Barry Blackwell: Pioneers and Controversies in Psychopharmacology

Chapter 11: Caution and Skepticism

Sir Aubrey Lewis: Lifetime Accomplishments

Aubrey Lewis: Psychopharmacology Accomplishments

Adumbration; a learning lesson

This Biography of Aubrey Lewis, the Institute's Director, explores the origins and impact of the critical mindset which was drilled into all of its graduates.

In 1938, just prior to World War Two, Aubrey engaged in an exhaustive tour of European Psychiatry on behalf of the Rockefeller Foundation in America, interested to know more about the state of psychiatry to help govern its philanthropic research grants. This provided the seed bed of Aubrey Lewis's own beliefs, implemented by his scrupulous and rigorous personality.

In his scientific paper, *Between Guesswork and Certainty in Psychiatry,* Aubrey expresses his philosophy in elegant style: "It is the common state of reflective and enquiring minds to be somewhere between untrammeled guesswork and certainty. It would be discreditable if psychiatrists were to be huddled at either extreme, wholly engaged in guessing or ignorantly certain."

Often regarded as nihilistic towards novel treatments in general and drugs in particular, the second brief biography records his generative influence on psychopharmacology ending with a quotation from his 1963 article on *Medicines and Afflictions of the Mind* which is a pithy and remarkably prescient comment relatively early in our odyssey: "Psychiatric advances have been less dramatic and less conclusive than in other therapeutic fields." Few probably felt this was true in 1963 but it certainly is today.

The final essay, *Adumbration,* is a personal reflection on the historical, scientific and ethical lessons learned from research on a discovery of my own that Aubrey Lewis facilitated and watched over with a critical eye and benign indulgence.

Aubrey Lewis: Psychopharmacology Accomplishments

David Goldberg, Barry Blackwell & David Taylor

Although he described himself, aged nine, in an essay while in primary school as "an Australian, and my essay is from an Australian point of view" (Shepherd 1986). Aubrey Lewis became the foremost psychiatrist in the United Kingdom of the 20th Century. He transformed psychiatry in Great Britain and produced a generation of academic psychiatrists; and he was directly responsible both for shaping the Maudsley Hospital from its early beginnings, and bringing about the existence of the Institute of Psychiatry as part of the University of London. He combined an encyclopedic knowledge of world psychiatry with an exacting standard of scholarship. He did his utmost to ensure that each of his trainees achieved the highest standard of both clinical care and the results of their research. This paper will describe how he came to work at the Maudsley, and finally will outline some of his major achievements.

Early Life and Training

Aubrey Lewis was born in Adelaide in 1900. His father earned a living in the 1890s in a small watch-making and repairing business and his mother was a prize-winning local teacher of elocution. In view of his later achievements it is of interest that he could not read until he was seven, nor was it financially possible for his parents to send him to the school of their choice. It is possible that his development was delayed because his parents would have been advised that he should avoid eye-strain following an attack of measles. Once he started his reading, there was clearly no stopping him. He was educated at the Catholic Christian Brothers College in Adelaide, where he soon attracted the attention of his teachers. In competition at the age of 14 the judge specially complimented "Master Aubrey Lewis, who, without notes of any kind, discussed Shakespeare and his works with agreeable delivery and wonderful fluency." In the following year,

his teachers recorded the prophetic words that his discourse on the origin and history of words “exhibited a remarkable grasp of philology” (Shepherd 1986). His earliest interests were in literature, history and languages, so much so that the school teachers in his home town of Adelaide, Australia, predicted a distinguished career in the humanities (Jones 2003). However, his early education formed a secure and lasting foundation for all his subsequent achievements.

During his years as a medical student at Adelaide Medical School he was a prominent member of the Medical Students' Society: “Mr. A. J. Lewis read his paper on 'Quacks', which proved to be one of the finest ever heard by the Medical Students' Society. His quick touches of humor, quiet sarcasm, balanced judgment, and above all, the brilliant style in which it was written, only go to show how great has been Medicine's gain, and I hope this will not prove to be literature's loss” (Shepherd 1986).

After house jobs in Adelaide his first piece of research was an anthropological study of the aborigines of South Australia which included their physical measurements, their implements, songs, vocabulary and psychological observations. Later that year he was awarded a Rockefeller medical research travelling fellowship for “study in psychological medicine and nervous diseases, with the special object of training the holder for studying the mental traits of the Australian aborigine.” He spent the next two years in North America working with Adolf Meyer at Baltimore; in London at Queen Square with Gordon Holmes; in Germany, at Heidelberg, with Karl Beringer; and at the Charité in Berlin with Karl Bonhoeffer. On a brief return visit to Australia it became clear that there were no appropriate opportunities for him at home and the Rockefeller Foundation allowed him to change from psychology to psychiatry and return to London.

After a brief spell at the National Hospital for Nervous Diseases in Queen Square in 1928, he applied for a job as a sleep researcher at the Maudsley Hospital, which had opened in 1923 under the direction of Dr. Edward Mapother. A British University Hospital had been the dream of Henry Maudsley, who had hoped to create a university psychiatric hospital similar to that founded by Emil Kraepelin in Munich. Mapother had served in the British Army in the First World War and Lewis expected from what he had been told that at the Maudsley he might have to re-

adjust his modes of thought to a somewhat insular, rigid materialistic and old-fashioned model, of which Mapother would be the exponent. In fact, he found it quite otherwise (Lewis 1969).

Mapother was concerned that research in the UK was carried out by clinicians in their spare time. This led to an unduly optimistic outlook and prevented "the laborious observation and experiment that forms the basis of every progressive science." He avoided a rigid adherence to any school of thought and firmly believed in the advance of knowledge through empirical research. He believed in the importance of hard facts, and disapproved of cross-discipline speculation about causation and the meaning of symptoms. He had a skeptical attitude to new treatments, thinking that a doctor's first duty was to do no harm, and distrusting new treatments for whose efficacy there was insufficient evidence. This aspect of psychological medicine was regarded as "spookery" and thought not to be an appropriate activity for psychiatrists.

Mental phenomena, or the immediate products of perception, were the only objects of knowledge. Where classification was concerned, manic-depressive psychosis was designated a provisional group of heterogeneous disorders, the neurotic-psychotic dichotomy was dismissed as meretricious; and the links between depression and such feeling-states as anxiety and phobias were admitted. Whilst Aubrey obviously felt at home and compatible with Mapother's views, he also brought to the subject additional dimensions of benevolence, creativity, innovation and calculated risk taking. That opinion is shaped partly by personal experience of one of us (BB):

> *"Lewis moved me from the B to the A stream, kept me under surveillance for 6 months and then gave me the opportunity of a lifetime, to work under Ted Marley with the only proviso that I was not to engage in psychoanalysis! While the Medical Director of SKF described the cheese idea as 'unscientific and premature,' Aubrey reminded me that Hippocrates 'had said something about cheese.' The quotation I found about why 'cheese was a bad article of food' became the prelude to my Cambridge M.D. thesis."*

Shortly after Lewis was appointed, Mapother was sent on a tour of major centers in the USA by the Rockefeller Foundation and, like Lewis before him, was impressed by the psycho-biology of Adolf Meyer at the Johns Hopkins Hospital in Baltimore (Jones 2003). Meyer insisted

on thoroughness in history taking, in probing the family and social background, and Aubrey clearly agreed with him.

