AMP

ARCHIVES OF MEDICAL PSYCHOLOGY

JOURNAL OF THE ACADEMY OF MEDICAL PSYCHOLOGY

ARCHIVES of MEDICAL PSYCHOLOGY

VOLUME 11, ISSUE 1

July 2020

AMP
ARCHIVES OF MEDICAL PSYCHOLOGY

July 2020 • Volume 11, Issue 1

AMP
ARCHIVES OF
MEDICAL PSYCHOLOGY

Editorial Policy

The Archives of Medical Psychology publishes original articles online regarding the application of medical psychology as it applies to the psychological, biological and sociological aspects of healthcare. Medical Psychology is defined by the Academy of Medical Psychology and appears on its website at http://www.amphome.org. Authors are invited to review this definition of Medical Psychology prior to submitting their manuscripts for publication.

Articles regarding diagnosis, treatment and practice of medical psychology for pre-vention and amelioration of disabling conditions or human suffering are welcomed. Documentation of current practices in the diagnosis, treatment and prevention of health disorders is essential for the development of techniques and methods of medical psychology and may be given preference. Issues dealing with the economics of access to health care, the political aspects of the scope of practice of medical psychology and comparison of techniques of diagnosis and treatment in healthcare are within the purview of this Journal. Articles dealing with the education, training and advancement of medical psychology in the public interest are included in the broad-spectrum of the definition of medical psychology. How advancements in other scientific fields will affect medical psychology will be considered for publication. The Journal also publishes timely brief reports of research germane to medical psychology and health care.

The Archives of Medical Psychology has chosen the electronic online medium for prompt distribution of articles of interest in medical psychology. Electronic transmission offers advantages of speed and economy for the distribution of important scientific works pertinent to medical psychology. The purpose of the Journal is to deliver accurate state-of-the-art information as quickly as they can be prepared. Therefore, articles will be published when they are deemed ready for publication and will not be collected and held to arbitrary publication dates. Subscribers to the Journal will be notified when new articles are published online. The page numbers of the articles will be in consecutive order in the Volume of the year in which they are published.

Information for Authors

Submit manuscripts electronically to http://www.amphome.org. Authors should submit their manuscripts of their original work in the style used in this issue of the Archives. Articles cited should be numbered in the order in which they appear in the text and then listed by number in the Reference section, but MLA style with alphabetized references by author is also acceptable (see: http://bcs.bedfordstmartins.com/resdoc5e/res5e_ch08_s1-0013.html)

and articles in MLA style will be followed by a foot note (Note: Author submitted article in the alternate MLA style!" Submissions of manuscripts should be double-spaced preceded by an Abstract of not more than 250 words. Up to five keywords or phrases should be included in the Abstract to assist in the review process. All manuscripts are copyedited for bias-free language. Graphic files are welcome when supplied as Tiff, EPS, or PowerPoint.

The publication policy of the Archives is to refuse manuscripts submitted concurrently for consideration in other journals. Authors are obligated to consult with editors of the Archives concerning prior publication of any data on which the article depends. The Archives adheres to the American Psychological Association (APA) Ethical Principles that specify that "after research results are published, psychologists do not withhold the data on which their conclusions are based from other competent professionals who seek to verify the substantive claims through reanalysis and who intend to use such data only for that purpose, pro-vided that the confidentiality of the participants can be protected unless less legal rights concerning proprietary data preclude their release."

Ethical Standards: Authors are required to state in writing that they have complied with APA ethical standards in the treatment of their sample, human or animal, or to describe the details of treatment. Authors are required to obtain and provide the Editor on the final acceptance all law all necessary permissions to reproduce in print and select electronic form in a copyrighted work, including, for example, test material or portions thereof and photographs of people.

Manuscript review is by a blind reviewing process with the author's names and locations concealed from peer reviewers. Authors will be notified when their article is submitted for peer review. Results of the peer review process will be e-mailed to the first author of an article.

Reference Style examples

Muse M & McGrath R. Training comparison among three professions prescribing psychoactive medications: Psychiatric nurse practitioners, physicians, and pharmacologically-trained psychologists. J Cl Psycho. 2010, 66, 1-8.

Norcross J & Goldfried M. Handbook of Psychotherapy Integration: Second Edition. 2003. New York: Oxford Univ Press.

Army Regulation 40-68, Medical Services, Clinical Quality Management (Revised). Issue Date: 22 May 2009, pgs 33 & 34. Department of the Army, Washington, DC: Author. Web link: http://www.army.mil/usapa/epubs/pdf/r40_68.pdf

Disaster Response Network 1991 http://www.apa.org/programs/drn/index.aspx

The *Archives of Medical Psychology* can be reached at PO Box 256 Marshfield, MO 65706, Ward M. Lawson PhD, ABMP, ABPP, 417-859-7746.

AMP
ARCHIVES OF MEDICAL PSYCHOLOGY
July 2020 • Volume 11, Issue 1

Archives of Medical Psychology

Table of Contents

In Memory of Nicholas A. Cummings

John Caccavale, Ph.D.

Dr. Nicholas A. Cummings, Ph.D., Sc.D., passed away on June 9, 2020. Nick would have been 96 years old on July 25, 2020. His wife of 74 years, Dorothy, his two children, Dr. Janet Cummings and Son, Andrew Cummings, two grandchildren, Mary and Kent, and two recently born great grand children survives him.

Professional Psychology has lost its champion—its last guiding light to relevance and we have all lost a friend and colleague. I personally am deeply saddened about Nick's passing. He was a close friend, colleague, and collaborator. However, I am more saddened that so many more psychologists have no idea about who is and was Nicholas Cummings. After announcing Nick's death, I received several emails asking me, "who is Nick Cummings?" Hiding my disappointment, I directed those inquires to Nick's published biography, "Nicholas A. Cummings: Psychology's Provocateur" by Dr. Carol Shaw Austad, which is available on Amazon. I also asked the inquirers to look at Nick's last video presentation on the NAPPP.org website.

I had no intention, as I do here, to list the multitude of achievements attributed to Nick because it is simply not possible to do so in an email or in these short pages to detail the life of a man who has done so much for professional psychology. Moreover, how does one really summarize the work of a man who has written 47 books, a few hundred articles, created and innovated a revolution in the education and training of psychologists, and created the first psychologist owned company providing services to millions of patients? It is simply not possible. I highly recommend, as I did to those inquiring about Nick, that anyone wanting to know why we even have a professional psychology, to pickup Nick's biography and to see and hear from Nick himself in his last video on the NAPPP website. Nick deserves your curiosity.

Here, I want to talk about Nick, the person. The type of man he was. His lifelong commitment to advocating for our profession, patients, and to lifting professional psychology to the highest level of acceptance. In the many years that I have known Nick, he never once wavered from that mission. Nick and Dorothy, aided by his children, devoted untold time and treasure to Nick's goal to develop effective and efficient therapeutic treatments and to provide practitioners with the tools and resources to become
effective professionals in both training and practice.

Some of Nick's critics in psychology's academic bureaucracy dismissed his work as being too focused on the "business" aspects of practice. Nick's response, as the true provocateur he was, created the first professional school of psychology in California and later, a company, American Biodyne, that was entirely owned and operated by psychologists. Nick demonstrated that practitioners could be both highly effective therapists and knowledgeable about the business aspects of running a practice. Nick was simply unwilling to accept that the work we do should not be reimbursed at a level appropriate to our education, training, and experience. Being a professional psychologist had value that, for many of us, had

Correspondence Address: NAPPP Executive Director, admin@nappp.org

been obscured and looked down upon by those same bureaucrats that were also critical of Nick's lifelong work.

Nick was a fighter as well as an innovator. Even as he assumed the presidency of the American Psychological Association, Nick could not be co-opted. He continued to fight APA's intransigence to private practice and reimbursement for our services and for the many roadblocks the academic bureaucracy put up to slow down the progression of private practice. In my many conversations with Nick about his time as APA president, he reveled in and took pride confronting resistance. Yet, one of the greatest aspects of Nick the man was the total lack of bad feelings he had for his critics, detractors, and those who desperately tried to derail him even to the point of betrayal. This was a man who accepted their calls for help and would not cast them off. I recall many times when I told him, "I couldn't be that generous so often." Nick would just smile. He accepted and understood the strengths and weaknesses of human behavior. Nick was the quintessential psychologist. He was a truly generous human being.

For patients, Nick advocated for access to quality mental health care. He served on many commissions and boards, many that he established to get greater access and funding for mental health. Throughout his career he lobbied Congress and presidents for patient care. He never accepted that people should not have access to care or could not be helped whatever the issues presented to a practitioner. It was a part of Nick's character to confront the issues that he cared about most. In my many conversations with him about how greater access to care could be achieved, Nick was never without ideas. Although retired from practice for many years, I could always sense his frustrations that organized psychology was continually dropping the ball and being mostly inactive in promoting the high goals that we all had in becoming professional psychologists.

Nick believed in patient advocacy as a part of practice. He never accepted the platitudes to practice and patient care without commitment that is so lacking in organized psychology. For the entire year prior to Nick's passing, he was concerned and disappointed, but not surprised, by the campaign by APA to downgrade the doctoral level as entry into professional psychology and the concomitant policy to gain independent practice for masters level practitioners. Nick had created and led the fight for licensure and fought over a 20 year period until every state licensed doctoral level psychologists for independent practice. To see that struggle dismissed and diminished was simply unacceptable to Nick Cummings.

His opposition was not to master level education. Nick believed that patients deserved the highest quality of care and that care was better delivered by a professional trained at the doctoral level. This is why he created and funded the Cummings Institute for Behavioral Health and created the Doctor of Behavioral Health degree. After creating the professional school movement, Nick saw that his vision and mission for doctoral level education had become entangled in APA politics and misplaced goals. The mission of the professional schools of psychology was to provide students with a practice-focused education and training and low to even no cost. That mission long gone and transformed into tuition driven enterprise.

When he established the California School of Professional Psychology in 1970, over half of the incoming students were on scholarship. Now, students in these schools hardly ever receive a scholarship and many accrue over a $100,000 in debt at graduation. Nick attributed this debt to the misplaced notions of an "uniformed" academic hierarchy committed to overburdening students with irrelevant and unneeded coursework resulting in a high cost, debt crunching education. This is why Nick set the cost for the Doctor of Behavioral Health degree at $20,000 to complete the entire program. Moreover, some students are on

full scholarship. Nick always put his energy, talent, and money into those causes he believed in.

To his colleagues, Nick was loyal and always available. If he believed in what you are doing, he was there to help. He didn't care what others would say about anything he became involved in. For example, in 2006, I approached Nick and told him that a number of us were not happy about the direction that APA was taking with respect to practice issues. I told him that I wanted to start a new organization based upon the principles of no bureaucracy and commitment to service for practitioners and patients. Without flinching or taking another breath, Nick said, "count me in and became a founding board member of NAPPP. Nick contributed to NAPPP until he retired from the board in 2016.

Nick's commitment to his colleagues and psychology was important to him. For many years his foundation funded so many programs that recognized important achievements our colleagues. The foundation also funded The Nicholas and Dorothy Cummings Center for the History of Psychology, located at The University of Akron in Akron, Ohio, that is a repository for collections and to preserve and provide access to the historical record of psychology and related human sciences. Clearly an important on-going project particularly when so many psychology programs have deleted courses on the history of psychology.

Nick was also a champion for his many colleagues, as well. For example, whenever he read something that a colleague wrote in a journal or elsewhere, the author could expect to receive an email or call from Nick with his kind words of praise and encouragement. He believed in recognizing the work of others. Although over the course of his professional career Nick received many awards and recognition, designated as a visionary and prophet by many, he was always humble about his achievements. With the passing of Nick Cummings as large part of psychology has also passed. For those of us who was his friend and colleague Nick's passing is an enormous loss. He was a unique individual and a model for every psychologist to emulate.

Psychotherapy Practice in the Pandemic and Beyond

Jerry Morris, Psy.D., ABMP & John Caccavale, Ph.D., ABMP

Abstract

COVID-19 is presenting the US healthcare system with many challenges, chief among them, however; is the effects on the healthcare system and particularly mental health services. The vast majority of practitioners of mental health services have seen their practices change dramatically. Whether in private practice or in a facility, all have been impacted by this pandemic. COVID-19 practice and beyond will require a substantially different skill set to meet the demands imposed by this pandemic.

