gifted, beautiful, witty and charming young people.” These friends, both male and female, included a group of talented musicians and with them she “went sailing, swimming, walking, window shopping and dancing.”

As Vanna reached puberty and early adolescence (not long after John visited Carrera) the Nazi’s occupied Trieste ushering in “years of near starvation, misery and fear.” In 1947, aged 17, Vanna and her friends welcomed the victorious New Zealand army, later joined by the British Navy and American troops.

Liberation brought “a whirl of swimming parties, balls, all sorts of get-togethers and social activities that went on day after day.” Allied officers distributed largesse in ample supplies of food; “after years of little more than boiled onions and stale bread soup, this was bliss for us.”

A year later, aged 18, and on the cusp of adulthood, Vanna decided it was time to leave home, escape from her relatives and “find something worthwhile to do.” When a friend offered to help her find work as an *au pair* in England she leapt at the chance. With an idealized view of the English she pictured a new life ahead. “Stimulated by the novels of Agatha Christie that I had

read, I dreamt of a large country house filled with gracious people, looked after by friendly servants I could gossip with, and possibly with a Rolls Royce outside the door. Here I could put on my nice clothes, stretch out my legs, flirt with a tall, slender and handsome heir to the estate and look after a bunch of blond and blue-eyed children.”

The reality that greeted her in suburban London was to find herself, “a skivvy in an awful house amid awful people.” She was dealing with a “small fat and ugly woman ... with a greasy little girl in tow.” The father and husband refused to pay her the agreed stipend, she hardly had any time off and had to defend herself from his attempts to fondle her and invade her barricaded bedroom door at night.

In England the post-war law for immigrant workers left Vanna with only one choice apart from domestic work which was nursing. At random she picked Charing Cross Hospital in central London and enrolled in a three-year nursing program, a wise but arduous decision. The profession was still entrenched in the Florence Nightingale ethos of servitude. Twelve hour shifts with dormitory accommodation several miles and a crowded Underground train away from work. “I was always cold and my nose was red, my hands were chapped and my feet felt like pancakes.”

But there were compensations, “I loved my work and was good at it. I relished the challenge of helping sick people. I found I could talk easily to patients, smile at them and then cheer them up – and they liked to tell me their problems. All my life I’ve been a good listener.” The job paid enough for annual visits to friends in Trieste and Vanna realized that, overall, she had earned her freedom, responsibility to make decisions and how to look after herself.

Meanwhile she was accommodating to the English way of life and becoming aware of differences in her two cultures. Invited to the homes of fellow nurses she was shocked to have to share a bed; “the semi-detached houses were mean, draughty and damp. We sat huddled in front of a small gas fire. Our cheeks were roasted whereas our rears remained icy.”

Despite the hard work and long hours there were opportunities for fun, dancing and dating. Vanna began to see an ardent medical student suitor until he invited her to, “Meet his Parents (shades of Jane Austen!).” Things did not go well: “I felt it in my bones that I was not cut out to be a nice proper wife of a nice proper lower middle class churchy doctor and spend the

rest of my life in a semi-detached, passing around tea and sandwiches. As a parting gift he gave me a Missal.”

Vanna’s concluding comment in this section (Escape) ushers in the next (The Coins meet). “I was soon to find the very right person in (almost) every way.”

In December 1949, Vanna, now aged 21, is on night duty (her favorite) and catches a glimpse of the new house surgeon on an adjacent ENT ward. “He appeared promising, tall, blond and slender.” They met formally at the annual Christmas Eve party and John became her partner at a reciprocal Nurse’s New Year Ball. They quickly fell in love and Vanna runs through her checklist for a suitable mate. John passes with flying colors save the exception of ‘Elegant’ where she bemoans the difference between “Englishmen who have no inborn dress sense and our dandified Italian men.” She is ambivalent about the fairness of this distinction; pages later in a final analysis of “How things look now”, Vanna enthuses about the marriage because, “He would always come with me to buy my clothes and I always relied on his excellent taste.”

Early on Vanna was most impressed by John’s “extraordinary ability to do several things at once. This was a sign of his quick intelligence. He always seemed to be two steps ahead of everyone else.” Her final prenuptial opinion was, “on the whole, affectionate and friendly as he was he would do – with a bit of give and take.”

The truth of this caveat was quickly revealed when, once again, a ritual meeting with her lover’s parents went awry. But this time it was Vanna who felt rejected. The meeting took place in his parent’s imposing castle in Ireland. John’s mother, the self-styled ‘Tiger Lady’, weighed up the candidate to become her daughter in law against her aristocratic ambitions and found Vanna wanting; “Her first glance raked me from stem to stern.” As previously told by John their relationship weathered this storm but they now confronted the archaic obstacle that she must obtain permission from the general Nursing Council to marry contingent on completing her training. Once grudgingly granted newly married student nurses were routinely assigned to night duty and posted to suburban locations that restricted contact with their spouse to once weekly.

Safely married this, “sensitive and high-spirited couple with lots of personality” needed room to express themselves and adapt to differences in cultural background that Vanna

identifies. John's "stiff upper lip," emotional reticence and polite, uncritical, understated manners contrasted with Trieste's ebullient tendency to poke fun, exaggerate everything and "scatter their feelings all over the place."