At the time of his arrival the Maudsley Hospital was small scale, so that the entire clinical and scientific staff could sit round a small table for lunch. However, by 1931 staff numbers had risen to 152 (including 17 permanent doctors), looking after 207 beds (Jones 2003). Lewis became a consultant in 1932, and Clinical Director of the Maudsley by 1936 – the same year that Mapother was appointed the first Professor of Psychiatry at the Maudsley. During the 1930s the Maudsley hospital trained many of those who became well known later, such as Eliot Slater, Maxwell Jones, John Bowlby, William Sargant, Denis Hill, John Sutherland and Wilfred Bion.

In 1938, on the eve of World War II, Aubrey Lewis was commissioned by the Rockefeller Foundation to undertake a review of European psychiatry. He embarked on a six-month journey during which he visited 13 countries, 45 cities and interviewed 234 individual clinicians and research workers in a wide variety of settings; clinics, Institutes, hospitals, asylums, laboratories and prisons.

From this he produced a tour de force that was 90 pages long (Lewis 2003). The report was archived unedited by the Foundation and not published until 65 years later when it was reviewed in an accompanying article (Angell 2003) which comments "while Lewis was sent to the Continent to gain the perspectives and knowledge that would help to make the Maudsley a more impressive candidate for Rockefeller patronage, his disappointments and criticisms perhaps indicate a desire on his part to take Continental psychiatry down a peg or two and dispel what certainly Lewis deemed a myth of excellence. Of course, it may simply be that Lewis' criticisms reflect the character traits that later led to his reputation as someone who spoke the truth, regardless of the views of others or the inconvenience it might cause. What Lewis' report very neatly reflects is a discipline in flux, whose membership was being worked out in a way that would shape the field's development. It was lucky that Lewis, a notoriously frank man, shared the Foundation's fundamental orientation and skepticism over certain branches of the field."

Lewis concluded his report with a four-page summary of his impressions. He starts by noting that most of the good things he found were in related branches of medicine, neurology,

physiology and biochemistry. “Psychiatry seemed everywhere a rather stagnant subject.” Research activity was “flawed by conflicting results, weak technique, idea-less repetition, excess of speculation or – probably most important of all – failure to see problems that are at once fruitful and attackable. Certainly, the fruits of psychiatric research seem very meager in relation to the volume, it is depressingly less alive and (intellectually if not practically) less exciting than some other branches of medicine.” In addition, psychiatry remained “outside the mainstream of medicine” while “the predominance of neurology and the extravagances of some psychotherapists seemed to have an almost equal share in delaying the social and psychological side of psychiatry.” To the recent reviewers this synopsis was “rather like a torchlight beam illuminating a previously dark corner” (Jones 2003).

He also addressed the way young psychiatrists were being taught: “little clinical acumen was displayed in assessing the outcome of treatment, the research possibilities were generally ignored and there was a risk that, as with psychotherapy, over-enthusiasm might in time provoke an excessive disillusionment.” He found that the standard of clinical work and knowledge was perceptibly lower in psychiatry than in neurology. *“People often had a very detailed knowledge of the literature and difficulties of some tiny problem that they had worked on for a dissertation or article, but they had a poor grasp of clinical psychiatry as a whole; partly, I think, because they had not time to examine all their cases thoroughly, and because they were unduly satisfied with text-book accounts and needlessly conversant with bygone controversies….they were a little right and a little wrong: names of people and of categories and quarrels usurped the place of immediate experience”* (italics added). Lewis was to return to these problems in his work as an educator after the end of the War. One can also see in these comments where his own future efforts might lie; with the application of stringent empiricism in carefully crafted studies on fruitful topics coupled with a devotion to strengthening psychiatry’s ties to medicine and the inclusion of psychological and social influences on outcome.

The Maudsley Hospital was moved out of London in 1939 because of the Blitz from the Luftwaffe, thus providing Lewis with a respite to contemplate the lessons learned from his 1938 European trip and to integrate them with his own bent toward social psychiatry. He became

Director of the Mill Hill Emergency Hospital treating servicemen, especially those with 'effort syndrome." This led to the first psychosocial treatment for this debilitating condition, from which Maxwell Jones developed into his concept of the "therapeutic community."

Mapother had launched an appeal for an Institute of Psychiatry to be attached to the University of London in 1931, but never lived to see it come about, as he died in 1940.

The Contributions of Aubrey Lewis

In 1946 Lewis was appointed as Professor of Psychiatry at the Maudsley Hospital, but opted not to combine this with medical superintendent of the hospital, but to confine himself to teaching and research and to be in charge of a professorial unit admitting its own patients. With the arrival of the NHS in 1948, the Maudsley was united with the Bethlem Royal Hospital, giving access to its rich endowment funds, and greatly expanding the number of beds available to what became the Joint Hospitals. He finally persuaded the University of London to adopt the Institute of Psychiatry (IoP) as part of the University of London in 1948, so that Henry Maudsley's dream became a reality. He also obtained funds from the Medical Research Council to support what became the MRC Social Psychiatry Research Unit, with Lewis as its Director. In addition to the psycho-pharmacologists mentioned in our companion article (Blackwell and Goldberg 2015), he ensured that the staff of the Institute included neurophysiologists, neuropathologists, biometricians and clinical psychologists.

Lewis as an educator of a generation of future academic psychiatrists

At the Maudsley Hospital, Lewis ensured that the psychotherapy department contained a wide range of approaches to psychological treatments and did not become dominated by one particular school. On one's first day, one was advised not to read a textbook, but to confine one's reading to scientific papers – an echo of Aubrey's pre-war complaint about European psychiatry.

As a clinical teacher, Lewis insisted on a carefully taken, detailed clinical history, and he was well known for interrupting junior doctors if they asserted something which they could not justify. "Are you sure that you asked the right question?" he might ask, and begin to drum his fingers on the desk. As a result, many found his manner intimidating, and all his trainees would

agree with Anthony Storr's comment "that once you had presented a case to him, no other public encounter, be it with a large audience, in a TV studio or a lecture platform, could hold any terrors for you." Although he did not intend to terrify us, he most certainly did so.

In one anxiety filled journal club presentation by an Australian registrar on the Burgholzli Centenary, Lewis asked him "how he could possibly know what Bleuler was thinking?", only to discover that he had flown to Zurich at his own expense and spoken with Bleuler in fluent German! This illustrates the lengths residents sometimes went to meet his expectations, their caliber and the climate that he created while still allowing us to talk back.

Nor was the Journal Club the only ordeal; the Friday Case demonstration also inspired anxiety in the trainees:

> "His teaching methods were rigorous in the extreme. All the registrars had to be present while one of them presented his case to the Professor. This had to be done from memory without recourse to case notes. After this the wretched registrar was subjected to a searching cross-examination, spiced with sarcasm and devastating wit. Sir Aubrey clearly believed that in order to keep his students on their toes, it was best to ensure they were trembling in their boots. For all that he was an inspiring teacher" (Blackwell and Goldberg 2015).

Dr. D.L. Davies, who served as the Dean, wrote that "training at the Maudsley had connotations that were partly positive and partly negative. It is not a place that is dominated by too many psychoanalytical or cognate speculations or theories. People recognize this characteristic and regard it therefore in a sense as hard-headed, perhaps hypercritical, perhaps skeptical, but not pie-in-the-sky or ethereal. On the positive side I should think empirical methods strengthened by the results of research which enable theory to be formulated and eventually applied to practice. But I think it's chiefly in the balance that is observed in Maudsley psychiatry" (Shepherd 1986). There were definitely aspects of the Maudsley that irritated and alienated reputable voices elsewhere in world psychiatry with misunderstandings that persist even today. An example would be controversies over lithium (Blackwell and Shepherd 1968) and the lithium controversy (Blackwell 2015).