This article addresses many aspects of the changes and challenges that COVID-19 presents to psychology practitioners and perhaps to many other types of providers. While epidemics and pandemics are not new phenomena, COVID-19 is the first healthcare crisis that has changed the way mental health services are provided. The transformation of face-to-face therapy, for example, has morphed into "digital face-to-face." Teletherapy has become the norm since the virus forced psychologists out of offices and facilities. Although there are studies reporting that Teletherapy is not significantly better or worse than traditional face-to-face therapy, the long-term effects of such a drastic change to practice remains unseen. What is certain is that practice in a pandemic requires specific professional skills and will be a hard earned and learned specialty that few have without intensive psychological, scientific, and personality training will master. As levels of anxiety, depression, and perhaps even suicides, are likely to increase, psychologists will be needed, essential, and accessible like never before. Everything from finding and learning new equipment, negotiating with insurers about reimbursement, and navigating state and federal rules and regulations are challenges that must be confronted and overcome. These and other important issues are addressed.

The Long History of Epidemics and Pandemics in the United States

Given the history of epidemics and pandemics that have been seen in the US, one would think that there would be some experience dealing with these epidemics. For example, starting with the Yellow Fever Philadelphia epidemic of 1793 that didn't see an effective vaccine until 1935. The 1832-1866 Cholera epidemic in New York City with three separate waves before it was contained. The 1858 Scarlet fever plague in New England that ravaged mainly children. The 1906-1907 Typhoid Fever and the now infamous Typhoid Mary scourge in New York. The 1918 Spanish Flu, which later emerged as the Asian Flu and killing nearly 70,000 people in the US. The 1921-1925 Diphtheria epidemic peaked with 206,000 cases before it was contained. The 1916-1925 Polio virus that peaked in 1952 with almost 58,000 reported US cases. The 1981-1991 measles outbreak coming in two waves. The 1993 Milwaukee contaminated water caused by a protozoan (Cryptosporidium) saw over 400,000 people infected and, until today, there are over 700,000 cases annually in the US. The 2010 and 2014 Whooping cough scourge caused by the bacteria Bordetella Pertussis that attacked the lungs. The HIV and AIDS epidemic of the 1980s infected 1,200,000 and thousands of deaths and still is without a cure or vaccine. The latest pandemic is the SARS/Covid-19 with the US leading the world in infections with over 1.2 million and 75,000 deaths at the time of this writing aided by containment blunders and vast

Correspondence Address: NAPPP Executive Director, admin@nappp.org

shortages of medical equipment and healthcare personnel. The US is prone to having to deal with Epidemic Spread Illnesses so what is different this time around?

Obviously, throughout history nothing is more deadly than infectious diseases. In 2017 top world virologists were writing articles and feature stories warning that the world is not prepared for another pandemic. White papers with dire warnings indicating that a flu pandemic was only a matter of time and that there are millions of undiscovered viruses in the world. Presidents Bush and Obama heeded the science and called for a US preparedness and funding . This was met with effective opposition from Republican's in Congress resulting in a lack of preparation that was attenuated well beyond the warnings from scientists. Diseases like Sars, HIV, and Covid-19 have increased rates of infection up to fourfold over the past century.

Maladaptive human behavior and other factors that contribute to increases in infection rates can be attributed to the spread of conspiracy theories that minimizes both the prevalence and danger of an infectious disease. Then there is the oppositional paranoid theories about vaccines, cultural opposition for protracted self and formal quarantining, mass testing and contact tracing, and scientific stratified random and targeted studies to develop strategic planning. Then there are those who have difficulty coping with strategic confusion. They engage in contrived ignorance and outright denial, the "head in the sand" scenario to control anxiety and existential dread. Distortive thinking finds its way into propaganda to minimize or prevent the assimilation of reality. All of these psychological variables and tendencies block prevention, preparation, containment and result in unnecessary death and economic damage. They create cultural tensions, division, and faction-based conflicts. Psychologists, as in the treatment of addiction and depression, will have to address these defenses while respecting individual differences. Psychologists will need to establish a therapeutic alliance with people with these inefficient and maladaptive defenses with sensitivity and empathy for their function and the ability to temporarily put off processing of long-term or teleological (Gordon Allport) thinking and appraisal (reality testing and insight and judgment) necessary to change attitude and behavior.

Providing Mental Healthcare During and After the Pandemic

The psychological treatment for those effected by an epidemic or pandemic requires specific professional skills and is a hard earned and learned specialty that few have without intensive psychological, scientific, and personality training. Thus, psychological therapies will be intensely needed both in the adaptation stage to a mass infection and tragedy, but also in the recovery phase when people with maladaptive of primitive defenses are experiencing guilt and shame, interpersonal blaming and opposition, and loss of social and personal esteem. Many in this subset will need intensive psychological healthcare services. Additionally, there is another group of people, which by scientific evidence may amount to 24% of the population in any 24-month research window and, perhaps much more in long-term snapshots, with mental disorders or addictions that succumb to or have conditions exacerbated by stress. This is especially true for protracted or chronic stress, high intensity stress, or stress for which there is no immediate solution or escape resulting in regressive feelings of helplessness and hopelessness. Some will become profoundly depressed and withdrawn. Others may present with paranoid and hostile and hyperirritability, some impulsively and recklessly seeking distracting stimulation and excitement and deflection relief, and others may cope with suicide or aggression against others (displacement). Psychologists will be needed, essential, and accessible like never before[1].

Facility Based Practice

Currently, many facility-based psychologists are answering the national call. They have remained in practice as “essential providers” and have been listed as such in Government

literature and bulletins[2]. They have adapted by investing in equipment and restructuring their facilities to accommodate patients rationally, scientifically, and safely. They have purchased extra computers, subscriptions to approved and encrypted Telehealth software systems getting the required and signed Business Associate Contract with the platforms and providing the background audit potential for time and function and coding of services required in Telehealth laws and rules. They have adapted to the temporary relaxed Telehealth requirements and, in some states telephone therapy to accommodate rural and poverty patients who do not have access to electronic equipment or adequate internet capacity, rules and bulletins (check your state, they are variable), and they have achieved appointment to insurance and Medicare and Medicaid approved vendor status to get paid for helping various populations needing care. Psychologists have refitted their clinics, offices, and comprehensive health facilities with expansions of waiting rooms to spaced seating, outdoor seating, frequent sanitation, diffusers and aromatics, glass barriers for administrative functions, hand sanitizers, and improved ventilation.

Many clinics have established internal Telehealth with several solo patient rooms with electronic transmission to the doctor's room and Telehealth transmission between the two. Separate entry and exit paths for patients, and well-marked no egress areas separating patient and staff portions of the facilities have been developed. Staff and patients are daily checked in with an electronic thermometer and their temperature taken, and there are Covid-19 symptom forms available that patients answer on phone or internet prior to being scheduled for an appointment. Always, areas and surfaces and air flow are sanitized several times a day. There is testing available and for free according to what Congress has done, though the private companies are responsible to try to bill your insurance. You can get several test kits to see if your staff is positive and then must close your facility for two weeks and test other staff who have potentially had contact with an infected patient.

Some of the wonderful options in the Telehealth approach is the ability to use the Share Screen and White Board functions of telecommunication. These important functions demonstrate test findings and teach about strengths and weaknesses, diagnoses and what it means, and to engage the patient in question and answer bonding exercises. Further, the approach lends itself well to manualized treatments and workbook exercises with the patients that like that and want to study and become a fully informed partner in understanding and directing their treatment. Finally, Telehealth is a platform that is well suited for multi-member group interventions. Many platforms will allow for 8-12 members to be spliced into a group. Some platforms allow the option of having the patient that is talking to be the focus of the screen and to switch back and forth among showing all the group members, and the talking member (or doctor) on the screen.

Telehealth also allows the psychologist to attach assignment and readings sheets for download and printing, to show YouTube films on techniques for discussion and demonstration, either made by the psychologist or available online, and to patch in distant family members for family therapy interventions. Juvenile officers, probation officers, teachers, separated spouses, foster children for family integration therapies, hospital and primary care emergency consultations, and licensure and specialty supervision sessions with trainees and interns and residents can also be contacted through the Telehealth platform. An effective and efficient Telehealth system is generally liked by about 75% of patients and staff once they become facile in using it.

Clearly, there are significant issues when using Telethealth related to planning, engineering, equipment, renovation, training, and maintenance costs necessary for practicing in health facilities over the next six months and possibly beyond. Already, states are talking about revising standards so that Telehealth stays as a core process in healthcare. Obvi-

ously, psychology practitioners and practices often have a need for help in adapting to the demands of new technology. Psychologists were not given the $44,000 per doctor to gear up for Electronic Records and Congress has neglected to remedy this for years. For example, the costs to purchase computers with Telehealth capability and software capacity is significant. Renovations for improved spacing and tech filtered airflow in waiting rooms, and perhaps the entire facility, is an added cost. Refitting waiting room and treatment room furniture to the types of furniture that can be cleaned and sanitized more effectively is another added burden.

Adding expertise, equipment, and additional hours for cleaning staff, erecting glass barriers with openings for temperature testing and to safely pass forms and other important documents will be costly. Establishing enrollment and questionnaire computer stations in waiting areas, establishing safe and regularly sanitized restrooms and a separate restroom for hand washing and sanitizing system adds to the continuing cost of operating a facility based practice. Hiring staff to link, test and train patients to effectively use home Telehealth equipment can present many challenges particularly with patients who have little to no experience with computers and software. Scheduling patients for their appointments with the doctor can take valuable time and cost, even though some states will reimburse for the cost of staff charges in addition to the doctor's charges. So, it's a good practice to check your state's reimbursement policies.

Consulting state regulations relating to establishing and making accessible Telehealth informed consent and agreement forms, getting them signed is essential. Also, practitioners should modify advertising and public information so that patients are aware of the ability to access the doctor’s services and how to access it and that insurance, Medicaid, and Medicare will pay for these services is important. Modifications to billing procedures and equipment to include Telehealth codes and payer source and Telehealth contract requirements, etc., is an important adjustment that must be made prior to taking patients in this modality.

As can be seen, the barrier to access appropriate and designated “essential service” care will require that the state and federal adaptive legislation and grants and funding streams must address these issues. We must all consider that gearing up to accommodating increasing patient needs for access and for psychological care for this Pandemic and future epidemics and annual flue and other infections is a must. The fact that we address nurses and physician and hospital needs but rarely address psychotherapy needs

is simply being oblivious about the incidence and prevalence of emotional disorders, the psychological components to epidemics and pandemics demonstrates the continuing dismissal by appropriators of the need and scope of mental healthcare. Moreover, frequently dismissed are the lifestyle aspects of most of the major chronic and budget breaking medical disorders that are generally only treated with inadequate medication only or surgical approaches by the medical system[4,5]. Psychologists need to be regularly communicating with legislators and state and national associations for advocacy in these areas.

Solo and Small Office based Practice

If there is one thing certain about COVID-19 is that nothing really is certain about when it will end and how pervasive will the effects of the virus alter every aspect of American life and institutions, and perhaps the whole world. As for psychology practitioners, one thing is becoming clear: Practice pre COVID-19 is not likely to be the same post COVOD-19. As practice has shifted to home base and Telehealth, it is not at all clear that office based solo practice can suddenly restart or go back to normal. Moreover, the longer this virus remains pandemic, the less likely there will or can be a return to any sense of normal. While the

healthcare emphasis remains on containing the virus and formulating a vaccine, mental health has taken a backseat as something less of a concern even as there is a mounting number of people who require mental health services.

From the little data that I have reviewed, State Boards of Psychology are offering little help or substantive guidance to practitioners. Because relatively few psychology practitioners in private practice have adopted wide use of Telehealth in their practices, gearing up from "zero to 60" in such a short time is a major problem. Questions relating to the rules and regulations governing Telehealth remain obscure to many and clearly may even be out of date with COVID-19. For example, I believe that every state requires licensing if doing Telehealth with a patient that is in state different from the practitioner. One would think that this type of restriction is not only out of date but really is not logical going forward. Should it matter that a practitioner, through Telehealth, is providing services to a patient in another state? The patient is coming to the therapist and the therapist has not left the jurisdiction that they are licensed. The therapist is not travelling. From the short survey that I have been doing by contacting practitioners in some states, their BOP has not relaxed any restrictions and have responded to such questions by reiterating the practice laws of the state in question.

