Barry Blackwell: “Adumbration”; A History Lesson

Collated Document

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This updated collated document includes Barry Blackwell’s essay “Adumbration”; A History Lesson, and the exchange that followed its posting. They were five participants, with a total of 10 postings: five contributed by Blackwell, two by Samuel Gershon and one each by Edward Shorter, Andre Barciela Veras and Donald F. Klein.

This collated document is now open to all INHN membersfor final comment.

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BARRY BLACKWELL: "ADUMBRATION"; A HISTORY LESSON

"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)

Over 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 & 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 6 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 9 months of my original letter to the *Lancet* I had collected 12 patients taking an MAOI, mostly Parnate, of whom 8 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. 8 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) 4 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 & 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 & 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 twentieth century physiologists discovered it was a hypertensive agent (Dale & 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 & 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 & 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 3 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, 1968 a & 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 & 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 fifteen 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 5 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 twenty 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 & Valentine 2007).

In 1999 Merck, concerned that Vioxx, like other NSAIDs, might cause gastrointestinal bleeding, launched an 8000 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 $5000 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 3 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 & 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 wider discussion of "Conflict of interest" see the "Controversies" program on the INHN.Org website.

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December18, 2014

Edward Shorter's comment

There is one error in the Blackwell piece: It was Henry Ford II, the original Henry Ford's grandson, who presided over the Ford Co18, 2014mpany at the time of the Edsel blunder.

Barry Blackwell's exquisite reflections highlight one big problem today in psychopharmacology and open a window on three smaller problems.

The big problem is industry's unwillingness to explore dangerous new side effects that do not show up in clinical trials at the time of registration. The reason for this foot-dragging is perfectly obvious: Companies may invest hundreds of millions of dollars in drug development, and the thought of this sum suddenly being erased because someone has a headache is simply too awful for executives to contemplate. A company's entire profitability may ride on one or two blockbuster drugs whose patents have not yet expired, and thousands of jobs may depend on keeping those agents selling. This reaction is perfectly human, if contrary to public health.

A perfect example of industry foot-dragging surfaced in the 1960s, as Sandoz, a precursor company of Novartis, displayed active resistance to Thomas Ban's discovery that the antipsychotic thioridazine (Mellaril) could cause sudden cardiac death by altering the Q-T interval. Ban had seen several patients simply fall over and he blew the whistle, but Sandoz showed a studied indifference because Mellaril was such a big seller. I told this story much later in: Shorter. inhn.org controversies 07.18.2013.

Earlier, Tom Ban and I had written an article about the thioridazine problem and attempted to get it published. Several first-rank medical journals, clearly beholden to Novartis' advertising, turned it down on vague grounds along the lines of "not feasible at this time." It was never even sent out to referees. So, yeah, the problems that Barry Blackwell highlights are not uncommon.

Now, I would like to make several other observations of a less prosecutorial nature. The story that Blackwell tells is a riveting one, and engagingly recounted. It is all the more poignant because such a story would be highly unlikely today. Consider some of the major turning points in his tale:

Blackwell initially blew the whistle on the cheese problem in a short note in the Lancet. He simply gathered a few cases together, wrote them up, and sent them in -- to one of the world's major medical journals. I have a bridge I'd like to sell to anyone who thinks this is possible today. Look at the pages of the American Journal of Psychiatry: They are covered with numbers. The letters section at the end, which might also harbor a space for such a contribution, is dominated by heavy hitters, and the editors have to cap the number of references at . . . what . . . 20? Dr. Blackwell, as a resident (registrar) would you have been able to take off the four months required for such an exhaustive literature review? And as for surviving the drumfire of the "referees," who preen with their superior knowledge, good luck.

Blackwell describes the helpfulness of Gerald Samuels, the drug rep of Smith Kline and French, as it then was, who suggested looking at the composition of the cheese, a capital idea! Might a drug rep today play such a key role in sending his employer's favorite agent to the bottom? I don't think so.

Blackwell was able to investigate the tyrosine issue thoroughly once Aubrey Lewis, the professor at the Institute of Psychiatry and the most powerful figure in the discipline in England, simply decreed that Blackwell was to receive what must have been a coveted plum: a two-year fellowship in pharmacology! In the great majority of institutions with which I am familiar today, this simply would not happen. There are committees that determine the distribution of such fellowships and prizes. Diversity and gender are considered at great length. To be sure, such safeguards militate against the distorting influence of an "old boys' network." That is the positive side of such procedural safeguards. The negative side is that such clever singletons as Blackwell, without powerful sociological considerations as a tailwind, will simply be overlooked.