In his paper on the Education of Psychiatrists (Lewis 1947), Lewis argues strongly for an all-purpose psychiatrist. “When he is asked to treat a child, to report on a criminal, to explain the origins of a strange symptom, to supervise a course of insulin, to diagnose a high-grade defective, or to avail himself of the results of psychological tests, he should not have to choose whether he will excuse himself …. The psychiatrist, like other specialists, must acquire knowledge, some technical skill and an attitude for what he has to do…. He may, it is true, become an administrator, or a psychoanalyst, or a forensic expert, or even a professor – very diverse activities, but all requiring a broad training.” He saw the primary task in psychiatric education being to train a future generation of teachers.

Until about 1980, it remained true that most of those appointed to the proliferating Chairs of Psychiatry in the years following WWII had trained at the Maudsley. The teaching of Psychiatry to medical students was thus indirectly due to Lewis, and this also due to the new generation of consultant psychiatrists coming from the Maudsley to British Medical Schools. These teachers had themselves been taught a disciplined discourse rather than been left to create their own from reading and observation. Even into the late 1950s medical student experience was of visits to various “Lunatic Asylums” where “residents” were shown on stage while a garbled account of their problematic behaviors was given by the resident doctor. Such displays, naturally, alienated students who might otherwise be drawn to the subject.

Research in social psychiatry

In 1935, Lewis had published a paper in Lancet on neurosis and unemployment (Lewis 1935) which argued that these men were social as much as medical problems, and one should aim at occupational as well as social interventions. He returned to this theme in 1944 from his position at Mill Hill (Lewis 1944).

After becoming Director of the MRC Unit in social psychiatry, he was responsible for the pre-eminent position of the United Kingdom in this field for the next 30 years or so, until new technology directed attention to genetics and neuro-imaging. Men such as Jack Tizard, Neil O'Connor, John Wing, Michael Rutter, Kenneth Rawnsley, Morris Carstairs and Peter Venables worked for him at the MRC Unit. John Wing and George Brown also worked on the Unit, and

made important contributions to the substantial body of knowledge that emerged from these important formative years. Lewis's contribution was to ensure that research findings were factual, used reproducible methods of assessment and included social measures.

The high-water mark of these especially productive years was the book on Institutionalism and Schizophrenia (Wing and Brown 1978), which was the first formal demonstration that the phenomena of schizophrenia were not the immutable manifestations of some inner disease process, but were partly a product of the mental hospital environment.

The value of his papers on various subjects

On the occasion of Aubrey Lewis' retirement in 1966, the members of the Junior Common Room undertook to gather together and edit a selection of his papers. In their introduction, they say "for his past students, now scattered throughout the world, these essays will, we hope, be something more: refreshing reminders of their training. For athletes training involves not only a gain in muscular strength, but a loss of excess fat. For psychiatrists Professor Lewis provided its intellectual equivalent. It has been through his teaching, with its challenging mixture of scholarship and common sense, that his influence has been most widely felt, and it is this which we, his present students, gratefully commemorate" (Lewis 1967a,b). In his review of the collected papers the writer says 'Sir Aubrey wears his scholarship lightly, never writes like a pedant, never descends to jargon yet is never far from that perceptive wit which always lay beneath the surface of his quite remarkable mind even in its most earnest deliberations' (Times Literary Supplement (1967). Lewis' commitment to empiricism was essential and profound - he took an unsentimental (but not overtly unkind) view of how to determine the truth and conveyed this in perspicacious, pithy, elegant prose. In addition, he was not (at least in his later years) preoccupied with his own reputation - either enhancing it or placing it in hazard by speaking the truth as he saw it.

We will here give examples of some of Lewis' more important papers. His early papers on melancholia (Lewis 1934, 1936) report an exhaustive descriptive study of 61 patients with depression. Lewis states that his findings have "compelled divergence from the accepted views, as expressed in textbooks and monographs" and the validity of (what were) accepted views on

the classification of depression. Lewis describes paranoid features, the patient's attitude to his environment, the various manifestations of retardation, anxiety and compulsive phenomena in depression. In these papers Lewis shows his almost encyclopedic knowledge of the history of psychiatry – undoubtedly helped by his ability to read papers in both French and German in the original language. He fails to confirm the various groupings described by his predecessors, and takes the view that there are no independent disease entities, but rather an overlapping set of clinical phenomena which defy easy grouping, but are affected by the patient's personality and social adjustment.

His views are best expressed in the section on Psychological Medicine in Price's Textbook of Medicine (Lewis 1956). In this he compresses the whole of psychiatry into less than 60,000 words of clear, pithy prose, in an attempt to influence a generation of medical students. He gives his own views about the classification of affective disorders, asserting that there are three forms, each existing in a major and a minor form: manic excitement and hypomania; melancholia and "neurasthenic" depression; and agitated depression and anxiety state. There are no rigid distinctions between each major and minor form, and in the third form he denies that there are clear distinctions to be made between depressive and anxiety states.

Having excited the interest of a medical student reading his section, the thoughtful student might go on to some of his more profound general papers, from which we will select only two. In "Health as a Social Concept" (Lewis 1953) he argues that health is a single concept: it is not possible to set up essentially different criteria for physical and mental health. We commonly assume a continuum between health and ill-health, for which there is no counterpart in the phenomena but which we cannot yet replace by a continuum since we lack the means of measuring some of the necessary dimensions. There are three criteria for any medical illness: the patient feels ill, a general, subjective datum; he has some abnormality of a part-function, a restricted objective datum; and he has symptoms which conform to a recognizable clinical pattern, a typological datum. Social criteria play no part. The criterion of health is the adequate performance of functions, physiological and psychological. While our estimate of the efficiency with which functions work must take account of the social environment which supplies stimuli

and satisfies needs, the criteria for health are not primarily social: “it is misconceived to equate ill-health with social deviation or maladjustment.”

In “Between Guesswork and Certainty in Psychiatry” (Lewis 1958), Lewis argues that “it is the common state of reflective and enquiring minds to be somewhere between untrammeled guesswork and certainty. It would be discreditable if psychiatrists were to be huddled at either extreme, wholly engaged in guessing, or ignorantly certain.” He goes on to consider why psychiatrists have been suspected of luxuriant speculation or invincible faith in our tenets. At the time one of us (DPG) was reading widely round the subject, and was finding a huge discrepancy between some of the wilder psychological explanations of symptoms I found in psycho-analytic books, and the dogmatic assertions of my undergraduate teachers at St Thomas Hospital. I found great comfort in this article, and decided that if there were brains like these writing in psychiatry, I had better leave my teaching hospital and relocate to the Maudsley. I found to my surprise on my arrival that there were more junior doctors from St Thomas than from all other London teaching hospitals combined. Perhaps this reflects William Sargant’s enthusiasm for the subject, suggesting to his students that mental disorders were very similar to physical illnesses, and all responded easily to energetic physical treatment.

We knew Professor Lewis in the closing years of his life, when early Parkinson’s Disease was making his face a mask, and his voice a monotonous whisper. The death of his wife had been a devastating blow and he shrank visibly after that. The oratorical feats of his early life were no longer possible for him, but his mind was still razor-sharp, and his knowledge of the subject detailed and precise. He had encouraged his colleagues at the Institute to undertake research in metabolic aspects of psychiatry, in genetics using twin studies, in the common mental disorders encountered in primary care, and as we mention in our companion article, in psychopharmacology — but he did not carry out research in these areas himself. Above all, the “remarkable grasp of philology” noticed by his school teachers never deserted him – he was easily the most scholarly psychiatrist that we have ever encountered.