Healthcare Insurers Need To Be Flexible

Responding to a clear need for action, Medicare quickly relaxed their rules for Telehealth giving practitioners the go ahead to provide services to recipients without the need to go through the typical bureaucratic maze pre COVID-19. However, most, if not all, healthcare insurers are still requiring practitioners to go through the process of redoing their contracts to include Telehealth. Although many of these insurers follow Medicare reimbursement rates, for example, one would think forcing practitioners to waste time with silly paperwork in a time of crisis is not in the public interest.

Post COVID-19 Solo Practice and Healthcare

There would probably be little disagreement that nothing beats face-to-face behavioral therapy. Yet, one thing that is predictable is that many practitioners and patients may soon prefer Telehealth over office based services. For many patients who are somewhat computer literate Telehealth is appealing. Others may prefer not leaving the comfort of their homes. Those that have a disability can make Telehealth a real option. For practitioners, Telehealth offers the additional benefits of cost savings related to transportation, office costs, and the ability to work from home. Nevertheless, a completely home based Telehealth practice may be difficult for solo and small practices.

This is likely to put a burden on practitioners because unless there is a 100% change-over to Telehealth, there will be the added cost of keeping an office for some patients along with all the costs of office based services. Many practitioners may be hard pressed to having an office for one or two days a week or perhaps even less. Given that this is likely to become an issue, it is probable that many practitioners will be seeking one day rentals from Executive Suite arrangements or seek out renting a room from other practitioners who have the space. Given the adoption of Telehealth, a lot of office space is likely to be available. One functional solution would be for practitioners to rent an office and split the costs as no one practitioner is likely to occupy the space on a full time basis. Financially, these costs would be very manageable and could actually be profitable between doing Telehealth for some days with patients who like that arrangement and having an office for those who need a face-to-face visit. The point is that practitioners have an opportunity to redefine practice in ways that benefit patients and themselves in an environment that will continue to be unpredictable. Taking control now would be to everyone's advantage. For newly licensed practitioners, this type of arrangement could make and sustain a developing practice.

Consequences

The major consequence of this Pandemic, and for that matter all the others in our long-history of mass infections, is increased awareness of the importance of evolving our healthcare system to be prepared. To become more interested in prevention and become equipped to address these healthcare challenges. These events happen in America and are well chronicled in our history. Yet, we have failed to be innovative, especially to fund and support the evolution of psychological facilities, solo practices, and clinics[6,7,8]. But, even as we have repeatedly written about these issues, we have, as a profession, neglected the necessity to have national laws, rules, and guidelines for required staffing of psychologists in the nation's hospitals and primary care facilities[9]. When we address healthcare inadequacies and population based initiatives to address major illnesses and facility certification and licensure, we habitually downplay the psychological and behavioral and lifestyle aspects of psychological and chronic medical disease. We cannot pretend that the medical industrial complex is geared and trained to address these needs.

The National Alliance of Professional Psychology Providers (NAPPP, national practitioner association in psychology) has published a major policy paper10 and has campaigned about one of the major consequences of a lack of valuing and support and deployment for doctors of psychology. The TruthinDrugs Campaign illustrates one of the major consequences of bio-reductionism relative to many illnesses[10]. There is ample evidence that psychology should be a required and mainstream discipline in the nation's healthcare facilities[11,12,13,14]. Many of us have written about this problem in the Archives of Medical Psychology and other publications (American Board of Medical Psychology, www.amphome.org). Many NAPPP leaders, founders, and members were involved in convincing then HICFA and Congress that psychologists are essential providers and we were included in OBRA 96 and are deemed essential vendors in Medicare, and we also got most state plans to deem us likewise and some states actually give parity with psychiatry[3,4] We had leaders that accomplished similar thing in the Virginia Blues and CAPP vs. Rank cases in the courts[15]. We were able to show that we can safely and wisely prescribe psychoactive medications. We have demonstrated that we are better collaborators with physicians and we are well trained in diagnoses and psychotherapy as opposed to psychiatrists and physician prescribers who generally do not have advanced therapy training and do not any longer do much psychotherapy. We have fought to have mental health and psychological services recognized as an essential service for Americans in general[16].

Still, in recent years, APA and State Associations have become weak and haven't accomplished much in the practitioner movement[17]. Additionally, many Doctor of Psychology have become passive and suffer

that delusion that "conflict is bad" and we don't want to be assertive or even aggressive about these issues. Obviously, when you lose your "passion" and assertiveness to address your important goals and those of society, it becomes a detachment that some in psychology mistake for "civility." In principle there is a time to value civility and there is a time to "stand your ground vociferously." The worship of civility reminds me of an Irish Psychiatrist that the first author was preparing for corporate testimony presenting to the Unicameral Legislature in Nebraska at a time when we were building psychiatric hospitals. We wanted to tone down the presentation of data showing neglect of the mentally ill in the state for an expressed fear that it would not make us "good losers if we lost." My colleague said something never to be forgotten in business: He said, "Show me a good loser and I'll show you a loser"!

As we stand our ground vociferously with our face into the squall and hand clinched to the wheel of the ship of the pandemic, it is time to aggressively assert psychologist importance in the essential provider category of the healthcare system. This is not just in the emer-

gencies, but in the regular operation of the healthcare system. This must not continue our losing to the Congress on appropriations and the Government on grants to gear up our practices and staff privileging for Telehealth but for the future of the healthcare system and psychology! We do not intend to just give up and be a "good losers"!

References

1. Morris, J. A. (2013). The Golden Age of Psychology: Serving the Public Health Facilities' Need in the Age of Integrated Care. In J. Caccavale (Ed.). *Medical Psychology Practice and Policy Perspectives* (pp. 205-222). NAPPP books.
2. Mental Health Parity Act Rules: Federal Register, Part IV, Department of the Treasury Internal Revenue Service, 26 CFR Part 54, Department of Labor Employee Benefits Security Administration, 29 CFR Part 2590. Department of Health and Human Services, Centers for Medicare & Medicaid Services, 45 CFR Part 146, Interim Final Rules under the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008; Final Rule; http://www.gpo.gov/fdsys/pkg/FR-2010-02-02/pdf/2010-2167.pdf.
3. Caccavale, J., Morris, J. The illusion of a quality healthcare system. Archives of Medical Psychology, Vol. 9, Issue 1 Aug. 2017.
4. Morris, J. an outdated health care system: Problems, barriers, blockades and solutions. Archives of Medical Psychology, Vol. 6, Dec 2014.
5. Caccavale, J (Editor). Medical Psychology Practice and Policy Perspectives. NAPPP Books, Los Angeles, California, 2013.
6. Morris, J. A. (1995). Alcohol and Other Drug Dependency Treatment: A Proposal for Integration with Primary Care. *Alcoholism Treatment Quarterly*, 13(3),4556.
7. Morris, J. A. (1986). Interdisciplinary treatment of alcoholism. Alcoholism Treatment Quarterly, 3(4),125-131.
7. Morris, J. Changing Healthcare in the Era of the Patient Protection and Affordable Care Act. Archives of Medical Psychology, Vol7, Issue 1, 2015.
8. Lawson, W. The practice of rural psychology. Archives of Medical Psychology, Vol7, Issue 1, 2015.
9. Morris, J.A. (2013). Changes in Medicare Hospital and Healthcare Facility Rules Affecting Psychology. Archives of Medical Psychology, August 2013 • Volume 4, Issue. P. 22-27.
10. Caccavale, J., Cummings, N., Morris, J., Reinhardt, D., Rubin, H., and Wiggins, J.(2010b) Failure To Serve: *A White Paper on The Use of Medications as a First line Treatment AndMisuse in Behavioral Interventions This report was prepared by:* The National Alliance of Professional Psychology Providers, www.nappp.org.
11. Cummings, N. A., Dorken, H. Henke, C., &Pallak, M. (1989). *The impact of psychological services on medical utilization in a Medicaid population.* Report on the Hawaii MedicaidStudy. Baltimore: Health Care Financing Administration.
12. Cummings, N. A., &Follette, W. T. (1968). Psychiatric services and medical utilization: An eight year follow up. In H. Dorken & Associates (Eds.).*The professional psychologist today*. San Francisco: Josey-Bass.
13. Cummings, N. A., Kahn, B.I., &Sparkman, B. (1965).*The effect of psychological intervention on medical utilization: A pilot project.* Oakland, CA. Kaiser Foundation Reports.
14. Cummings NA, O'Donohue WT, Cummings J L .JClin Psychol Med Settings. 2009 Mar; 16(1):31-9. Epub 2009 Jan 11.
15. Berger, S. Fighting for psychology: From hospital privileges to prescribing privileges (RxP). Archives of Medical Psychology, Vol. 6, Dec. 2014.
16. Morris, J. A. (Ed.) (1997). *Practicing Psychology in the Rural Setting: Hospital Privileges and CollaborativeCare.* Washington, DC: AmericanPsychological Association.
17. Caccavale, J., Morris, J. The world of psychology does not revolve around APA. Archives of Medical Psychology, Vol7, Issue 1, 2015.

A Primer on Precision Medicine: What Prescribing and Medical Psychologists Should Know

Erin Conway, PsyD, MSCP, BCB, BCN
Chief Operations Officer and Partner of The Elemental Center

What is Precision Medicine?

Precision medicine has been defined as a new treatment and prevention approach that considers individual characteristics in a person, such as gene variability, environmental factors, and the person's lifestyle (Fernandes, Williams, Steiner, Leboyer, Carvalho, & Berk, 2017). Precision medicine is an idea that has been gaining traction in all areas of medicine. Psychiatry in particular has shown a great need for precision medicine due to the huge cost mental illness places on society and the potentially long wait time that is associated with achieving therapeutic benefits from psychotropic medication, as well as potential adverse individual responses to medications (Serretti, 2018). While medication is often a small part of comprehensive care, it can be a difficult task to prescribe a medication that works the first time.

Choosing the most appropriate medication based on the patient's presentation can be an arduous task. The initial consultation is very short in duration and there are numerous medications to consider as well as many individual factors such as symptom profile, previous medication efficacy, comorbid diagnoses, individual preferences, family history, among many other things (Serretti, 2018). Picking an adequate medication comes with its own challenges. For example, there are currently more than 40 psychotropic medications available to treat depression with varying levels of efficacy, so the process of finding a medication that meets the patient's needs can be a complex undertaking (Serretti, 2018).

Precision medicine aims to reduce the complexity of prescribing medications by tailoring treatment to meet the individual needs of each patient based on the best evidence available regarding effectiveness and tolerability using biological measures as well as observable clinical presentation. While precision medicine as a concept may seem simple enough, psychiatric disorders can be uniquely intricate in their own way and for many psychiatric disorders we only have a partial understanding of their biological determinants (Serretti, 2018). Biological determinants are a key component of precision medicine, so understanding them as they relate to a specific mental illness is important. Further, many psychotropic medications can take four to six weeks to achieve relief, a time frame which can be extended if the initial medication chosen is ineffective due to variations in a person's genetics.

The most current research has demonstrated that approximately 50% of the variance reported in antidepressant response rates and tolerability is controlled by genetics (Serretti, 2018). Based on genetic components alone, identifying the best treatment using individual factors in the genetic profile is the basis for precision medicine. Precision medicine does not just rely on biological markers to determine the best course of treatment. It has been suggested that combining biological markers with individual clinical variables, such as behavioral interventions, is likely the best strategy to achieve the most optimal treatment plan (Serretti, 2018). To begin to understand how genetics and individual clinical variables interact with each other, a large-scale study named the Precision Medicine Initiative is being

Correspondence Address: Erin Conway, 444 S. Rand Rd, Suite 214, Lake Zurich, IL 60047,
Email Drconway@cerebrumil.com

conducted in the United States. The Precision Medicine Initiative will track one million participants over a period of several years and collect clinical and biological variables with the goal of identifying the "signature" of each treatment based on the disease outcome (Serretti, 2018). By combining traditional, clinically proven behavioral interventions, including psychotherapy, exposure, and a healthy lifestyle, with the use of psychotropic medication, finding a course of treatment that works well as soon as the patient enters treatment is more feasible.