What we gain on the swings of fairness, we may lose on the roundabouts of brilliance. It is a trade-off, but one that does not favor inspired intuitive investigation.

Blackwell's tale should be required reading today for residents, who need to learn that they are being trained as scientists and not just as clinicians. But of course it won't be…

June 11, 2015

Barry Blackwell's reply to Edward Shorter's comment

I thank Ned Shorter for his informative and kind response to my essay as well as correcting an historical error regarding the Ford dynasty. I regret blaming the son for the sins of the father when his only fault was as a designer – although attitudes can travel down the generations. But good history and biography should shun such speculations. I apologize.

With regard to the walls that contemporary editors erect to preserve their reputations and revenue stream, I believe Ned is partly correct as a very recent experience in attempting to get a letter published in JAMA reflects, although I am an 81 year old has-been, not a neophyte. (This exchange with the JAMA editorial board, involving lithium, will be posted shortly on INHN). My youthful experience with the Lancet was more nuanced.

The Editors first became acquainted with me as a medical student when they published a provocative letter to them about "Human Relations in Obstetrics" over my own name and hospital designation. When I took my final exams six months later this cost me an additional six months training in obstetrics before graduation. (My Memoir, "*Bits and Pieces of a Psychiatrist's Life*" tells this in detail). As a first year house officer at Guy's Hospital, I sent them an article based on my rotation through the Emergency Room, "*Why Patient's Come to an Emergency Room."* To my surprise, the Lancet published it. So I was not entirely unknown to the editorial staff when I started at the Maudsley and sent them my letter about cheese. Our relationship developed further; while still a registrar they invited me to contribute anonymous editorials and annotations on topics of their choosing. Every few months, the Deputy Editor, Ian Munroe, rewarded me with lunch at the *Athaneum* – where Aubrey Lewis would sometimes sit in front of the fire, reading the Times as we passed by. He never seemed to notice, nor said a word.

I suspect Ned may be right about Gerald Samuels. Later, in America, I invited a drug representative from Roche to co-author a paper titled "*Diazepam on Demand*" published in the Archives of General Psychiatry. Rather than help his career, I fear it may have damaged it. Despite everything I did to acknowledge Gerald Samuel's support, nothing placated him; he vented his anger towards me for many years – perhaps a displacement of his employer's displeasure at mixing sales with science and its impact on his own career.

Next, the situation at the Maudsley in 1962 was very different from that in America. When Sir Aubrey Lewis offered me the chance of working with Ted Marley in animal pharmacology, it was a unique situation, not a regular post to be filled. Nobody preceded or followed me, it was tailor made to fit a specific opportunity. The same might have been the case earlier with the basic science support for Philip Connell's discovery of amphetamine psychosis. After I moved to America in 1968, I became aware of the way research opportunities were advertised and applied for, funded and farmed out by NIMH. I never took advantage of these opportunities or found a mentor to facilitate them. As told in my memoir, I engaged in many different research projects throughout my career in a variety of areas, most published in leading journals. Not a single one was supported by Government or Foundation support. Like much research in Britain and Sam Gershon's experience in Australia, it was all part of the job description and university salary, the way it had been at the Maudsley.

Ned Shorter's last comment is germane. There seems to be a certain lack of curiosity in medical training today, perhaps because technology wraps a blanket of pseudo-certainty over clinical details that stifles the impulse to ask questions beyond the obvious. Productivity requirements, massive student debt, lucrative procedures and simple greed may do the rest. There is no time or energy for enquiry. I wish there were a way to have residents and research fellows read and respond to INHN.