References:

Angell K (2003) Defining Psychiatry: Aubrey Lewis's 1938 Report and the Rockefeller Foundation. In Ed. Angell K, Jones E, Neve M. Aubrey Lewis, the Maudsley Hospital and the Rockefeller Foundation in the 1930ies. European Psychiatry on the Eve of War. Medical History, Supplement No 23. Also London, Wellcome Trust Centre for the History of Medicine at UCL.

Blackwell, B and Goldberg D.P. (2015) Sir Aubrey Lewis and Psychopharmacology INHN.org in Biographies. 29.01.2015.

Blackwell, B; and Shepherd M. (1968) Prophylactic Lithium: Another Therapeutic Myth? Lancet 1: 968, 968-971.

Blackwell, B: The Lithium Controversy: A Historical Biopsy INHN.org in Controversies. 17.01.2015.

Jones E. 2003. Aubrey Lewis, Edward Mapother and the Maudsley, in In Ed. Angell K, Jones E, Neve M. Aubrey Lewis, the Maudsley Hospital and the Rockefeller Foundation in the 1930ies. European Psychiatry on the Eve of War. Medical History, Supplement No 23. Medical History, Supplement No 23. [Also London, Wellcome Trust Centre for the History of Medicine at UCL].

Lewis A. (1969). Edward Mapother and the making of the Maudsley Hospital. British Journal of Psychiatry 115, 1349-1366.

Lewis A. (2003) Report on Visits to the Psychiatric Centres in Europe. In Ed. Angell K, Jones E, Neve M. Aubrey Lewis, the Maudsley Hospital and the Rockefeller Foundation in the 1930ies. European Psychiatry on the Eve of War. Medical History, Supplement No 23. Also London, Wellcome Trust Centre for the History of Medicine at UCL.

Lewis A. (1947) The Education of Psychiatrists. Lancet 2, 79-83.

Lewis A. (1935) Neurosis and Unemployment Lancet 2, 293-297.

Lewis A. (1944) Vocational Aspects of Neurosis in Soldiers Lancet 2, 105-109.

Lewis A (1967a) Volume 1: Inquiries in Psychiatry. Clinical and Social Investigations; London, Routledge & Kegan Paul.

Lewis A (1967b) Volume 2: The State of Psychiatry Essays and addresses. London, Routledge & Kegan Paul.

Lewis A. (1934) Melancholia – a clinical survey of depressive states. Journal of Mental Science 1934, 80, 277 – 238.

Lewis A. (1936) Melancholia: a prognostic study. Journal of Mental Science 82, 488 – 558.

Lewis A. (1956) Psychological Medicine in Price's Textbook of Medicine [9th Edition] Ed. Donald Hunter, OUP]. London, Oxford University Press.

Lewis A. (1953) Health as a Social Concept British Journal of Sociology 4, 109 – 124.

Lewis A. (1958) Between Guesswork and Certainty in Psychiatry Lancet 1, 171 – 176.

Shepherd M. 1986 A Representative Psychiatrist: the Career, Contributions and Legacies of Sir Aubrey Lewis. Psychological Medicine. Monograph Supplement 10, January 1986, pp 1 – 31.

Smythies J and V (2005) Two Coins in the Fountain; A Love Story Self Published. (available on Amazon).

Times Literary Supplement (1967) The Man at the Maudsley. December 14th. 1967.

Wing JK & Brown GW (1978), Institutionalism and Schizophrenia. Cambridge, Cambridge University Press.

EDITOR'S NOTE

All three authors began psychiatric training at the Maudsley Hospital and Institute of Psychiatry in 1962 as registrars (residents). All went on to fill department chairs in Britain and America. Sir David Goldberg became Director of the Institute and like his predecessor was knighted by the Queen. They have remained friends and colleagues since, now all retired.

Sir Aubrey Lewis

By Barry Blackwell and David Paul Goldberg

Aubrey Lewis was born into a new millennium (November 1900) in Australia and died in London at age 74 in 1975. After anthropology research in Australia and clinical work in America, Britain and Germany he joined the staff of the Maudsley Hospital in London in 1929 and was named inaugural Chair in 1946 when it also became the Institute of Psychiatry at London University. Knighted by the Queen in 1959 Sir Aubrey is recognized as having raised the profile and respect of Psychiatry in Britain and worldwide both through his own contributions and those of the Faculty and trainees he recruited and mentored. His major biographer notes (Shepherd 1986) that Lewis had a "formidable and disciplined mind" coupled with an empirical clinical approach that did much to dispel the then prevailing view that, compared to other branches of medicine, Psychiatry's "pretensions were greatest and its foundations least secure."

Far from being a psychopharmacologist himself, Aubrey had his finger on the pulse of the discipline when, in 1957, he became a founding member of the Collegium Internationale Neuro-Psychopharmacologicum (CINP), one of only three psychiatrists from the U.K among 33 worldwide. All three clinicians were from the Maudsley, Aubrey Lewis, Michael Shepherd (Ibid) and Linford Rees (early work on imipramine in depression). The following year Aubrey Lewis chaired the opening ceremonies of the First International Congress of the CINP (Rome 1958).

Sir Aubrey's later contribution to psychopharmacology was not 'hands on' but generative, due largely to the atmosphere and environment he created. He built the Institute of Psychiatry with five full University of London departments including neuropathology, biochemistry, biometrics, physiology and psychology, coupled with a large emergency room and clinical units at the Maudsley and Bethlem Royal Hospitals. Trainees from Britain and around the world rotated through these programs and were exposed to an environment where the major impact was the "internalization of a high standard of critical capacity."

Combined with a requirement for a research Dissertation (later M.Phil.) this created a seedbed for graduates who went on to populate many of the world's leading academic institutions. Among them was a cadre of psychopharmacologists who became pioneers in the field. Included were, John Smythies (Hallucinogens and mechanism of drug action), Philip Connell (Amphetamine psychosis), Eugene Paykel (Depression), Malcolm Lader (Benzodiazepines), Trevor Silverstone (Bipolar Disorder), Ted Marley (Basic neuroscience), Alex Coppen (MAOI) and Barry Blackwell (MAOI and Tyramine and Lithium Prophylaxis).

Sir Aubrey's views on the contribution of new drugs to the field of psychiatry were modestly stated in his paper, *"Medicines and the Afflictions of the Mind."* (Lewis 1963).

> *"We are not living through a period that marks a new epoch; there is no Darwin, no Harvey or Newton in psychiatry and psychology, nor to put our aspirations on a more realistic plain, have there been discoveries during the last twenty years comparable to those that have signaled the growth of therapeutics and surgery in other fields. Psychiatric advances have been less dramatic and less conclusive. Still, to those who have taken part in them,*

they have given the satisfaction and excited the hopes out of which enthusiasm is generated."

At the time this was written, in the heyday of new drug discoveries for every psychiatric disorder, the comment was viewed as skeptical, perhaps pessimistic. Today, as we wallow in the doldrums of no new drug development the words sound prescient.

Had Aubrey Lewis' own work on the nosology and natural history of mental disorders been better known and understood by psychopharmacologists and clinicians five or more decades of frustrated optimism might have been abbreviated. His doctoral dissertation on melancholia recorded the putative biological components evident in this condition; anhedonia, early morning awakening, diurnal variation in mood, loss of libido, amenorrhea, loss of weight and appetite, and suicidal ideation. These peculiarities became lost in the DSM fog of "major depression" or worse still in the ignorant and indolent category, depression NOS. Specificity of outcome was diluted and disappeared in a flood of antidepressants allegedly differing in biochemical profiles but yielding undifferentiated outcomes.