Precision medicine is gaining traction in the psychiatric community due to decreasing costs of genetic testing and the availability of quantitative electroencephalograph readings. The general consensus within the field is that while clinical variables alone serve as a useful tool, they are not always correctly used in clinical practice. The addition of precision medicine techniques to the understanding of clinical variables further individualizes the treatment available for each patient. Thus, by improving the ability to prescribe a tolerable drug that may be effective upon the onset of treatment could better provide symptomatic relief and can be good support for other psychological interventions, such as psychotherapy or social skills improvement (Serretti, 2018).

Quantitative Electroencephalograph & Precision Medicine

Electroencephalography (EEG) is one method of precision medicine that has been well studied over the years. Several attempts have been made to apply electroencephalography to aid in the diagnosis of psychiatric disorders; however, there has been limited success (Bolwig, 2008). By reading electrical impulses that create different wave lengths, it is possible to generate a readable brain map that identifies specific biomarkers known to cause mental illness. Those brain maps can then be compared to a database of neurotypical brain maps, which can provide very useful information regarding an individual's neurobiology (Bolwig, 2008). Of the available imaging techniques, quantitative electroencephalography (qEEG) is the only method that provides quantitative comparisons to neurotypical subjects. Further, qEEG combines many individual qEEG data gathering processes into a single, multivariate measure, which allows for categorization of individual patients into areas of interest that can be used for further study (Bolwig, 2008).

The qEEG technique can be used by prescribing medical psychologists to provide a more definitive diagnosis and narrow down the field of potential beneficial medications. In many cases, there is diagnostic overlap between areas of the brain as well as symptoms; however, qEEG has the potential to rule out a specific disorder, or to identify the more dominant clinical presentation. For example, Attention Deficit Hyperactive Disorder (ADHD) and Anxiety Spectrum Disorders often have a similar clinical presentation in terms of duration and symptomology, but looking at brain wave presentation, they are very different. Attention disorders, such as ADHD, are caused by an abundance of slow wave activity, typically theta, over the sensory motor region and a lack of fast wave activity, or beta, which causes the brain to feel tired and leads to inattention. Anxiety on the other hand is an overabundance of fast waves, generally beta or beta two waves, which causes symptoms like racing heart rate or thoughts, excessive worry, etc. Additionally, the medications used to treat ADHD and anxiety are very different. The first line of treatment for ADHD is generally stimulant medication, and while stimulants often work well in many individuals, they can exacerbate an Anxiety Spectrum Disorder, while the Selective Serotonin Reuptake Inhibitors (SSRIs) used to treat anxiety will likely have minimal impact on ADHD symptoms.

Researchers have succeeded in using qEEG to classify children with attention deficit hyperactive disorder (ADHD) and have been able to correctly predict how these children would respond to a course of methylphenidate based on the qEEG data (Bolwig, 2008). Further, researchers have been able to anticipate the desired response to a course of

Selective Serotonin Reuptake Inhibitors (SSRIs) in a population of patients with Obsessive Compulsive Disorder, which was later replicated (Bolwig, 2008). Pharmaco-electroencephalography, or pharmaco-EEG, is a subset of precision medicine that applies qEEG concepts to prescribing medication, which aids in forming a well-rounded course of treatment. In recent years, research using qEEG has identified commonalities in certain electrophysiological features in specific diagnostic categories, such as mood, autism, anxiety spectrum, and attention deficit disorders (Swatzyna, Kozlowski, & Tarnow, 2014). Pharmaco-EEG studies have been conducted for over four decades and the technique has been suggested as an area of precision medicine that could dramatically increase the effectiveness of assigning a diagnosis using neurological data (Swatznya, et al., 2014).

Further, other studies regarding pharmaco-EEG, and specifically the application of qEEG has improved diagnosis, responses to medication, and has led to better selection of treatment interventions including behavioral interventions. There are complex psychiatric cases that arise where the individual does not respond to the traditional course of psychotropic medication (Swatznya, et al., 2014). A thorough evaluation that gathers detailed background information regarding a person's current presentation and family history is required to in order to inform treatment and improve medication selection. But, even with a thorough evaluation, a medication only approach may not be successful. In some cases, psychological testing may be used to narrow down a diagnosis, which may also narrow down the number of medications and behavioral interventions available. However, without identifying the physiological cause of the individual's symptoms, the medication or other interventions may fail, which is where qEEG may be helpful (Swatznya, et al., 2014). Identifying specific neurobiomarkers that create electrophysiological abnormalities in the qEEG may account for one of the reasons medications fail and the difficulties with treatment that follow. In addition, many antidepressants may only prove effective in the more severe depressive disorders. By utilizing EEG and qEEG, along with clinical presentation to highlight neurobiomarkers and identify dysregulated brain wave patterns and their potential correlation to the presenting mental illness, we can link neuronal irregularities to the symptoms they cause and develop a successful individualized treatment plan that includes psychotherapy, medication, and other behavioral interventions (Swatznya, et al., 2014).

Genetic Testing & Precision Medicine

Genetic testing is a relatively new concept in precision medicine, but is more well-known in the field of psychiatry. Currently, there are many effective treatments besides medication available for a variety of mental illnesses; however, not everyone is able to access them. When treatment has been established, it may take a long period of trial and error to reach the optimal treatment for that particular individual (Thompson, Hamilton, & Hippman, 2014). Mental illness is costly to society and comes with limitations regarding treatment efficacy and individualization, which has motivated researchers to refine and personalize the treatment of psychiatric illnesses. To this end, researchers have focused on identifying the causes of psychiatric illness as it has been demonstrated that all psychiatric disorders have a genetic component that contribute to the environmental component, as well as increasing evidence to suggest that particular genes play a role in the etiology of psychiatric disorders (Thompson, et al., 2014)

As our knowledge of the genetic components of mental illness continues to evolve, so has our understanding of how genetics contribute to how a person responds to medication. Utilizing pharmacogenetic test results to be able to customize psychiatric medication and dosage based on how the person's cytochrome P450 enzymes metabolize the medication presents a new opportunity to decrease the time between first contact with a mental health provider and achieving wellness (Thompson, et al., 2014). Molecular genetics has potential regarding the successful management of psychiatric disorders such as, early inter-

vention, more aggressive treatment when needed, implementation of specialized behavioral interventions, improved education about the importance of healthy lifestyle and diet, increasing positive social contact, and identifying medications that may be ideal or medications that should be avoided based on the person's individual genetics. Molecular genetics also provides information on optimal individual dosing, and helps differentiate between medication side effects and the side effects created as a result of other conditions (Thompson, et al., 2014).

Polymorphisms in specific genes have been known to be associated with response to certain drugs and the metabolism of these drugs. For example, polymorphisms in CYP2D6, CYP1A2, CYP2C19, SLC6A4, and HTR2A have proven to be related to how a person responds to and metabolizes a particular drug. In 2013, studies showed that the use of pharmacogenetic testing targeting the aforementioned polymorphisms improved treatment response and doubled remission when applied as a guide to the treatment of depression. Clinician attitudes towards pharmacogenetics are generally positive; however, the reports generated by genetic testing may be difficult to read and some prescribers may not feel they have the adequate skills to interpret the results (Thompson, et al., 2014). Clinical attitudes and lack of training aside, studies have suggested merely providing psychiatric genetic counseling in the absence of genetic testing increases feelings of empowerment and self-efficacy, while lowering internalized stigma and self-blame (Thompson, et al., 2014). When genetic testing is added to a comprehensive treatment plan involving behavioral interventions, treatment is optimized to provide the best result for remission.

Conclusion

The move towards creating diagnostic tests that are accurate and sensitive at predicting whether a disease is present is gaining momentum as a new tool to aid in treatment planning. Precision medicine, including qEEG and genetic testing, holds promise towards being able to prescribe the right medication the first time based on the individuals background, genetics, brain profile, and symptom presentation. Precision medicine has the potential to reduce the back-and-forth, trial and error nature that is typically associated with beginning psychotropic medications, thus making treatment more accurate and effective and an overall better experience for the patient and the clinician. By crafting an inclusive treatment plan that combines behavioral approaches including psychotherapy, social skills development, a healthy lifestyle, and the right medication, we as prescribing medical psychologists will be better able to provide optimal care for our patients.

References

Bolwig, T. G. (2008). EEG and psychiatry: Time for a resurrection. *Aeta Psychiatric,* 117, 241-243.

Fernandes, B. S., Williams, L. M., Steiner, J., Leboyer, M., Carvalho, A. F., & Berk, M. (2017). The new field of 'precision psychiatry.' *BMC Medicine,* 15(80).

Serretti, A. (2018). The present and future of precision medicine and psychiatry: focus on clinical psychopharmacology of antidepressants. *Clinical Psychopharmacology and Neuroscience,* 16(1), 1 – 6.

Swatzyna, R. J., Kozlowski, G. P., & Tarnow, J. D. (2015). Pharmaco-EEG: A study of individualized medicine and clinical practice, *Clinical EEG and Neuroscience,* 46(3), 192-196.

Thompaon, C., Hamilton, S. P., & Hippman, C. (2014). Psychiatrist attitudes towards pharmacogenetics testing, direct-to-consumer genetic testing, and integrating genetic counseling into psychiatric patient care. *Psychiatry research*, 226(2015), 68-72.

Iatrogenic Complications of Psychiatric Medications: Problems Without Defined Solutions & Cautions

Rory Fleming Richardson, Ph.D., ABMP, TEP
Greater Ozarks Rural Psychologists LLC

Abstract

This article explores medications and conditions which can induce mania or manic like symptoms. Some of these reactions are temporary, but others result in longer term residual impact. Elements examined in this article include: (1) systemic, neurologic and medication- induced mania and other psychiatric symptoms, (2) possible impact of other conditions on risk level, and (3) possible sources for intervening on these manic-like and obsessional anxiety states which could reduce oxidative stress, promote homeostasis and return the patient to premorbid functioning. Proposed cautionary factors are suggested, and possible areas to be explored and researched in the future are discussed.

Introduction

Based on two studies (1984 in New York and 1992 in Utah and Colorado), the percentage of hospital admissions because of medical mismanagement was between 2.9 and 3.7 percent (Institute of Medicine, 2000). The risk of prescribed medications that cause harm is an ever present concern. Medical literature is filled with articles noting the potential hazards of medication-induced physical and psychiatric conditions which have caused harm to patients. What is even more concerning is that, outside of treating symptoms, being able to undo the damage done has not been discovered for many of the resulting iatrogenic conditions.

In an extensive search of the literature for treatment options for prolonged residual reactions to antidepressant-induced mania and atypical antipsychotic-induced mania, obsessive/compulsive symptoms and anxiety, few, if any, studies even come close to suggesting treatment options. The closest is to provide treatment of symptoms. One would hope that, if you discontinue a medication, the problematic symptoms would remit. The reality is that these sometimes take a month or more to resolve, and, in some cases, do not resolve. Some individuals are left with profound symptoms requiring hospitalization for extended periods. Left with no other option, patients seek compensation via litigation which sometimes requires a non-disclosure agreement. Thus, the problem is buried so the problem is never addressed.

In the 1990's, I was sitting in a court room while a psychiatrist was providing expert testimony for the State of Oregon in a case where an individual was being adjudicated for causing harm while in what appeared to be a manic episode. The individual was middle-aged and never had any previous manic episodes. The psychiatrist was asked if mania could just start in someone over 40-years-old. The answer given was “No!” The assumption was that it must have been a substance-induced state from use of an amphetamine drug. In addition, the continuing manic behaviors were seen as the individual’s attempt to malinger, using the behaviors to avoid prosecution. There was no proof that the individual had ever used a psychostimulant, but in the absence of other testimony, this assumption was accepted. If the psychiatrist had reviewed the literature, he would have found an article by Larsen and Richelson entitled “Organic Causes of Iatrogenic Complications 4 Mania” which outlines several systemic, neurologic and medications which can induce mania.