Later on, some of John's lifelong traits became more apparent: a tendency to introspection, note taking, forgetting social commitments and taking solitary walks. To this reader it sounds somewhat like the stereotype of an "absent-minded English Professor." Once again Vanna adapts; she learns to assertively and effectively manage their travel plans and domestic environment. If walks are indicated she takes the entire family with her. "So, there were lots of differences to be ironed out. But with perseverance we managed to do so quickly."

In less than 20 pages and two sections, "Off around the world" and "Edinburgh and after," Vanna describes their travels and adaptation to differing work environments John chose in his lifelong career crusade. Conforming to English upper class social traditions their two sons Adrian and Christopher were enrolled at birth to follow in the Smythies' tradition as pupils at Rugby public school, now gender integrated. Vanna agreed it was best "but I gritted my teeth, hid my tears and missed them every day."

In the midst of the turmoil of many moves and different cultures, illustrated by a cornucopia of interesting and amusing anecdotes, Vanna notes, "I preserved my balance by focusing at times on my own values, needs and talents." She lists them: running a restaurant with a friend, making jewelry, buying or selling antiques, knitting, dressmaking, professional flower arranging and embroidery. And regular visits to Italy were "a means of recharging my batteries."

Vanna sums it all up: "Life on this basis was usually fun ... or if not ... interesting." Together the Smythies struck a balance "between John treading on the accelerator and my reaching for the brake."

The final paragraph in the memoir reflects Vanna's sense of lifelong contentment and achievement, culminating in a family reunion at La Jolla attended by all their children and grandchildren. Her husband a content accomplished academic; their sons happily married, one the Vice-President of a bank, the other a neurosurgeon. Trevi Fountain fulfilled its promise!

The INHN website is intended to lay bare the lessons of history for posterity and the future of our field. What can be learned from “Two Coins in the Fountain?” Posed as a love story it invokes the role of marriage and its influence on a creative scientific career. In an essay “*Physician Lifestyle and Medical Marriages*” (Blackwell 1984) I reviewed what the medical literature had to offer and in a later talk to graduating residents in psychiatry (Blackwell 2012) I suggested, “choose a life partner who is psychologically minded, who is at least as intelligent as you are, and who has a strong sense of humor. Above all do not marry a real or metaphorical patient.”

The marriage of John and Vanna Smythies epitomizes these ideals and echo’s the advice of Henri Nouwen that, “Man and woman do not have to cling to each other but can move graciously in and out of the others circle.” Each of the memoirs on our website paints a similar but less detailed portrait of marital harmony and titrated interdependence.

John Smythies career span and trajectory is impressive, stretching from the earliest biochemical theories of schizophrenia to the contemporary hiatus in drug development. Following a conversion experience John’s rigorous pursuit of the best training necessary to fulfill his ‘Schweitzerian’ ideals lasted 16 years from graduation as a physician in 1945 to his first academic appointment at Edinburgh in 1961. This was indeed a “purpose driven” life further illustrated by the tenacity demonstrated pursuing his chosen areas of interest.

The fact that these were cutting edge issues exposed him to risk and controversy that effected his career in a manner reminiscent of Jose Delgado’s need to relinquish his mid-career tenure at Yale for an endowed chair in his native Spain (Blackwell 2014). Delgado’s life span (1915-2011) is only a few years different from John Smythies and although a changing social and scientific Zeitgeist influenced both careers John’s reputation remains untarnished. He never made the mistake of confusing science with philosophy, acknowledging the difference between proof and speculation, a distinction Delgado blurred in his pioneer work on brain stimulation. Both men remained active into their ninth decade but John’s creativity continues to flourish, further informing novel areas and clarifying issues that became controversial since their conception earlier in his career. Since the publication of the memoir John has remained productive in new fields of neuroscience, generating twelve papers including the function of the

claustrum, adding to the unfinished work of Crick and Koch (Smythies, Edelstein and Ramachandran 2014a), as well as new molecular mechanisms in information processing of the brain (Edelstein, Smythies and Noble 2014b). His work on exosomes has implications in several key areas including Lamarkian inheritance, the function of telocytes and cancer neogenesis. John Smythies' burst of late life productivity certainly makes one wonder about the wisdom of Sir William Osler's conviction concerning "the comparative uselessness of men above forty years of age" (Osler 1932).

There is an interesting resonance between Osmond and Smythies interaction with Aldous Huxley over mescaline and Frank Berger's experience concerning meprobamate, the first 'minor tranquilizer' he had discovered. In 1956 Frank invited Huxley to give a keynote address to a national conference celebrating the science and success of his discovery. Huxley's enthusiastic endorsement coupled with his book *Brave New World* and its panacea "soma" may have helped ignite the subsequent heated debate about the wisdom of widespread prescribing and potential abuse of minor tranquilizers (Blackwell 2014). However, like Smythies, Berger drew careful distinctions between his scientific work and his philosophical speculations published by his widow after his death (Blackwell 2015).

I hope that students of neuroscience will read the Smythies' memoir in full as well as the other biographies and memoirs published on the INHN website. They may cast light on the potential challenges, training, trajectory and success of their chosen career.

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February 15, 2018