Perhaps Sir Aubrey's most prescient and potentially game-changing contribution on the relationship between drug use and psychopathology is contained in a short but sadly overlooked article he wrote in the mid nineteen sixties (Lewis 1967). This is emblematic of his intellectual and literary style and concerns the use of the term "anxiety" in the psychiatric literature at exactly that time when the "minor tranquilizers" were on their way to becoming among the most widely used drugs in medical practice (Blackwell 2015). Although the timing of Sir Aubrey's article and its concerns may have been triggered by these unfolding events, Sir Aubrey discretely avoids mentioning the role of medication use and the pharmaceutical industry in influencing psychopathology.

The article begins by defining the historical usage of the term "anxiety" first in France and Germany, then in Britain. He is careful to note this excludes literature from Russia, Scandinavia, Japan, Holland and other countries. He also notes anxiety's tardy and sparse appearance in England despite the affects growing theoretical significance in Freud's emerging psychological theories.

Concentrating on Anglo-American literature Sir Aubrey notes the “far from subtle or precise use” of the term anxiety which appears across a lexicon of emotional states that includes “insomnia, fears, phobias, apprehensiveness and depression as well as cognitive symptoms and social behaviors.” He dissects the ubiquitous use of the term in the psychosomatic and stress domains, the relationship of fear with anxiety and the use of the term, “unconscious anxiety” in psychoanalytic jargon which he dismisses as “a contradiction in terms.”

Sir Aubrey next refers to psychological attempts to define anxiety as a physiological conditioned response or a symptom on rating scales. “Critics emphasize that the scales measure and define only manifest anxiety. Other workers stress the need to recognize ‘unconscious anxiety’ but do not define it.”

Finally, he notes attempts to identify and define anxiety in children by educational psychologists; “in regard to which there is much written but little clearly established.”

Sir Aubrey’s conclusions based on his review of the literature are characteristic of his pithy, frank and perceptive style. “Evidently while many voices proclaim that anxiety is the alpha and omega of psychopathology and that it permeates every sort of mental disorder, there are even more voices insisting that anxiety means what they choose it to mean.” Having reached this conclusion Sir Aubrey proceeds to provide his own succinct seven-item definition of the term ‘anxiety’ and its manifestations.

1. It may be “normal” or pathological.
2. Mild or severe.
3. Detrimental to thought or action or, in some respect, advantageous.
4. Episodic or persistent.
5. Due to physical disease or, not of psychogenic disorder.
6. Accompany other mental disorders or alone.
7. An attack may or may not affect perception and memory.

This honest but highly ambiguous itemization leads Sir Aubrey to pose a final question about use of the term 'anxiety': "Should we do away with it?"

His conclusion and its timing are prescient: "The prospect of killing the term is slender, as is the prospect of a successful convention devoted to making the concept and word scientifically successful."

More than half a century later we can state, in retrospect, that the burgeoning use of drugs to stifle anxiety in its many manifestations succeeded in reifying the concept of "anxiety" and that while DSM nosology defined some of its manifestations the questions so elegantly posed by Sir Aubrey remain largely unanswered (Blackwell 2015).

References:

Shepherd M. *A Representative Psychiatrist: Career, Contributions and Legacies of Sir Aubrey Lewis.* Psychological Medicine. Monograph Supplement 1986; 10: 1-31.

Lewis A. *The Later Papers of Sir Aubrey Lewis.* Oxford: Oxford University Press; 1979.

Lewis A. *Medicine and the Affections of the Mind*. Brit Med J 1963; 2 (5372): 1549-57.

Lewis A. Problems presented by the ambiguous word "anxiety" as used in psychopathology. Israel Annals of Psychiatry & related disciplines 1967; 5 (2): 105- 21.

Blackwell B. *The Anxiety Enigma,* INHN Controversies 03.10. 2014.

"ADUMBRATION"; A HISTORY LESSON

By Barry Blackwell

"History is more or less bunk. It's tradition. We want to live in the present and the only history that is worth a tinker's damn is the history we make today" (Henry Ford: Chicago Tribune, 1916)

OR

"What is past is prologue"

(Shakespeare: The Tempest, 1610)

More than three centuries apart, these oft cited quotations set the boundary markers of a ubiquitous dichotomy of viewpoints over the benefit of exploring or ignoring the past to explain the present.

"Adumbration" is an ideal semantic companion to this dispute between the man who invented the Edsel and the world's most famous poet and playwright. It is a fickle word plagued by ambiguous meanings and variable usage. It derives (OED) from the Latin, *"umbrare"* – **shadow** coupled to *"an"* – ***fore.*** Hence it is defined both as "foreshadowing" or "overshadowing" an idea or a discovery, faintly predicting or disparaging the event.

In manifold writings Robert Merton created a subspecialty of sociological enquiry surrounding scientific discoveries, the behavior of scientists and the dubious role of adumbration in that process. (Merton, 1967, 1968 a, 1968 b, 1969). Within this framework I will examine one scientific discovery in which I played a key role and discuss its relevance to contemporary psychopharmacology. A full description of this process is available (Blackwell et al 1967) and its relationship to the process of discovery is described elsewhere (Ayd and Blackwell 1971).

This essay will set the stage with a barebones outline of the discovery itself before an historical dissection of the manner in which it was foretold in the literature accompanied by reflections about adumbration and other contemporary implications.

In 1962, aged 28, I began as a first-year registrar (resident) at the Institute of Psychiatry (Maudsley Hospital) in London. I had completed my medical training at Guy's Hospital as a House Officer followed by a six-month neurology rotation at the Whittington Hospital in North London. I had already published several articles showing an interest in research but, devoid of the desired Membership in the Royal College of Physicians (MRCP), I was relegated to the "B stream" on Lindford Rees' Unit at the Bethlem Royal Hospital. Lindford was a founding member of the CINP

and had engaged in early research on the tricyclic antidepressants which were just beginning to compete with the MAO inhibitors. Iproniazid (Marsilid) had been marketed since 1958 but was quickly overtaken by tranylcypromine (Parnate) from 1960, popular both alone and combined with a small dose of Stelazine as Parstelin.

During neurology training I worked under a senior registrar who had published a letter to the *Lancet* about a patient who suffered a subarachnoid hemorrhage while taking Parnate; taking a drug history in every patient admitted in such cases was mandatory but unproductive. Until, several months later, I was eating lunch in the Maudsley cafeteria and overheard registrars at the next table discussing a young woman who had just suffered a subarachnoid bleed. Had she been taking Parnate I asked? She had! Soon afterwards, chatting with my G.P. he told me of two similar cases seen in a matter of weeks. Eager to "publish or perish" I fired off a letter to the Lancet suggesting this serious, potentially fatal side effect, might be commoner than appeared. (Blackwell 1963). There had been six similar letters in the previous 20 months describing a syndrome of hypertension associated with a pounding occipital headache and, more rarely, a subarachnoid hemorrhage.

Two weeks later I received a letter from a hospital pharmacist in Nottingham, G.E.F. Rowe, who had read the *Lancet* and recognized the symptoms as identical to those his wife had experienced twice after eating cheese. He described the episodes in detail in a letter that concluded:

"Could there be a link between the effects and the amino acids of cheese? No effects are caused by butter or milk. Although treatment has continued, no further episodes have occurred. If cheese is indeed the factor it could perhaps explain the sporadic nature of the incidence of the side effect. I hope my comment will be of some use to you in your investigations."