Correspondence address: Rory Fleming Richardson, Ph.D., ABMP, TEP, Greater Ozarks Rural Psychologists LLC, 7586 State Highway BB, Seymour, Missouri 65746

Atypical Antipsychotic-Induced Mania (AAIM) is not new. It has been documented as occurring with various newer antipsychotics for more than two decades. Prior to that, various medications and organic conditions have been found to cause manic symptoms. In Larson and Richelson's article "Organic Causes of Mania", various organic causes for mania are discussed including Levodopa, Baclofen, Corticosteroids, and others (Larson & Richelson, 1988). Over the years, many of these iatrogenic causes have been forgotten by many practitioners. In addition, head trauma and temporal lobe seizure disorders have also been found to cause mania (Shukla, Cook, Mukherjee, Godwin, Miller, 1987). The list of various organic causes of mania is much larger than most practitioners realize (See Table 1).

Purpose

The purpose of this article is to explore possible approaches to addressing iatrogenic medication- induced unrelenting anxiety, mania, and/or extreme obsessive/compulsive patterns. Some of the most troubling side effects of antidepressants and atypical antipsychotics are that they can cause the very symptoms that they are touted as controlling stopping.

Being aware of the vast list of mania inducing substances and conditions is essential for healthcare practitioners. Although the traditional treatment of symptoms consists of the medications one would use to treat mania, it is important to explore other, less toxic, options. Using anti-manic medications to treat symptoms would include consideration of lithium carbonate and anti-convulsive medications. Also, consideration of interim use of anxiolytics is likely. If a patient has had an adverse reaction to a medication, the last thing that is wanted is to be put on more medications. In addition, finding a way to undo the damage causing the manic behavior is essential. Some individuals with atypical antipsychotics-induced mania (AAIM) or antidepressant-induced mania (AIM) do not have the symptoms disappear after discontinuing the medication. Berns and Nemeroff have summarized various areas of function which have been studied in better understanding the physiology of bipolarity, but more information is needed. These areas of study include alternations in brain structure, utilization of glucose and cerebrovascular flow, brain chemistry, neurochemical dynamics, neuroendocrine aspects, and signal transduction (Berns & Nemeroff, 2003).

Case Example One

An example of one medication is Rexulti (brexpiprazole). Although it may be helpful to some, there are prudent cautions. One of the more common severe side effects of this medication is "a feeling of restlessness with inability to sit still." At first glace, this does not seem to be that severe of a side effect, but to witness it first hand (especially as a healthcare provider) is extremely eye-opening. This is an anxious, distressing compulsive feeling that no amount of movement or activity can sedate or resolve. The individual I observed was driven to be continuously active for days, only sleeping when completely exhausted and only for a short time. She was a 60-years-old woman who suffered from chronic pain, refractory seizure disorder, adverse reaction to several medications, and history of neurotoxic exposure approximately thirty years ago. Prior to taking the brexpiprazole, she was relatively stabilized on a combination of medications including clonazepam for seizures, opioid pain medication for intractable pain, citalopram for anxiety and depression, and baclofen. She had evidence of malabsorption issues with lifelong history of B12 and potassium deficiencies. To augment the citalopram, she was given a sample of brexpiprazole by her primary care provider. After two weeks of taking the medication, she continued to experience adverse reaction, and discontinued the brexpiprazole. The problematic symptoms continued which included:

- immobilizing stress and anxiety, stressed,
- inability to function,
- tremors,

- clonazepam not controlling refractory seizures,
- significant pain increase,
- elevated blood pressure,
- heart rates altering between 62 to 168 with extreme chest discomfort,
- feeling like her entire body is vibrating,
- dizziness,
- increased anger and easily annoyed,
- obsessive compulsive thoughts and behaviors (from “Can’t Stop” moving and doing, to compulsive shopping),
- fears & phobias,
- inability to concentrate, comprehend (editing and proofing), and remember things,
- unrelenting “Can’t Stop” driven-ness,
- chills, cold,
- worsening depression, hopelessness, and fear.

After five weeks of being off the medication, the episodes of extreme driven compulsive agitation and inability to sit still continued, as did the other symptoms. Anxiety and sensitivity to stressors were severe. The drive to continuously move was present, but pain issues and fatigue had become so elevated that she was afraid to get up because of risk of falling. To complicate this picture further, this atypical antipsychotic also carries with it warnings of weight gain, increased possibility of cardiac death in older people, warning regarding seizures, warning about diabetes, and several other side effects. In her history, she had a seizure disorder, unstable glucose with history of severe hypoglycemic attacks and diabetes, long term chronic pain, obsessive compulsive disorder, and history of adverse reactions to several medications. There was no history of medication-induced mania nor any family history of bipolarity. The pounding heart beat she dismissed as a panic attack. After being in a manic-like state drive to continuously clean and be busy for over 24 hours, she realized that something was wrong. The continuous anxiety and compulsion to move resulted in extreme elevation of pain. Between the fatigue and impaired sleep, she was afraid to get up because of dizziness and weakness. Because of the continued complaints about her heart beating rapidly, the primary care physician had her wear a EKG halter monitor for two days. After five weeks of continued symptoms, she was losing hope of recovering, was filled with extremely angry about the situation, and had lost her faith in the medical community to help. After six weeks, the symptoms started to very slowly reduce. During the latter part of the six weeks, attempts to reduce the factors which could undermine recovery were used. This included the use of what is known as a “mitochondrial cocktail” consisting of CoQ10, curcumin with Piperine, L-Carnitine, Vitamin B Complex, Vitamin E, and Vitamin C. She also continued to take N-acetylcysteine. She had used some of these prior to the reaction to the brexpiprazole. The rationale of this was that it is sometimes used in the neurotoxic responses associated with Gulf War Syndrome and Agent Orange. She continued her treatment for the B12 and potassium deficiencies, as well as the other medications taken before. Attention to hydration and electrolyte balance was also given. In consulting with various psychiatrists and neuroscientists, no other options were offered except to use an older antipsychotic such as Haloperidol to suppress symptoms. This option was not acceptable to the patient. After seven weeks, the symptoms lessened, but were still present. At eight weeks, episodes of inability to sit still, being driven to continuously move, and pronounced anxiety continued. Despite the discontinuation of the brexpiprazole, the episodes remained.

Discussion

From examining the patient reviews, it is very possible that some of these side effects can result in extended residual problems and/or hospitalization. Some patients have had very negative life- changing effects from taking Rexulti. In examining even the positive patient reviews, some patients experience significant weight gain, but are extremely happy on the medication. Even when the physician wanted to take them off the medication, the patients were extremely resistant to giving it up.

A medication which is known to cause severe obsessive-compulsive symptoms with pathological gambling, hypersexuality and pathological spending is Rexulti, an atypical antipsychotic which is similar to Abilify. A significant number of lawsuits are in process against the manufacturer of this medication.

Approximately three decades ago, I remember when Prozac was being used extensively. Some of the patients who had been on the Prozac experienced a medication-induced mania with compulsive spending (thousands of dollars per day), unpredictable behavior, and other manic symptoms. Significant cautions were made about using SSRI medications. Many of these individuals who had manic symptoms emerge had a family history of bipolarity.

Case Example Two

In another case, a young woman shared that she had an adverse reaction to clonazepam (klonopin) which induced manic-like aggressive state with irrational impulses. She quickly let her prescriber know of the problem. She was told that this was not possible. She discontinued the medication, and the mania disappeared. She went back to her psychiatrist and was told to go back on the clonazepam. She again started to experience mania. Like the first case, this woman did not have any family history of bipolarity, but did have family history of Obsessive Compulsive Disorder. Stress, severe anxiety and depression were the presenting problems. In clinical practice, I have had other patients who have had clonazepam-induced aggressive mania. Despite the assertions of the psychiatrist, a medication-induced mania caused by clonazepam is noted in clinical literature (Dorevitch A, 1991).

Possible Areas Of Investigation

When faced with few clear options, it is not unusual for physicians to explore use of older medications, such as low dosages of haloperidol to reduce mania and other extremely disruptive symptoms. Although this would help to control extreme anxiety or mania (a lesson learned in emergency rooms over the last fifty years), it adds yet another medication to a complicated clinical picture. When examining the possible areas in play, several areas need to be considered, including:

- pharmacological interactions and dynamics involving various receptor response,
- impact of the medications on preexisting conditions (i.e., deficiencies, malabsorption, impact on electrolytes, impact on hormonal levels, other),
- mitochondrial injury and oxidative stress,
- impact of adverse physiological reactions on psychological health and function.

Pharmacological Interactions and Dynamics Involving Various Receptor Response

When SSRI antidepressants are used as augmentation with antipsychotics, there is an altered expression of GABAA receptor and related genes (Silver et al, 2011). This may also be a factor in adverse responses.

With multiple neurotransmitters and receptor sites impacted by some atypical antipsychotics (such as Abilify and Rexulti), clarification of the dynamics in play with post discon-

tinuation residual effects is complicated. One possible reason for the prolonged post discontinuation residual effects may be a synergistic action of a SSRI and atypical antipsychotic on the up- regulation and down regulation of the receptor sites. This could explain the post discontinuation residual effects which last upwards of six weeks.

The unfortunate reality is that many medications used have a toxic impact on intracellular function and overall health. Valproic Acid inhibits fatty acid oxidation, the citric acid cycle, and oxidative phosphorylation. It also depletes carnitine. Beta-blockers can reduce an individual's tolerance for exercise and result in oxidative stress. Metformin can inhibit oxidative phosphorylation and enhance glycolysis. Use of acetaminophen results in oxidative stress and contributes to hepatopathy. Statin medications can result in myopathy. Aspirin inhibits and uncouples oxidative phosphorylation. Antiretrovirals impairs mitochondrial DNA replication (Parikh et al, 2009). In the current reality of medical treatment of multiple co-morbid conditions, polypharmacy is common. This increases the risk of unforeseen reactions.

Impact of the Medications on Preexisting Conditions

Another thing to consider is that, if there has been medication-induced mania or psychiatric symptoms, the possibility of one medication-induced reaction may increase the likelihood of future reactions. In the neurology of seizure disorders, this tendency is called "kindling." Further examination of this possibility is needed. In cases where seizure disorders are present, one of the likely problems which can emerge as a part of the profound anxiety caused by the medication reaction is increased seizure activity.

Mitochondrial Injury and Oxidative Stress

In order to understand the significance of mitochondrial DNA (mtDNA), we need to first understand that the cells of our body have to convert the chemical energy from food into adenosine triphosphate (ATP) which provides energy for the cell to function. The role and importance of intracellular function in maintaining optimal neuronal homeostasis has increasingly been recognized. Both central and peripheral neurons use an enormous amount of cellular energy. In other words, these neurons are dependent on continuous supply of ATP for conversion into energy. This energy is used to control membrane potential by the Na+/K+ ATPase pump, regulation of intracellular Ca++, and exocytosis/recycling of synaptic vesicles (Carelli & Chan, 2014). In the past, the focus of psychiatry, psychopharmacology, and biopsychology have been monoamines and synaptic function. The attention then moved to the role and competition for cytochromes such as P450 for the breakdown and processing of substances involved in clinical interventions. At this point, the landscape of several clinical fields is slowly expanding to include molecular neurophysiology. With the literature on the role of oxidative stress and mitochondrial DNA in various neurologic, psychiatric and medical conditions, we are having to face the fact that toxins have been introduced into our everyday environment (including some of the foods we eat) and that deficits in our modern Western diet are significantly contributing to the increasing maladies seen in the population worldwide.

Mitochondrial DNA and glycolysis generate the energy involved in neuronal signal transmission. As mitochondrial function becomes impaired, neuron function and the transmission of neuronal signals are affected. Understanding the role of mitochondrial DNA dysfunction is key to understanding various psychiatric and neurologic conditions. At this point, natural treatment using supplements in the form of "mitochondrial cocktails" appear to provide the best hope. A "mitochondrial cocktail" consists of CoQ10, Riboflavin, L-Creatine, L-Arginine, L-Carnitine, Vitamin B Complex, Vitamin E, Vitamin C, Alpha-lipoic Acid, and Folinic Acid (Parikh et al, 2009). It will be interesting to see if other mitochondrial treatment methods such as infrared light, which has been shown to improve mitochondrial function, will provide other adjunctive options (Nguyen, Malamo, Larkin-Kaiser, Borsa,

Adhihetty, 2014). It will also be interesting to see if practices such as grounding (earthing) which has been shown to reduce systemic inflamation, may provide other options (Oschman, Chevalier, Brown, 2015).

All biological processes require a balance of base biochemistry. For example, if mitochondrial activity is increased, the chemicals needed to support the activity needs to be present. If not, the increased activity could result in additional damage and dysfunction.