August 27, 2015

André Barciela Veras' comment

Dr. Blackwell describes an interesting step of scientific discovery that he baptizes Adumbration. As a 37-year-old young professor and investigator, I can imagine the excitement of a ten years younger resident, as Blackwell was in his story, experiencing an important scientific discovery.. That time, in the middle of the 20th century, clinical psychopharmacology was a landscape with many things to be discovered. Nowadays, other areas like genetics and neuronal regeneration seem to be the unexplored new world of psychiatry. However, those scientific fields demand high technology to be explored and such technology is naturally suited to well established research centers with their well-endowed professoriate. This reinforces the process described by Robert K. Merton, the main reference cited by Dr. Blackwell in his essay. Merton analyzes the behavior of scientists, recognizing the role of competition as a central driving force for scientific production. These motivations cause conflictual priorities, as Blackwell asserts. As an example, Merton describes the of the trend in modern science is to award well-recognized research leaders while overlooking junior contributors. Who is awarded with the Nobel Prize when a worldwide consortium makes an important discovery? It seems analagous to Steve Jobs being glamorized by the creation of *his* innovative gadgets. Perhaps in science, this is also the era of CEOs more than master craftsmen. Not a problem if you are aware of it, but beginners in science never are.

Although important findings in clinical psychiatry might still be possible for the beginner - the one who looks at everything with the privilege of unacquainted eyes - insights that could lead to Adumbration are usually followed by frustrations over priorities of society. These experiences make me remember one of the professors I had during psychiatry residency, who used to say, “Every genius idea that you think you had, someone already had before”. With the availability of PubMed I can now easily attest to his observation…

…but my professor forgot to say that not all these previous ideas had the same intention. If the bad news is that there are not so many entirely new ideas to be thought, the good news is that there are infinite ideas that can be used in different ways. Moreover, as a translational researcher, I could certainly agree with this perspective. In Blackwell`s description of his discovery process, there is a moment he goes to the laboratory. There, he starts to live with researchers from different fields, where he (and every translational scientist will) identifies the infinity of inspiring ideas that “someone already had before”, but for another purpose. More than

seeing translational research as the act of bringing insights from clinical research and practice to the laboratory and vice-versa, it can be broadly seen as the act of bringing knowledge from one field to the other. Adumbration may be identified as in the past, as Dr. Blackwell highlights, but it may also viewed as the transition of knowledge between two fields of enquiry.

Pharmaceutical companies have made impressive advances, while pushing psychiatric treatment forward, although not always based on patients` needs; but the pharmaceutical industry has to keep looking in the rear-view mirror while driving, as Dr. Blackwell recommends. Besides, taking into consideration the debate raised in this comment, my additional recommendation is that pharmaceutical companies be more cautious with, and even more interested in, the crossroads of science.

October 1, 2015

Barry Blackwell's reply to Andre Barciela Veras' comment

Andre Veras is the first colleague to comment on this essay and does so with pertinent and intriguing insights and some memorable phrases, raising issues that invite further discussion.

He asserts that new discoveries of the kind I describe are today more likely in areas of "high technology in well stabilized research centers" but also implies that psychiatry is still a clinical arena where a beginner "with the privilege of unacquainted eyes" might discover something novel. I agree that curiosity and naiveté are important ingredients and that new fields are more likely to yield fresh findings. Some pioneers in the *Oral History of Neuropsychopharmacology* commented on the reinforcing effects of working in an environment where everything was new and often statistically significant.

At the same time, technology can exert an inhibiting influence. Many clinicians bemoan the contemporary absence of bedside teaching in history taking, clinical examination and diagnosis with early resort and undue reliance on laboratory tests and imaging studies, diverting eyes away from the patient and their concerns.

The contemporary example I cited of sudden onset hypertension provoked by a Cox 2 inhibitor for arthritic pain raises a relevant question. How could Vioxx have been taken by 20 million Americans, an estimated 88,000 of whom suffered heart attacks and 8,000 died before it was withdrawn? How many young doctors who cared for these patients must have heard their complaints or witnessed their distress without making a connection to the treatment or not reporting it if they did?

Several factors are probably in play, some briefly alluded to in the essay, but worthy of elaboration. We live in an era when television advertising (permitted only in the USA and New Zealand) creates a Pollyannaish picture of drugs, in which known side effects are mentioned but drowned out and evicted from memory by distracting imagery. In this atmosphere, curiosity is dulled or even extinguished, obliterating cause and effect concerns on the part of patients and physicians if an untoward event occurs.

When I reported my own experience to the pharmaceutical company and the FDA, the former gave me bland and inaccurate reassurances and the latter was silent. Fifty years ago, the pharmaceutical representative was encouraging about cheese and the company started their own research (although they did try to steal priority of publication, foiled by a Lancet editor).