My first response to this remarkably prescient description was skepticism tinged with humor, until I shared the letter with the manufacturer's representative, Gerald Samuels, of *Smith Kline and French.* He had heard of similar reports including one in a patient taking tryptophan and tranylcypromine in a research study. Perhaps I should look into the composition of cheese? Instead, together with a fellow female resident, we took Parnate for a week before eating

cheddar cheese from the cafeteria and measuring our blood pressure. Nothing happened. But when I checked the hospital menu for the night the Maudsley patient had suffered her hemorrhage I discovered she had eaten a cheese flan for supper.

Not sure what to do next, *chance favored the prepared mind* (Louis Pasteur). Moonlighting for a local family practitioner (the commanding officer of my reserve army field ambulance) I received a call one evening from a distraught husband whose wife was experiencing a sudden severe occipital headache. She was taking Parnate and had eaten a cheese sandwich for supper. I jumped into my car to do a home visit and found her in the middle of a hypertensive crisis which subsided without treatment while I took her blood pressure. Determined to gather further cases I was unsure of where to look. But not long afterwards, working late at the Maudsley, I ran into the duty registrar (Bob Kendall) on his way to the psychotherapy unit. He had been called to see two women in adjacent beds both taking Parnate, suffering from sudden severe headaches, having returned from the cafeteria after eating cheese.

Convinced now of the relationship between eating cheese and suffering a hypertensive crisis I wondered why we had not experienced this in our self-experimentation with Parnate. Perhaps the interaction was due to some propensity peculiar to patients? Boldly, and by today's standards perhaps unethically, I asked a female inpatient taking Parnate (Mrs. Borrett) and her husband if she would be willing to eat cheese while I took her blood pressure. After I explained the risks and steps I would take to counter any major increase in pressure they agreed. She ate cheese and I sat by her bedside for two hours uneventfully before leaving to see patients on another ward. Within ten minutes my pager went off: the nurse caring for my patient asked, "Could she give her aspirin for headache?" I rushed back to the unit, found her in the midst of a hypertensive crisis that subsided without complications or treatment within 45 minutes.

Within nine months of my original letter to the *Lancet* I had collected 12 patients taking an MAOI, mostly Parnate, of whom eight had eaten cheese prior to the event. The publication in the *Lancet* (Blackwell 1963) included a graph of the blood pressure recordings in my volunteer patient. The article produced a rapid response. A patient wrote to say she had known of the association for some time but "doctors laughed at the idea". The Medical Director of *Smith, Kline*

& French dismissed my findings as “unscientific and premature”. Another doctor had treated hundreds of patients with an MAOI and never seen a severe headache although headache occurs at least once weekly in a third of the population. This spectrum of responses illustrates the dual meanings of adumbration; from faintly predicting to critical disparagement.

It is not uncommon for a serious side effect to be discovered several years after a drug is approved for marketing. In this instance it was unusually long. Eight years elapsed between the first use of an MAOI to treat depression and discovery of the tyramine interactions during which time 40 fatal cases occurred. This hiatus is generally attributable to the inadequacy of short term double blind studies needed to obtain FDA approval. Sample sizes are small and populations highly selected with treatment lasting only long enough to determine statistical significance compared to placebo but inadequate to reveal rare or unusual side effects. It is interesting to note however that among the earliest studies of iproniazid, (Marsilid) in the treatment of tuberculosis (Ogilvie 1955) four out of 42 patients suffered hypertension and headache but a cause was never pursued.

There were other reasons why recognition of the causative factor was delayed. It is a truism that “everyone eats cheese.” Eating cheese is common but the side effect was rare while even those who suffered an attack ate cheese again with impunity serving to obscure a cause and effect relationship. An analogy can be made to sex and pregnancy. The first is common but the second is relatively rare; there are many intervening variables between the act and the outcome.

Doubt, disparagement and skepticism were short lived after the publication of the *Lancet* article. Within weeks a team of researchers at a London teaching hospital ate Gorgonzola cheese and identified tyramine with spectroscopy in their body fluids. (Asatoor, Levi and Milne 1963).

It would soon become my responsibility to identify other factors producing a variable response to eating cheese while taking an MAOI. Suddenly in the limelight, I was promoted to the Professorial Unit at the Maudsley and came under the eagle eye of Sir Aubrey Lewis. After observing my work for several months, he took me aside and asked was I “by any chance in psychoanalysis?” Approving of my denial he offered me the chance to learn about research in a

pharmacology fellowship under the mentorship of Ted Marley. For two years I worked in a World War II Nissan hut on the margins of the campus surrounded by cages of cats, rats and baby chicks until I completed the work necessary to explain the mechanism of action of the interaction between MAO inhibitors and tyramine containing foods.

Not long after starting my research Sir Aubrey, who was multilingual and a Greek scholar told me he "thought Hippocrates had something to say about cheese." I found a book on Greek Medicine (Brock 1929) to discover the doubts Hippocrates expressed; "*It is not enough to know that cheese is a bad article of food in that it gives pain to anyone eating it in excess, but what sort of pain, and why, and with what principle in man it disagrees…"* This quotation became an apt prologue to the Doctoral dissertation presented at Cambridge University at the conclusion of research answering those questions (Blackwell 1966).

Working with the National Institute for Research in dairying we learned that the tyramine content of cheese varies considerably depending on the amino acid composition and the abundance or activity of decarboxylating bacteria that convert tyrosine to tyramine. A myth developed that mostly mature and "smelly" cheeses were at fault but our research on multiple samples of identically appearing cheddar cheese (including several that had caused hypertension) varied widely in tyramine content; pieces of cheddar cheese were like cans of garbage – identical on the outside but differing in their content. (Blackwell and Mabbitt 1965). Excavating the literature revealed that tyrosine was first identified in cheese and named after the Greek word for it, *tyros* (Liebig 1846). Later on, tyramine was also discovered in cheese and in the early 20th century physiologists discovered it was a hypertensive agent (Dale and Dixon 1909).

Two years later an internist developing the sphygmomanometer injected tyramine into adults and children to calibrate the instrument (Findlay 1911). In the process he expressed concern that rapid rises in blood pressure might cause a cerebral hemorrhage. Observations on patients taking an MAOI and suffering food induced hypertension revealed several factors determining the outcome. Development of severe throbbing occipital headache occurs when there is a large rapid increase in blood pressure (approximately 50mm or more in less than 10 minutes). Ingestion and absorption of small amounts of tyramine produced less dramatic

increases in blood pressure and were asymptomatic. Even if headache occurred the blood pressure usually returned to normal within 45 minutes without treatment. These factors are responsible for the unlikelihood that most people experiencing the symptoms of a hypertensive crisis would be seen by a physician.

Another factor influencing the occurrence and severity of an interaction was the MAOI prescribed its dosage, and the regimen. Although cases were reported with all the MAOI Parnate was by far the most common drug incriminated and early on it was known as "Parnate headache." In part this may have been contributed to by the fact that in a study on Maudsley outpatients (Blackwell and Taylor 1967) it was the most often prescribed and most effective of the MAOI before the discovery of the tyramine interaction. This was probably due to the drug's therapeutic index and pharmacologic properties. The starting therapeutic dose produced sufficient inhibition of intestinal MAO to allow ingress of tyramine while the drug's amphetamine like structure and effects likely contributed a release of stored nor-epinephrine, augmenting the effect of tyramine. Metabolic studies on a patient taking a less potent MAOI, phenelzine (Nardil) revealed that blood pressure responses to graduated amounts of tyramine in Marmite were influence by dosage, duration of treatment and proximity to an antecedent dose of the drug. (Blackwell, Marley, Price and Taylor 1967).