One of the elements of recovery from any neurotoxic or physical malady is sufficient hydration. When we look at helping the body to eliminate toxins, and restore electrolyte balance and rebalance, it is obvious (although sometime overlooked) the importance adequate fluid intake.

Research has found that the energy function of the cells, specifically the mtDNA, is related to the various psychiatric disorders (Hroudová & Fišar, 2011). A complex set of biochemical steps exist to maintain cell homeostasis. Mitochondrial dysfunction is a disturbance in the efficiency of the electron transport chain reducing the production of molecular energy such as ATP. The outcome of this dysfunction is aging and chronic conditions. Other aspects of mitochondrial dysfunction include reduced mitochondria and an inability to provide essential substrates to mitochondria. As a result of mitochondrial dysfunction, there is reduced energy metabolism, unstable calcium homeostasis, oxidative stress and cell death. The variability between these intracellular processes are believed to be the reason behind different reactions to medications (Hroudová & Fišar, 2011). There have been studies as to the mtDNA of individuals with Major Depression and Bipolar Disorder. The mitochondria are responsible for cell signal transmission. These studies suggest that mitochondrial dysfunction and the complex molecular system are at the heart of bipolar disorder. In turn, mitochondrial dysfunction and oxidative stress impact the presentation of psychiatric symptoms. Thanks to the extensive research that has been done on the effects of Agent Orange and the Gulf War Syndrome, there is significant evidence of a link between oxidative stress and mitochondrial dysfunction to exposure to neurotoxic chemicals, including organophosphates and glyphosate. It is possible that techniques of reducing oxidative stress and improving mitochondrial function could help counteract some damage done by various chemicals (Ghanizadeh & Berk, 2013).

As much as pharmacological preparation can help, they also introduce chemicals which can react in a toxic manner. We do not have control over the current condition of a patient's molecular and mitochondrial health, nor do we have a way of fully understanding the impact of various chemicals which have been introduced over time. Chemical exposures, exposure to radiation, use of over-the-counter preparations, and even the food we eat can impact our molecular physiology. If we consider the genetic factors inherited combined with environmental factors, the determination of individuals at risk of adverse and synergistic reactions to medications is impossible to predict.

One of the factors which is not widely known is that research has shown the role of mitochondrial DNA in psychiatric disorders including bipolarity and anxiety disorders (Salim, 2014; Bouayed, Rammal, Soulimani, 2009). Another fact which is not widely known is that bipolarity is a neuroprogressive condition. Any neurologist or neuropsychologist who treats patients with seizure disorders has heard of "kindling." This is the increased likelihood that seizures will occur with increased seizures. In bipolarity, the presence of bipolar episodes increase over time and result in changes in the neurological structures resulting in reduced gray matter. Just as there are substances and events which can promote neurodeterioration and neuroprogression, there are also factors which can provide neuroprotection (Berk et al, 2010). Most of these same promoters of neuroprotection are the same as used for

the treatment of oxidative stress and mitochondrial dysfunction. Oxidative stress and mitochondrial dysfunction can be treated with natural supplements, including: Vitamins C, D and E, thiamine, riboflavin, Magnesium, calcium, phosphate, CoQ10, microencapsulated NADH, L-carnitine, á-lipoic acid, and others (Nicolson, 2014; Berk et al, 2010). It is possible that these techniques may be able to provide some help for patients with medication induced mania and manic-obsessive compulsive symptoms.

Acquired Cumulative Systemic Neurotoxic Effect (extensive exposure to toxins over the lifetime) could increase the risk of a substance-induced manic reaction to a medication (Richardson, 2018). This could provide practitioners with clues as to possible tendencies toward atypical side effects such as substance-induced mania. If an individual has had a substance- induced mania reaction to one medication, it is prudent to consider the possibility that other substances could trigger mania. One factor which has not been significantly studied is the neurotoxin exposure. Common sense would dictate that if you have a malady, adding neurotoxins to the body system is likely to make the condition worse.

Research in the area of oxidative stress, systemic damage, and exposure to pesticides and related toxins may provide some hope for medication-induced mania like symptoms. There are two substances which have been examined in dealing with toxic reactions. These are N- acetylcysteine (NAC) and Curcumin (Ahmed, Pathak, Mustafa, Kar, Tripathi, Ahmed, Banerjee, 2011). One of the more natural options which may hold some hope is N-acetylcysteine (NAC) which has been shown to be beneficial in the treatment of acetaminophen toxicity, infertile patients undergoing assisted reproductive techniques, ulcerative colitis, chronic bronchitis, liver cancer, hemodialysis, oxidative stress in muscles, Parkinson, asthma, chronic obstructive pulmonary disease, and Alzheimer' disease. Research has also been done on its use in treatment of obsessive-compulsive disorder, schizophrenia, bipolar disorder, compulsive gambling, and various addictions.

Another natural option which is being explored at this time is Curcumin. The root of the curcuma longa plant is used to produce a popular spice in India known as turmeric. Turmeric contains a group of curcuminoids which has been shown to have several health benefits. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) has been researched for use in various conditions which include psychopharmacological use in bipolarity (Brietzke E, Mansur RB, Zugman A, Carvalho AF, Macedo DS, Cha DS, Abilio VC, McIntyre RS, 2013). One of the greatest difficulties in using curcumin is bioavailability. This can be corrected by using piperine which is the alkaloid found in black pepper (Hewlings & Kalman, 2017). Having been used as a traditional medicine in Southeast Asia and India, curcumin acts by providing antioxidant, anti-inflammatory, anti-cancer, antimicrobial, neuroprotective, cardioprotective and radioprotective effects (Amalraj, Pius, Gopi, & Gopi, 2016). Curcumin increases brain BDNF levels, enhances the neurotrophin expression, and modulates the second messengers in BDNF signaling pathway. Research has shown that recovery from either poles of bipolarity is accompanied by an increase in the neurotrophin "brain-derived neurotrophic factor (BDNF)." BDNF is implicated in neuronal differentiation, survival and synaptic plasticity. During acute bipolar episodes, BDNF decreases (Fernandes, Gama, Cereser, 2011). When the stress response of the hypothalamus–pituitary–adrenal (HPA) occurs, BDNF level decrease. The signaling pathway of BDNF in the hippocampus has been suggested as having a role in neurogenesis and neuroprotection in maintaining homeostasis protecting neurons. Its action as an antioxidant and reducing oxidative stress has been well established (Brietzke, Mansur, Zugman, Carvalho, Macedo, Cha, Abilio, McIntyre, 2013).

Another supplement which deserves consideration is Omega-3. It is well known as an anti-inflammatory and, more recently, as a mood stabilizer. Omega-3 is an essential fatty acid

and potentially a neuroprotector. As such, exploring the use of this supplement to reduce the damage from substances which induce mania is warranted (Shakeri J, Khanegi M, Golshani S, et al, 2016).

Coenzyme Q10 is another supplement also deserves examination. As an antioxidant, it holds promise in the treatment of oxidative stress. It has been examined to help treat Gulf War Syndrome and to help with reducing mitochondrial toxicity (Hargreaves I, Al Shahrani M, Wainwright L, Heales S, 2016).

Folic acid (also known as Vitamin B9 or folate) is found in leafy green vegetables and in fortified grain products. Unfortunately, it is inactivated by cooking and processing food. Folate is essential for several biological processes including nucleotide biosynthesis, remethylation of homocysteine, synthesize DNA, repair DNA, and methylate DNA. When combined with B12, folate is used to create S-adenosyl-L-methionine (SAM-e), which is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. There is some research that suggests a relationship between low folate and mitochondrial DNA (mtDNA) instability (Ormazabal et al, 2015). With the fact that folate is significantly decreased by many unhealthy lifestyle activities (smoking, poor diet, alcohol use) and various medications, attention to folate intake is warranted.

The other side of the argument is that curcumin has been shown to inhibit multiple human cytochromes P450 which would interfere in the clearance of medications. Also, piperine, which is used to potentiate the absorption of curcumin, is a relatively selective CYP3A4 inhibitor (Volak, Ghirmai, Cashman, & Court, 2008). This inhibition of cytochrome enzymes is also found in various health foods (Sasaki, Sato, Kumagai, Yoshinari & Nagata, 2017). In contrast, brassica vegetables such as broccoli, cauliflower, brussels sprouts, and cabbage have been shown to induce P450 cytochromes, thus, increasing drug clearance (Johanna et al, 2000). All these factors can complicate the clinical picture. In addition, use of other medications will further complicate the clinical picture. For example, using an atypical antipsychotic to boost the effect of an SSRI can result in prolonged manic-like symptoms which may take 6 weeks or more to clear. We sometimes forget that the complexity of biochemical processes and tissue reactivity is sometimes unpredictable and that the mechanisms of some of these medications are not fully understood.

Impact of Adverse Physiological Reactions on Psychological Health and Function

The possibility that some of the symptoms of anxiety and inability to sit still may be subtle biochemical imbalances. For example, individuals who suffer from malabsorption issues impacting potassium, and/or folate, and/or electrolyte balance are at higher risk. Imbalance in these chemicals can impact cardiac function, creating a sense of overwhelming anxiety by triggering the autonomic nervous system. Monitoring and close examination of biochemical balance and EKG monitoring may well be fruitful in symptoms management. Anecdotally, intake of electrolyte drinks has been found to help in some cases in getting through residual effects of atypical antipsychotic-induced mania/anxiety and withdrawal from opioid medications. This is supported by some research (Shah, Huecker, 2019).

We need to remember that several psychiatric symptoms can be caused by physiological conditions. Just as palpitations and a pounding heart beat can be symptoms of a panic attack, paroxysmal supraventricular tachycardia can mimic symptoms of a panic attack or severe anxiety (Frommeyer, Eckardt, Breithardt, 2013). Some individuals who have had a residual unrelenting anxiety response to atypical antipsychotic medications may be having reactive anxiety from the sympathetic nervous system activity. This is a valid concern especially since cardiac problems are also associated with use of atypical antipsychotics. These medications can result in prolongation of the QT interval which can lead to a po-

tentially fatal polymorphic ventricular tachycardia (Del Rosario, Weachter, Flaker, 2010). Cardio-metabolic risk complications are not the only potential adverse reactions to atypical antipsychotics. Other factors which need to be considered are impact on hormonal level and on glucose metabolism (Goodwin et al, 2009). Hypoglycemic episodes also present with significant psychiatric symptoms which could be misinterpreted. For individuals with a history of glucose instability, this is a significant concern. It is all too easy for both patients and professionals to dismiss psychiatric issues as psychogenic in nature rather than to realize that there are frequently physical and chemical causes which can mimic psychiatric disorders. The gold standard for any psychiatric diagnosis is to fully rule out physiological causes. Unfortunately, this is rarely done.

Idiopathic neural signal dysfunction can be the result of several potential physiological conditions which may include everything from polar lipid (structural lipids) impacted by preoxidation damage through the alteration of mitrochondrial DNA impacting intracelluar physiology (Ayala, Muñoz, Argüelles, 2014). This field of molecular biopsychiatry is evolving every day. Being able to understand the implication of this new research as it relates to specific pharmacological structures and the enormous number of variables differing from one patient to another will take time. The fact that scientists worldwide are working on better understanding of these extremely elusive details does give hope that one day we will be able to prevent some of the potential harm to patients. In the interim, one of the tools which may be of value to clinical practitioners in assessing risk of adverse reaction is genetic testing which provides assessment of cytochrome and enzyme levels and function.

Precautions

Given the current information on medication-induced conditions, the following is a proposed list of factors which be considered before prescribing medications which may induce mania:

- Past history of adverse reactions to medications.
- Multiple medications being taken, including SSRI medications.
- Familial history of adverse reaction to medications.
- Two or more blood transfusions at birth.
- History of seizures.
- Autoimmune disorders.
- Past history of medication-induced mania.
- History of significant toxin (i.e., pesticide, herbicides, solvents, other) exposure.
- Hypersensitivity to medications.
- History of paradoxical response to medications.
- History of mania induced by any other condition.

Conclusions

Human physiology is dependent on maintaining a balance of all the various systems and biochemical dynamics. In the situation of the Case One, the residual affects of the Rexulti subsided except for the tremors after four and a half months with the use of a mitochondrial cocktail and N-acetylcysteine.