The influence of money generated by “blockbuster drugs” has become more powerful and pervasive, corrupting industry and academia. The cost of denying, litigating and eventually compensating for life threatening side effects is built into the high cost of new medication and sequestered as “the price of doing business.” When a “black box” warning is eventually mandated by the FDA, the burden of liability now rests with the physician who prescribes and the patient who ignores it. The manufacturer remains unaccountable and profitable.

Worse yet, testing of new psychotropic drugs is almost entirely in the hands of industry, often including research design, statistical analysis, write up and decisions about publication. Independent analysis and dissemination of the results before and after marketing by clinical guideline panels, professional organizations, conferences, medical educators and FDA panels is often tainted by conflicts of interest generated by generous grants, stipends and fees for advisory functions, lectures, conferences, endorsements or serving on committees; all willingly provided by influential academics. These conflicts are disclosed but never assessed or examined for

evidence of influence, the lack of which is optimistically assumed. (See “Conflict of Interest” in Controversies on INHN).

Residents aspiring to an academic career assume the “publish or perish” burden, which is more difficult to accomplish now, especially for neophytes reporting a serious side effect. Journals have become dependent on pharmaceutical advertising and editors are cautious about their revenue source as well as fear they may incur liability or blame for endorsing or prior publications concerning the drug.

Andre was taught, just as I learned, that the “original” ideas we espouse have almost always been voiced before, but often in a different framework. This is why it is incumbent on pharmaceutical company scientists to be diligent and held accountable for researching the history and diverse properties of drugs they seek to market, avoiding a commercially driven focus on a single indication or mode of action.

Finally, Andre makes a similar point related to the benefits of translational dialog, “bringing knowledge from one field to another.” Here there is also cause for concern. When the ACNP was founded over 60 years ago, this was a core principle well served by a balance in membership between clinicians active in human research and neuroscientists working mostly in animals. Despite the fact that more members now have joint degrees (M.D. and Ph.D.), the balance has tilted to one side, brought about by the virtual exit of NIMH from support for clinical research of the type once conducted by the NCDEU Program and the hegemony of an industry driven more by profit than science. The ratio of meaningful translational findings to the number of posters and their multiple authors on display at ACNP annual meetings is hardly encouraging.I

October 22, 2015

Donald F. Klein’s comment on Barry Blackwell’s reply to Andre Vera’s comment

I share Barry's pessimism, particularly since this problem has been obscured by the wave of enthusiasm over new mind blowing technologies and wonderful basic biology discoveries. Further, these remarkable advances are firmly entrenched within the formidable bench to bedside ideology.

In my 1980 ACNP Presidential address, an analysis of member's interests, in terms of their year of entering ACNP, was presented. It was overwhelmingly plain, even then, that ACNP was becoming a neuroscience organization.

On the credentials committee, bibliography size loomed large. Human controlled studies often took years. PhD studies usually of animals often took a few months or less. They were statistically stronger with a tiny dropout rate. This seems a fact of contrasting specializations.

Further, much clinical work was fairly pedestrian, if clinically useful. In contrast, neuroscience was rich with fascinating hypotheses, advanced methods, and optimistic forecasts, even if seldom leading to clinically useful results.

This problem has not had much discussion. Trying to sort out the realities impeding clinical progress. Currently, lacking useful substantive notions, NIMH has promoted the fishing expedition to discovery science, while methodology is the fact free villain. Categories are just straightjackets but dimensions are the Royal Road to eventual deep knowledge that also pays off clinically. Optimism reigns.

December 24, 2015

Barry Blackwell’s reply to Donald Klein’s comment on his reply to Andre Veras’ comment

I thank Don Klein for his sage comments on my reply to Andre Vera's earlier contribution. He addresses the significant issue also raised by Sam Gershon's recent comment on the scientific response by individuals and the entire field due to a changing Zeitgeist. This reminded me of points made in an essay I wrote in 1970 on *The Process of Discovery* (Blackwell, 1970) as a prelude to the first Taylor Manor Award Series on *Discoveries in Biological Psychiatry* (Ayd & Blackwell, 1970). In the conclusion, I cite Lawrence Kubie's cautionary note (Kubie, 1954). In Kubie's analysis of unsolved problems in the scientific career, he questions whether students should be warned that scientific success is often determined by social forces beyond individual creativity or the will to work hard. He expresses concern that a frustrated urge to discover might breed a generation of cynical, amoral and disillusioned young scientists suffering from "a new psychosocial ailment that may not be wholly unrelated to the gangster tradition of dead end kids." A few years later, Robert Merton comments on Kubie's concern and points out that "for most artisans of research, getting things into print becomes a symbolic equivalent of making a new discovery" (Merton, 1957).