Monoamine oxidase was named tyramine oxidase after its first know substrate (Hare 1928) and then renamed monoamine oxidase. Its distribution and purpose in the gut was first described by Blaschko to include the denial of access to the circulation of amines present in foods (Blaschko 1952). This knowledge and speculation was made only three years before an MAO was first used to alter the brain chemistry of patients suffering from depression.

The fear that toxic substances absorbed from the gut might cause serious and unpleasant symptoms has a long history up to the present preoccupation with probiotics and colonic "regularity" (Blackwell 1966). In the late 19th century the German scientist Metchnikoff suggested the colon was a "putrefying sac" from which toxic amines in foods might be absorbed into the bloodstream. Queen Victoria's surgeon, Sir Arbuthnot Lane, subscribed to this belief and made a fortune removing the colon for constipation. In 1906 Bernard Shaw wrote the play, "*The Doctor's*

Dilemma", which parodied this practice with a character named Sir Colenso Ridgeon who removed an offending organ, the "nuciform sac." The controversy surrounding this topic became the subject of a conference convened by the Royal Society of Medicine in 1913 during which headaches were among the offending symptoms and cheese a potential foodstuff. These events were contemporaneous with the discovery of the hypertensive properties of tyramine and its associated dangers discussed earlier.

If, as this case study suggests, scientific discovery can be predicted or disparaged (adumbration) it is not surprising that controversy can arise over related aspects of the process. Robert Merton writes about several (Merton 1968a,b). These include conflicts over priority (who made the original or major contribution?), the tendency of scientists to deny an interest in claiming priority (Freud included), the willingness of leading scientists to accept prestigious awards overlooking the contribution of junior colleagues (the "Mathew effect") all of which are abetted by selective forgetting ("cryptomnesia").

Two examples in the modern history of neuropsychopharmacology are the 1964 Lasker Award to Nathan Kline for the introduction of MAOI into psychiatry and the 1978 Lasker Award to Sol Snyder and others for discovery of opiate receptors. In both cases junior colleagues claimed their contributions were overlooked.

The cheese story is not immune from such problems. Two people had reasons to feel slighted. GEF Rowe deserves full credit for the first documented mention of a link between cheese and sudden severe headache while taking an MAOI. My first article describing this interaction (Blackwell 1963) did not make attribution but every subsequent publication has done so. My recollection is that I also sent him copies of all papers we published at the conclusion of the research but this is contested.

The second person, Gerald Samuels, complained vociferously and continuously. Three years after we first met and he encouraged me to pursue the contents of cheese, we met again when he visited me in his role as the pharmaceutical representative for Smith Kline & French. I learned how bitter he was for not being acknowledged in any of our publications. Feeling his resentment was justified and wishing to make amends I suggested we write a joint article

describing his role and contribution. This was published with Gerald as first author in the *Journal of Hospital Medicine* (Samuels and Blackwell 1968). Shortly afterwards he came to dinner in my home and presented me with a cheese board engraved with the words, *"Everyone Eats Cheese."* I assumed we were reconciled but about 15 years later he published an angry letter in the *British Journal of Psychiatry* again complaining bitterly. He had contacted Mr. Rowe and alleged he was also aggrieved and had never heard from me. I decided not to respond, feeling that there was nothing further I could do to assuage such deep seated and long-lasting emotions.

Carefully construed there are a plethora of allies to whom I am grateful in the discovery process. In this instance to mentors and colleagues who assisted or encouraged my enquiries; Lindford Rees, Gerald Russell who welcomed me onto his Metabolic Unit and David Taylor, fellow registrar and lifelong friend. To Sir Aubrey Lewis who opened the door to research. To Ted Marley who endured my clumsy efforts at animal research and pled my ability for doctoral work to Cambridge University. To the female colleague and two women patients who volunteered to be experimental subjects. To the microbiologist who analyzed cheese and educated us in food science. To the scientists at another hospital who identified tyramine in cheese and gave the story credibility.

Still, in addition to adumbration, perhaps there are other ways to think about the lessons learned from the MAOI-tyramine story. Was the field of psychiatry well served by the discovery? Certainly, lives were saved – perhaps five or so patients a year at the peak of MAOI prescribing. But we had learned how to deal with this side effect by avoiding tyramine containing foods; perhaps too many and indiscriminately as recently suggested (McCable et al. 2006). But still the drugs were too useful to be quickly abandoned. Parnate use declined abruptly, followed over a few years by almost no significant prescribing of MAOIs after the SSRI antidepressants appeared. Eager for the field to move on this transition occurred before we had fully defined the features of patients who benefitted. The vague term "atypical depression" was proposed and included increased sleep and appetite perhaps combined with features of apathy, lack of motivation, decreased libido and self- blame. These sound like the same features that for many years were

treated by outpatient use of amphetamines, properties that tranylcypromine shared but for which a comparison was never made.

What might the pharmaceutical industry learn from this story? Industry is always eager to identify a putative "mechanism of action" as part of persuasive advertising. Interfering with an enzyme, receptor system or neuro-transmitter should always raise the question of where else that entity exists in the body, what function it fulfills and the likely consequences of tampering with it. Manifestly this was not so, judged by the speed with which the first article was brushed aside. But the information was all there in plain sight on the pages of credible scientific journals, waiting to be read.

Based on this history of adumbration it would be reasonable to assume that a competent and ethical pharmaceutical company would search the literature to find all the known possible pharmacological effects that might result from the drug they planned to promote including preclinical research in animals and cautious Phase 1 studies in humans followed by specific anticipatory data collection relevant to the risks in Phase 2.

POSTSCRIPT

"Those who cannot remember the past are condemned to repeat it"

(George Santayana 1863-1952)

In 1998 Celebrex (celecoxib) was marketed by Pfizer close on the heels of Vioxx (rofecoxib) already on its way to being a blockbuster. Both drugs belonged in the category of non-steroidal ant-inflammatory drugs (NSAIDs) for the treatment of pain and inflammation in arthritis. Both claimed to be safer and more effective than earlier drugs in the same widely used category. They share a mechanism of action on the enzyme cycloxygenase-2 (Cox-2). Like monoamine oxidase the enzyme exists in two forms, is widely distributed throughout the body with manifold functions.

Sales of Celebrex reached $3.1 billion in 2001 and around that time my joints and spine began to ache and groan from the burden imposed by 20 years of playing rugby and pushing in the scrum. A hip replacement seemed inevitable, but in the honeymoon of this new drug my internist thought it was worth a try.

One week after starting treatment my face erupted in exfoliative dermatitis but, unaware this was a side effect, I continued until a few days later I suddenly became breathless while climbing the stairs at home. Alarmed, though not in pain, my wife drove me to an emergency room where my blood pressure was 210/170 mm Hg. Normotensive throughout my sixty-five years I was on the verge of left ventricular failure. After inserting an I/V and a dose of mild sedative the blood pressure fell to near normal over two hours. It has remained mildly elevated since, responding to conservative treatment. The package insert made no mention of cardiovascular complications so I informed the FDA and the manufacturer. The FDA was silent but Pfizer, knowing I was a physician, mailed several reassuring publications implying the absence of any similar problems.

I was naturally struck by the similarity between this drug reaction, without the headache, and my experience almost forty years earlier with the MAOI tyramine story. I even toyed with the idea of self- experimentation to test the hypothesis but wisely declined. I only had to wait 3 more years for the truth to unfold.

In 2004 Merck withdrew rofecoxbid (Vioxx) from the market. The story is told by NPR on the internet (Prakash and Valentine 2007).

In 1999 Merck, concerned that Vioxx, like other NSAIDs, might cause gastrointestinal bleeding, launched an 8,000-patient study comparing Vioxx to Naproxen, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR). The company appointed a Data and Safety Monitoring Board (DSMB) chaired by Michael Weinblatt (Brigham & Women's Hospital) who owned $73,000 in Merck stock and earned $5,000 a day as a consultant.