As our understanding to the specific mechanisms of bipolarity and mania improve, hopefully our understanding of the cause of “-induced mania” etiologies will improve. Some of the medication-induced conditions have a significant residual, long-term impact on patient function. Until the time when we can determine the risk level of various patients in developing substance- induced mania, significant caution and thorough informed consent of the patient is needed.

Each individual has a different set of genetic factors, lifestyle practices, history of exposure to toxins, and combination of medications which can complicate response to different medications. Once a medication-induced reaction occurs, there are no “one-size-fits-all” ways to address the results. As we have become aware of the multiple toxins impacting health, we need to develop ways of coping with the consequences. This is especially true when the medications one would usually use to treat these reactions can actually make the condition worse. Prescribers are faced with not only the risk of adverse reactions, but also having to find solutions from both prescriptive medications and natural supplements. It is imperative for these prescribers to expand their knowledge of molecular biochemistry and naturally occurring nutrients. There is also a fine art of balancing and addressing the factors undermining homeostasis while also providing the patient with some relief from immediate symptoms.

In relationship to the psychology side of patient care, it is imperative that if there is a prolonged response, the patient be reassured that reaction to the medication is biologic and that they are not losing their mind. Loss of hope is one of the most damaging aspects of the AAIM or AIM experience. Reassurance and compassion are truly part of the healing process.

References

Ahmed T, Pathak R, Mustafa M, Kar R, Tripathi AK, Ahmed R, Banerjee B. (2011). Ameliorating effect of N-acetylcysteine and curcumin on pesticide-induced oxidative DNA damage in human peripheral blood mononuclear cells. Environmental Monitoring and Assessment. August 2011, Volume 179, Issue 1-4, pp 293-299.

Albert U, De Cori D, Bogetto F & Maina G. (2014). Hypomania Associated with Adjunctive Low-dose Aripiprazole: Two Case Reports and a Brief Review Of the Literature. Psychiatria Danubina, Vol. 26, No. 1, pp 80-83.

Amalraj, A., Pius, A., Gopi, S., & Gopi, S. (2016). Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives - A review. Journal of traditional and complementary medicine, 7(2), 205–233. doi:10.1016/j.jtcme.2016.05.005

Ayala A, Muñoz M, Argüelles S. (2014). Review Article: Lipid Peroxidation: Production, Metabolism, and Signaling: Mechanisms of Malondialdehyde and 4-Hydroxy-2-Nonenal. Oxidative Medicine and Cellular Longevity. Volume 2014, Article ID 360438, 31 pages, http://dx.doi.org/10.1155/2014/360438

Benyamina A1 & Samalin L (2012). Atypical antipsychotic-induced mania/hypomania: a review of recent case reports and clinical studies. Int J Psychiatry Clin Pract. 2012 Mar;16(1):2-7. doi: 10.3109/13651501.2011.605957. Epub 2011 Aug 31.

Berk M, Conus P, Kapczinski F, Andreazza A, Yücel M, Wood S, Pantelis C, Malhi G, Dodd S, Bechdolf A, Amminger GP, Hickie I, McGorry P. (2010). From neuroprogression to neuroprotection: implications for clinical care. Med J Aust. 2010 Aug 16;193(4 Suppl):S36-40.

Berns G & Nemeroff C. (2003). The Neurobiology of Bipolar Disorder. American Journal of Medical Genetics Part C (Semin. Med. Genet.) 123C:76-84.

Bou Khalil R. (2017). Are Hypomanic/Manic Episodes "Induced by" or "Associated with" Quetiapine Initiation?. Drug safety - case reports, 4(1), 21. doi:10.1007/s40800-017-0063-y

Bouayed, J., Rammal, H., & Soulimani, R. (2009). Oxidative stress and anxiety: relationship and cellular pathways. Oxidative medicine and cellular longevity, 2(2), 63–67.

Brietzke E, Mansur RB, Zugman A, Carvalho AF, Macedo DS, Cha DS, Abilio VC, McIntyre RS. (2013) Is there a role for curcumin in the treatment of bipolar disorder? Med. Hypotheses 80, 606–612.

Carelli, V., & Chan, D. C. (2014). Mitochondrial DNA: impacting central and peripheral nervous systems. Neuron, 84(6), 1126–1142. doi:10.1016/j.neuron.2014.11.022

Cummings JL & Mendez MF. (1984). Secondary mania with focal cerebrovascular lesions. Am J Psychiatry 141:1084-1087.
Danovich L, Weinreb O, Youdim M, Silver H. (2011). The involvement of GABAA receptor in the molecular mechanisms of combined selective serotonin reuptake inhibitor-antipsychotic treatment, International Journal of Neuropsychopharmacology, Volume 14, Issue 2, March 2011, Pages 143–155, https://doi.org/10.1017/S1461145710000106
Del Rosario, M. E., Weachter, R., & Flaker, G. C. (2010). Drug-induced QT prolongation and sudden death. Missouri medicine, 107(1), 53–58.
Donohue A. (2010). First manic episode in a 55-year-old man after initiation of aripiprazole. Psychiatry (Edgmont (Pa. : Township)), 7(4), 37–39.
Dorevitch A. (1991). Mania associated with clonazepam. DICP. 1991 Sep;25(9):938-9.
Fernandes BS, Gama CS, Cereser KM, et al. (2011). Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res, 45, pp. 995-1004.
Fishbane S. (2008). N-Acetylcysteine in the Prevention of Contrast-Induced Nephropathy. Clin J Am Soc Nephrol. 3(1):281-7. Epub 2007 Nov 14.
Frommeyer G, Eckardt L, Breithardt G. (2013). Panic attacks and supraventricular tachycardias: the chicken or the egg? Neth Heart J. 21(2):74-7. doi: 10.1007/s12471-012-0350-2.
Ghanizadeh A & Berk M. (2013). Molecular hydrogen: an overview of its neurobiological effects and therapeutic potential for bipolar disorder and schizophrenia. Medical Gas Research. volume 3, Article number: 11 https://medicalgasresearch.biomedcentral.com/ articles/10.1186/2045-9912-3-11
Goodwin G., et al. (2009). Advantages and disadvantages of combination treatment with antipsychotics, Eur. Neuropsychopharmacol. doi:10.1016/j.euroneuro.2009.04.003
Hargreaves I, Al Shahrani M, Wainwright L, Heales S. (2016). Drug-Induced Mitochondrial Toxicity, Drug Saf DOI 10.1007/s40264-016-0417-x
Hewlings SJ & Kalman DS. (2017). Curcumin: A Review of Its' Effects on Human Health. Foods (Basel, Switzerland), 6(10), 92. doi:10.3390/foods6100092
Hroudová J & Fišar Z. (2011). Connectivity between mitochondrial functions and psychiatric disorders. Psychiatry and Clinical Neurosciences 2011; 65: 130–141 doi:10.1111/j.1440-1819.2010.02178.x
Institute of Medicine (US) Committee on Quality of Health Care in America; Kohn LT, Corrigan JM, Donaldson MS, editors. To Err is Human: Building a Safer Health System. Washington (DC): National Academies Press (US); 2000. 2, Errors in Health Care: A Leading Cause of Death and Injury. Available from: https://www.ncbi.nlm.nih.gov/books/NBK225187/
Johanna W. Lampe, Irena B. King, Sue Li, Margaret T. Grate, Karen V. Barale, Chu Chen, Ziding Feng, John D. Potter, Brassica vegetables increase and apiaceous vegetables decrease cytochrome P450 1A2 activity in humans: changes in caffeine metabolite ratios in response to controlled vegetable diets, Carcinogenesis, Volume 21, Issue 6, June 2000, Pages 1157–1162, https://doi.org/10.1093/carcin/21.5.157
Kavoor AR, Mitra S, Mondal SK, & Das B. (2014). Risperidone-induced mania: An emergent complication of treatment. Journal of pharmacology & pharmacotherapeutics, 5(4), 258–260. doi:10.4103/0976-500X.142448
Khalil RB1, Baddoura C. (2012). Quetiapine induced hypomania: a case report and a review of the literature. Curr Drug Saf. 2012 Jul;7(3):250-3.
Kodama M, Hamamura T. (2010). Aripiprazole-induced behavioural disturbance related to impulse control in a clinical setting, International Journal of Neuropsychopharmacology, Volume 13, Issue 4, May 2010, Pages 549–551, https://doi.org/10.1017/S1461145709990976
Krauthammer C, Klerman GL. (1978). Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 35:1333-1339.

Larson E, Richelson E. (1988). Organic Causes of Mania. Mayo Clin Proc 63:906-912.
Millard H, Wilson B, Noordsy D. (2015). Low-Dose Quetiapine Induced or Worsened Mania in the Context of Possible Undertreatment, JABFM January–February 2015 Vol 28 No 1.
Millea P. (2009). N-Acetylcysteine: Multiple Clinical Applications. American Family Physician. Volume 80, Number 3: 265-269.
Mokhtari V, Afsharian P, Shahhoseini M, Kalantar SM, Moini A. (2017). A Review on Various Uses of N-Acetyl Cysteine. Cell Journal(Yakhteh). Vol 19, No 1, Apr-Jun (Spring) 2017, Pages: 11-17.
Muzina D. (2004). Bipolar maintenance: Are atypical antipsychotics really 'mood stabilizers'? Current Psychiatry. 2004 April;3(4):14-30.
Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., & Walters, M. A. (2017). The Essential Medicinal Chemistry of Curcumin. Journal of medicinal chemistry, 60(5), 1620–1637. doi:10.1021/acs.jmedchem.6b00975
Nguyen LM, Malamo AG, Larkin-Kaiser KA, Borsa PA, Adhihetty PJ. (2014). Effect of near-infrared light exposure on mitochondrial signaling in C2C12 muscle cells. Mitochondrion. 2014 Jan;14(1):42-8. doi: 10.1016/j.mito.2013.11.001. Epub 2013 Nov 15.
Nicolson G. (2014). Mitochondrial Dysfunction and Natural Supplements. Integrative Medicine • Vol. 13, No. 4 • August 2014 35
Oguz N, Gulec M, Erol A. Mania possibly induced by clozapine: a case report: The Journal of Psychiatry and Neurological Sciences : 2014;27:348-351 http://www.dusunenadamdergisi.org/ing/fArticledetails.aspx?MkID=1033 ISSN: 1018-8681
Ormazabal A, Casado M, Molero-Luis M, Montoya J, Rahman S, Aylett SB, Hargreaves I, Heales S, Artuch R. (2015). Can folic acid have a role in mitochondrial disorders? Drug Discov Today. 2015 Nov;20(11):1349-54. doi: 10.1016/j.drudis.2015.07.002. Epub 2015 Jul 14.
Oschman, J. L., Chevalier, G., & Brown, R. (2015). The effects of grounding (earthing) on inflammation, the immune response, wound healing, and prevention and treatment of chronic inflammatory and autoimmune diseases. Journal of inflammation research, 8, 83–96. doi:10.2147/JIR.S69656
Parikh, Sumit & Saneto, Russell & J Falk, Marni & Anselm, Irina & Cohen, Bruce & Haas, Richard & Mitochondrial Medicine Society. (2009). A Modern Approach to the Treatment of Mitochondrial Disease. Current treatment options in neurology. 11. 414-30. 10.1007/s11940-009-0046-0.
Richardson R. (2018). Acquired Cumulative Systemic Neurotoxic Effect: The Future of Medicine & Biopsychology. On J Neur & Br Disord 1(4)-1/2. OJNBD. MS.ID.000119.
Sasaki T, Sato Y, Kumagai T, Yoshinari K & Nagata K. (2017). Effect of health foods on cytochrome P450-mediated drug metabolism. Journal of Pharmaceutical Health Care and Sciences, 3:14 DOI 10.1186/s40780-017-0083-x
Sadowska AM, Verbraecken J, Darquennes K, De Backer WA. (2006). Role of N-acetylcysteine in the management of COPD. Int J Chron Obstruct Pulmon Dis. 1(4): 425-434.
Salim S. (2014). Oxidative stress and psychological disorders. Current neuropharmacology, 12(2), 140–147. doi:10.2174/1570159X11666131120230309
Santos C, Caeiro L, Ferro J, Figueira L. (2011). Mania and Stroke: A Systematic Review. Cerebrovasc Dis, 32:11–21 DOI: 10.1159/000327032
Shah M, Huecker MR. Opioid Withdrawal. [Updated 2019 Jun 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from:
https://www.ncbi.nlm.nih.gov/books/NBK526012/
Shakeri, J., Khanegi, M., Golshani, S., Farnia, V., Tatari, F., Alikhani, M., ... Ghezelbash, M. S. (2016). Effects of Omega-3 Supplement in the Treatment of Patients with Bipolar I Disorder. International journal of preventive medicine, 7, 77. doi:10.4103/2008-7802.182734
Shukla S, Cook BL, Mukherjee S, Godwin C, Miller MG. (1987). Mania following head

trauma. Am J Psychiatry 144:93-96.
Silver et al. (2011). SSRI augmentation of antipsychotic alters expression of GABAA receptor and related genes in PMC of schizophrenia patients. International Journal of Neuropsychopharmacology, 14, 573–584. f CINP 2010 doi:10.1017/S1461145710001471
Traber R, Schneiter R , Modestin J. (2007). A case of aripiprazole-induced mania. Pharmacopsychiatry. 2007 Jan; 40(1): 37–38. doi: 10.1055/s-2006-951609
Tsai S, Chen-Jee Hong C. (2005). Pharmacogenetic Studies of Psychotropic Drug-Induced Adverse Effects, Current Pharmacogenomics, 2005, 3, 000-000 11570-1603/05 Bentham Science Publishers Ltd.
Volak, L. P., Ghirmai, S., Cashman, J. R., & Court, M. H. (2008). Curcuminoids inhibit multiple human cytochromes P450, UDP-glucuronosyltransferase, and sulfotransferase enzymes, whereas piperine is a relatively selective CYP3A4 inhibitor. Drug metabolism and disposition: the biological fate of chemicals, 36(8), 1594–1605. doi:10.1124/dmd.108.020552