Don makes the interesting point, contrasting clinicians with neuroscientists, that the latter can pad their resumes by short-term animal studies with low dropout rates and strong statistical conclusions. This is compounded by multiple authors on display in the ACNP poster sessions.

A sizeable bibliography may also be an anodyne for lack of clinical relevance and a dwindling bench to bedside translation contributed to by Don's prescient Presidential observation a quarter of a century ago, that the ACNP was "becoming a neuroscience organization." What a shame the leadership allowed its membership to become so lop-sided and that the NIMH virtually extinguished long term support for expert and independent clinical research.

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January 7, 2016

Samuel Gcrshon's comment

This is a very important and insightful document. It raises many issues that are diluting the quality of medical education, and therefore, the quality of medical care. There are many causes for this in today's interconnected causalities. Many medical centers have centralised control of physician's style of practice by having a master appointment center making doctors' appointments for them without knowing anything about the particular patient. The appointments are classified as first visit and follow up with the latter getting about a 12 min allocation. There are medical centers which are producing a profit but curtailing expenditures for medical staff and for staff time for medical education. I am familiar with several examples of this, where staff time for teaching is curtailed and to facilitate this, some topics are cut from the curriculum, e.g., clozapine and lithium. I hope that opening this issue up for wider discussion will be followed up by other articles elaborating on these issues. I would like to open up the pressures on scientific journals and the enormous cost cutting instituted by publishers. We should not believe for a moment that these costs are not paid for in other ways, which end up diminishing the value of some published material.

October 29, 2015

Barry Blackwell's reply to Samuel Gershon's comment

Sam's kind comment is directed not so much to the specifics of my essay but to the underlying issue, which is "exploring or ignoring the past to explain the present." This is a topic

for which he advocates a “wider discussion” involving contemporary medical practice, medical education and scientific journalism.

I believe it is true that economic factors, eroding ethics and professional greed have created a radically different modern Zeitgeist compared to the early days portrayed in the ten volumes of *The Oral History of Neuropsychopharmacology* edited by Tom Ban (ACNP, 2011). Much of this is discussed in my memoir, *Bits and Pieces of a Psychiatrist’s Life* (Blackwell, 2012) and some of the impact and implications for contemporary psychopharmacologists are portrayed in the biographies of prominent pioneers in our field. (See INHN.org in *Biographies*).

With this larger scope available as background, I will comment briefly here on the three domains Sam mentions. With regard to medical practice Sam draws attention to the consequences that flow when formerly independent practitioners become salaried employees of large healthcare corporations, a rapidly increasing problem including all full-time hospitalists, many primary care physicians, some psychiatrists and occasional psychiatric administrators or CEO’s. Despite their alleged “not-for-profit” status (to evade taxation) these corporations are driven by a “bottom line” mentality expressed by the administrators at my former hospital uttering the glib axioms *“No Margin, No Mission”* and *“Every bucket must carry its own water.”* Resources were diverted away from faculty stipends and medical education towards administrative salaries, advertising campaigns and competitive building programs to create hegemony, aggravated by declining bed occupancies and income due to federally mandated DRG’s, managed care guidelines, insurance company parsimony (prior to alleged parity) and low Medicaid reimbursement. During the 1980’s and 1990’s, five inner city hospitals in Milwaukee merged and later went bankrupt. Some of these events are described in my JAMA editorial (Blackwell, 1994).

Eventually, the hospital, where I was Chair of the academic program in psychiatry, was taken over by the largest health care consortium in the region. In the Department of Family Medicine, faculty was given the choice of no longer treating inner city Medicaid patients or resigning. The Department of Psychiatry was disbanded, the inpatient unit closed and the residents dispersed, contributing to a lack of psychiatrists and beds in a city plagued by homelessness and chronic recidivism reminiscent of the early days of deinstitutionalization,

aggravated by the remaining psychiatrists in private practice declining to accept Medicaid patients.

The academic family medicine department and its residency program were eventually closed; the Chairman accepted a job with the health care corporation and is now it's CEO, earning an annual salary in excess of $4 million.