During 2000 the results of VIGOR were submitted to the FDA and published in the *NEJM,* but the journal article omitted three cases of heart attack along with other cardiovascular events.

Reanalysis of the data by independent researchers cast doubt on the VIGOR conclusion that the increase in cardiovascular risk might be due to Naproxen protecting the heart rather than Vioxx damaging it. Between 2002 and 2004 further epidemiological studies confirmed Vioxx's increased cardiovascular risk.

In September 2004 Merck withdrew Vioxx from the market after it had been used by an estimated 20 million Americans. Subsequent research in the *Lancet* estimated that 88,000 Americans had heart attacks while taking the drug and more than 8,000 died.

Further FDA analysis of the data on Vioxx revealed that cardiovascular events began shortly after starting the drug and remained long after the drug was stopped.

In 2007 Merck agreed to pay $4.85 billion to end thousands of law suits coupled with a statement that it did not admit fault.

After Vioxx was withdrawn Pfizer benefited from an increase in its sales cut short by further bad data and an FDA "black box" warning in 2005 that all NSAIDs shared comparable cardiovascular risks. For a two-year period, they suspended direct advertising to the public but resumed in magazines in 2006 and television in 2007 where their "*For a Body in Motion*" commercials continue to run frequently, casting a "quality of life" glow and drowning out dire mandatory warnings with distracting happy visual images.

In 2009 Scott Reuben (Chief of acute pain at Bayside Medical Center, Springfield, Mass) revealed that 21 studies he conducted on Celebrex and other NSAIDs were fabricated to exaggerate analgesic effects.

The current package labelling for Celebrex conveys the following information: "*As with all NSAIDs, Celebrex can lead to the onset of new hypertension or worsening of previous hypertension, either of which may contribute to the increased incidence of cardiovascular events. Blood pressure should be closely monitored with all the NSAIDs."*

With the wisdom of hindsight, history and adumbration it seems paradoxical that one drug which provoked hypertension for which the cause was removed, should almost perish while

another still thrives making $2 billion or more a year while its risks remain intact. Worse still, it feels unjust and unscientific!

The word “unscientific” is used advisedly, providing yet another lesson. The difference between the Parnate and Celebrex stories is that between commerce and science and the conflicts of interest this creates. Both involved unanticipated and potentially lethal cardiovascular effects caused by drugs in widespread use for several years. By reason of how each was discovered Parnate fell into the academic domain of medicine, Celebrex into the commercial. Academic motivations involve both personal and social/ethical goals; publishing scientific papers, obtaining advanced degrees, promotion or tenure, and recognition within one’s field. Traditionally also, doctors are sworn to doing good with minimal harm to patients. The target of my investigations was to explain the mechanism of action involved to the benefit of my career as well as making MAOI safer to use and even, perhaps, saving a few lives.

In the case of Parnate, once tyramine was identified the truth was out. Ted Marley and I were invited to SKF headquarters to meet their pharmacologist. We made an agreement to publish the results of our animal research on the mechanism of action simultaneously. Some months later the editor of the *Lancet* informed us that SKF had reneged and submitted their results unilaterally. We were given a month to submit our own research; working day and night we met the deadline and both papers were published back to back (Blackwell and Marley 1964; Natoff 1964).

With Celebrex the story was different. No attempt was made to study or explain the mechanism of action. But like SKF’s initial response Pfizer’s entire effort was devoted to denying and then minimizing the problem. The unanticipated nature of the side effect, its severity and frequency, created liability and provoked litigation. To the extent physicians were involved one falsely exaggerated the drug’s efficacy while another participated in minimizing its risk; both benefited financially.

Once serious side effects are recognized by the FDA and ‘black box’ warnings mandated companies use their vast profits to stifle law suits without admitting culpability. Industry views this as “the cost of doing business” which is built into the high price of the drug in question. The

only evidence of penitence or accountability on the part of Pfizer was a brief hiatus in advertising directly to the consumer, soon resumed with gusto; observing the letter of FDA law but skirting its spirit. Now that all the official warnings are in place Pfizer no longer has culpability for the drug it sells. Side effects become the responsibility of the physician who prescribes the drug and the patient who is beguiled or bemused into taking it.

Note: For a more complete discussion of "Conflict of interest" see the "Controversies" program on the INHN.Org website.

References.

Asatoor, A.M., Levi, A.J., and Milne, M.D., Tranylcypromine and Cheese. Lancet *2*: 733-734, 1963.

Ayd. F., Blackwell, B. (Eds.) *"Discoveries in Biological Psychiatry",* Ayd Medical Communications, 1971.

Blackwell, B, Marley, E, Price, J, and Taylor, D., Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. Brit. J. Psychiat. *113*: 349-365, 1967.

Blackwell, B. Tranylcypromine. Lancet *1*: 168, 1963.

Blackwell, B. Hypertensive crisis due to monoamine oxidase inhibitors. Lancet *2*: 849-851

Blackwell, B., Mabbitt, L.A., Tyramine in cheese related to hypertensive crises after monoamine oxidase inhibitors. Lancet *1:* 938-940, 1965.

Blackwell, B., Taylor., An operational evaluation of monoamine oxidase inhibitors. Proc. Roy. Soc. Med. *60*: 830-833, 1967.

Blackwell, B., *"Interactions between monoamine oxidase inhibitors and tyramine containing foods."* M.D. Thesis (pharmacology and medicine), Cambridge University, 1966.

Blackwell, B Marley, E., Interaction between cheese and monoamine oxidase inhibitors in rats and cats. Lancet *1*: 530-531, 1964.

Blaschko, H., Amine oxidase and amine metabolism. *Pharmacol*. Rev. *4*: 415-458, 1952.

Brock, A.J., *"Greek Medicine"* p.49. London, Dent & Sons, 1929.

Dale, H.H., Dixon, W.E., Action of pressor amines produced by putrefaction. J. Physiol. (London) *39*: 25-44, 1909.

Findlay, L., The systolic pressure at different points of the circulation in the child and adult. Quart. J. Med. *4:* 489-497, 1911.

Hare, M.L.C., Tyramine oxidase; new enzyme in the liver. Biochem. J. *22*: 968-979, 1928.

Merton, R.K., Priorities in scientific discovery: A chapter in the sociology of science. Amer. Sociol. Rev. *22*: 635-659, 1957.

Merton, R.K., The Matthew effect in science. Science *159*: 56-63, 1968a.

Merton, R.K., "*Social Theory and Social Structure."* Free Press, 1968b.

Merton, R.K., Behavior patterns of scientists. Amer. Sci. *57:* 1-23, 1969.

McCable-Sellers, B.J., Staggs, C.G., Bogle, M.L., Tyramine in foods and monoamine oxidase inhibitor drugs; a crossroad where medicine, nutrition, pharmacy and food industry converge. J. Food Composition and Analysis, *19(Suppl)*: 58-65, 2006.

Natoff, I.L., Cheese and monoamine oxidase inhibitors in cats. *Ibid* 532-533.

Ogilvie, C. The treatment of tuberculosis with iproniazid and isoniazid. Quart. J. Med. *24*: 175-189, 1955.

Prakash, S. Valentine, V., Time line: the rise and fall of Vioxx. Internet Nov.10, 2007.

Samuels, G., Blackwell, B., Monoamine oxidase inhibitors and cheese; a process of discovery. Hosp. Med. *2 (#8)*: 942-943, 1968.

February 22, 2018