Sam notes that employed physicians are now subject to productivity quotas and hospital residency training programs now progressively restrict the time allowed for interviews. After entering practice, salary levels are adjusted according to "productivity". This discourages physicians from accepting time consuming patients, the elderly, mentally ill, Medicaid or Medicare recipients.

As a medical student at our local private Medical School, my son's tuition was $40,000 a year. A previous magna cum laude student at another university in politics, philosophy and economics, he was ineligible for health insurance under his parent's policy. The medical school, with a large well organized practice plan, offered no heath care to students but would loan him another $10,000 to purchase it. He declined, obtained Medicaid and was offered food stamps he never asked for! The medical school auditorium has a ten foot statue of Hippocrates guarding the entrance to its library. His oath, that students are asked to endorse, states medical education should be "*without fee or covenant"*. There is no better example of the greed that is now endemic in medicine than the disappearance of *"professional courtesy"* coincident with the ability of our procedure performing colleagues to become millionaires. My son opted for family medicine and is very happy, living one block away from where he grew up and in walking distance to his office.

During my fifty year career as an academic with the "publish or perish" motto hanging over my head, I had cordial relationships with the editors of many journals who accepted my research or for whom I worked *pro bono* as a reviewer. After retirement, I sought to obtain a copy of the editorial I had written for JAMA twenty years before (No Margin, No Mission). I was told I could only do so after paying a substantial fee and even then, only if I rejoined as a subscriber. I reluctantly did so, leisurely scanning the contents of the journal for psychiatric material. Some months later, I read a review of an article on emergency room visits and

admissions due to the side effects of psychotropic drugs (see Blackwell, 2015). In brief, the author of the review noted that lithium was the most frequent cause of admissions and attributed this to excessive and unwise use of the drug. Evidence for this was absent, as well as any attempt to address or establish the use of well-established prescribing guidelines. I wrote a letter to the Editor suggesting this was incorrect and eventually received a reply stating that a group of sub-editors had decided my letter lacked sufficient "impact". The journal made no attempt to contact either the original authors of the study or the reviewer who had drawn a faulty conclusion. The letter informed me I could contact them myself but it was uncertain they would reply. I concluded that editorial ethics had deteriorated since the days when I was a resident and wrote anonymous editorials and annotations for the Lancet.

It remains to speculate on the degree to which a changing Zeitgeist in the future may create barriers to success for psychiatrists, in general, and psychopharmacologists or neuroscientists, in particular. In writing the biographies of our pioneers, three attributes appear to assist in negotiating the unexpected but inevitable obstacles to be faced during a career. They are *prescience* (an ability to anticipate change), *flexibility* (a capacity for adaptation) and *fortitude* (a resilient attitude to surmount challenge and frustration). A forthcoming biography to be posted on INHN describes and explores this aspect in more detail (Blackwell & Charalampous, 2015).

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December 17, 2015

Samuel Gershon's response to Barry Blackwell's reply

I am deeply indebted to Barry Blackwell for his response to my concerns about medicine as a discipline. His response made the picture clearer and with more impact. We are both talking about how medical teaching is influenced by medical care, both its quality and availability and the newest limitations in medical management. The influence of corporate trends in medicine is almost complete and dictatorial and its policies affect every component in its domains. Barry and I mentioned briefly the effects on medical publications. These also cover medical publications from textbooks, once considered the bibles, in which one could find the unbiased truth to scientific journals that cover a very wide range of specialization, quality and reliability, etc. Colleagues! This is where the truth is supposed to be presented for open discussion and debate and hopefully to improve care and produce cures. There are now other publication and information sources of uncertain reliability; magazines with target populations; and television and the new electronic gadgets for communication. ALL of these can be, and are influenced by financial interests which impinge on all of the above core factors in health care. I am the co-editor of a scientific journal and have been for the last 18 years. The journal was funded by the publisher. That is, paid editorial staff in our office, paid rent for office space, paid office equipment including telephones and other forms of communication. So, now we are down to Zero funding from the publisher and the co-editors have to produce the journal and maintain scientific quality and integrity. I must tell you that this cannot be done. This is not just my story; it is the story throughout the medical publishing industry. The consequences affect every aspect of the quality of scientific information. So, be sure there is a cost and there will be a true trickledown effect on the quality and cost of medicine as a discipline. I invite others to consider these questions and raise the necessary alarms! \

December 31, 2015