Table 1

Organic Causes of Mania		
MEDICATION	**NEUROLOGIC CONDITIONS**	**SYSTEMIC CONDITIONS**
• Abilify	• Focal Lesions (frontal & temporal lobes & subcortically in the head of the caudate & the thalamus)	• Hyperthyroidism
• Rexulti	• Traumatic Brain Injury	• Hypothyroidism
• Risperidone	• Tumors (hypothalamic, diencephalic, frontal)	• Starvation Diet
• Seroquel (quetiapine)	• Cerebrovascular Lesions (temporal, hemispheric)	• Uremia
• Selective Serotonin Reuptake Inhibitors (Prozac, Zoloft, Paxil, others)	• Temporal Lobe Seizures	• Hemodialysis
• Ketamine	• Thalamotomy	• Uremia with Progressive
• Levodopa	• Right Hemispherectomy	• Dialysis Dementia
• Bromocriptine	• Huntington's Disease	• Puerperal psychosis
• Metoclopramide*	• Wilson's Disease	• Q fever
• Cocaine	• Postencephalitic Parkinsonism	• Infectious Mononucleosis
• Sympathomimetics	• Idiopathic Calcification of Basal Ganglia	• Niacin Deficiency
• Isoniazid	• Posttraumatic Encephalopathy	• Vitamin B,2 Deficiency
• Procarbazine	• General Paresis	• Carcinoid
• Cyclobenzaprine*	• Multiple Sclerosis	• Use of Hyperbaric Chamber
• Yohimbine*	• Viral Encephalitis	• Postoperative Excitement
• Cimetidine	• Cryptococcal Meningoencephalitis	• Premenstrual Psychosis
• Corticosteroids	• Pick's Disease	• HIV
• Thyroid preparations	• Klinefelter's Syndrome	
• Baclofen	• Kleine-levin Syndrome	
• Bromides		
• Procainamide		
• Metrizamide		
• Procyclidine		
• Clonazepam		
• Phencyclidine		
• Alprazolam*		
• Triazolam*		
• THC		

Modified and expanded from Larson & Richelson's Organic Causes of Mania, 1988.

* Occurring in individuals with history of affective disorders.

Irritable Bowel Disease and Mental Health: Putting Humpty Dumpty Back Together Again

Brian Bigelow, PhD, C.Psych, ABPP, ABMP
Professor Emeritus, Laurentian University

Jeffrey D. Cole, PhD, ABMP
American Board of Medical Psychology

Abstract

The role of chronic stress and mental illness has been largely ignored in terms of a host of medical diseases such as Irritable Bowel Disease (IBD). Irritable Bowel Disease (IBD) subtypes encompass such disorders as Inflammatory Bowel Disease (IBD), Crohn's Disease (CD), Ileitis (I) and Ulcerative Colitis (UC), depending on their GI location and infection. These IBDs often have incapacitating and at times fatal longer-term consequences. Unfortunately, there is no known intervention that actually reverses or even successfully treats IBDs. Accordingly, interventions for IBD resort to treating its adverse symptoms, such as abdominal pain, bloody stool, infections and severe digestive distress. Pharmacy commercials make it seem so ridiculously simple. Clearly, it is not easy to reverse the effects of a lifetime of adverse stressful events and their impact on one's physical health. However, integrated psychological and medical intervention could hold the key to greater improvement of symptoms as well as quality of life and, if applied early enough in the development disease there is theoretical basis to believe the progression of the disease could be arrested if not reversed. As medical psychologists, we think that interdisciplinary science should come to the rescue. Fortunately, there are fledgling attempts to penetrate a reluctance to apply more comprehensive therapeutic approaches, including the National Health Services (NHS) web based Cognitive Behavioral Therapy (CBT) IBS protocol. (Independent, April 11, 2019). A more detailed analysis of behavioral interventions is attempted.

Introduction

There are few other things like IBD that invite feelings of impotence and despair in both a patient and a caring clinician. One such patient had a long history of sibling abuse directed at her physical appearance. She developed a deep insecurity because of this. During early adolescence her UC began. Then her impending marriage ended directly due to her severe somatoform image disorder and associated flight response. She married another man and had a severely autistic and deaf child. Her family continued to be very insensitive to her and offered little or no support. Her UC also made it impossible for her to continue work as her symptoms were too disruptive.

Physiologically, IBD is an inflammatory autoimmune response that invades and inflames the intestinal wall and impairs the transport of serotonin (5HT) from entering the blood stream. Most of the body's serotonin is manufactured in the gut. Serotonin is a regulatory hormone that has major mental health effects as it is implicated in mediating mood. Quite understandably, depression and anxiety are common presentations with UBD. Opportunistic infections can also often occur. While medical interventions such as use of steroids,

Correspondence address: B. J. Bigelow, Ph.D. C. Psych. ABMP (Ret.), 6-71 Eldorado Drive, St. Albert, AB T8N7E3, Oh: 705-677-9048

benzodiazapines, antidepressants and antibiotics are appropriate, psychological/behavioural interventions are all too often ignored or not fully implemented as they are either not well understood or available Unknowns are whether psychopathology is the contributing cause of IBD, the result of IBD or an independent process. Though evidence suggests it is a reciprocal, interaction effect. Our position is that reducing chronic stress through competent psychotherapy is an essential component of effective comprehensive treatment.

Who gets sick?

Not everyone becomes ill with IBD when subjected to the same history of chronic stresses, but now we are beginning to have a clearer explanation. This vulnerability to stress has a natural distribution as exemplified by Ebner, Muigg, Singewald and Singewald (2008). They observed that rats bred with higher levels of Substance P (SP) neurokinin-1-receptor (NK-1R) knockout treatment had lower levels of neuronal activity in stress circuitry. SP release in the medial amygdala is related to severe stress. Serotonin and norepinephrine are implicated in the regulation of stress, mood and affective behaviours. Given certain parallels between human and rat brains along stress and reward circuitries, application of this model to humans is reasonable. Clearly, it would be valuable to have a biological screening test to help identify patients with a higher level of SP.

We emphasize the primary role that early interpersonal and developmental disruptive problems play in how people differentially respond to future life stressors. We need to stipulate very clearly that major interpersonal stressors (e.g., insecure attachment, fractured early object relations, abuse, neglect, and assault) early on fundamentally and differentially—see Ebner et al. above—change physiologically how we deal with future stressors and how these affect our biochemical reactivity to them.. We want to avoid falling into the trap that many physician scientists, neuroscientists and others do of simply noting that patients have variations in biochemistry without ever addressing where these variations come from, (i.e., the relational and developmental triggers which then invite psychological, psychotherapeutic and behavioral interventions.) Unfortunately, psychotherapy is often treated as if it is a vague, amorphous and biochemically irrelevant process. On the contrary, mental illness and physical symptoms interface at the endorcrine and cellular level via affecting hormonal communication and neurotransmitter activity. This is particularly true for IBDs.

The Brain-Gut Connection

Sajadine et al. (1992) provided an in-depth examination of IBD. Inflammatory reactions to stress implicitly involve the Hypothalamic, Pituitary Adrenal Axis (HPA), which is over-active in patients who are under excessive psychological stress (Singewald and Singewald , 2008). Hence, the symptomatology of IBD is both caused and aggravated by excessive stress. Genetic defects of OCTN1 and OCTN2—organic cation transporters implicated in Crohn's Disease (CD) are also involved (Stein, 2014). A basic issue with UC is that the key neurotransmitter 5HT (serotonin) is largely manufactured in the walls of the intestinal lumen. This is precisely the location in which UC inflammation and infection occur. The OCT2 monoamine transporter system is then impaired (Stein, 2014). The result is that there may well be a buildup of 5HT but an impairment of its serum transport. Serotonin normally attaches to platelets and is then available to cross the Blood Brain Barrier (BBB). Interference with this transport fosters an increase in anxiety and depression.

IBD is highly disruptive, painful and humiliating. Chronically high levels of anxiety, family history of abuse, and the need for cortisol, anti-inflammatories and antibiotics, are quite common. Vexingly however, studies (e.g., Helzer et al., 2012; Magni et al., 1982) vary considerably as to the connection between IBD and psychopathology. Astonishingly, Magni et al. reported that psychiatric problems were seldom reported in the clinical charts. Were physicians alert to them? Nevertheless, the symptoms of IBD are exacerbated by higher

levels of stress (see Laird et al., 2015). High levels of chronic arousal or parasympathetic 'tone' play havoc with the unmet need for serotonin which may be at toxic—untransported - levels in the intestinal lumen. Depression and anxiety are thus difficult to treat with medications when depletion of catabolized serotonin is chronic. This is but one case where integrating psychotherapeutic and behavioral interventions with medical interventions is appropriate. Stress management and regulation remain a primary objective toward the goal of resolving IBD. As illustrated in our index case above, almost 20% of primary care patients, including those with IBD presentations, have intransigent somatization disorders (Kroenke, et al., 1994). Such disorders are historically very resistant to change.

Mawdsley and Rampton (2005) reviewed the stress response in IBD and concluded that adverse life events, chronic stress, and depression increase the chance of an adverse impact on the immune system and relapse in patients with "quiescent" IBD. Family stress is very common. These authors noted that the immune and nervous systems are linked, with stress induced alterations in gastrointestinal inflammation, with alterations in GI mucosal inflammation and corticotrophin releasing factor (CRF). More examinations of the effect of stress reduction therapy in IBD were strongly encouraged. CRF is released from the hypothalamus, causing release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which then releases cortisol from the adrenal cortex, which inflames the enteric nervous system—the gut. Immunosuppression and infection often result. Kawahito et al. (1995) also determined that CRH is a major regulator of the HPA axis and is a proinflammatory agent. CRH was considerably enhanced in biopsies of the large bowel of patients with UC. The clinical evidence to date is that there may well be a permanently altered and dysfunctional response to stress in patients with UC and its related diseases. The challenges to medicine and psychology are profound and the need for collaborative medicine—with a much greater emphasis on psychological factors as primary determinants and psychological and behavioral interventions as primary treatments—is great.

At the molecular level, 5-hydroxytryptamine, (5-HT, serotonin) is an inhibitory indolamine monoamine neurotransmitter found in the human body, derived from the amino acid tryptophan and is inhibited by monoamine oxidase. 5-HT inhibits and is necessary for gut transport. 5-HT carries signals along and between neurons and is mainly found in the gut, brain, and blood platelets, where it is transported. 5-HT is created by a biochemical conversion process which combines tryptophan with tryptophan hydroxylase to form 5-HT. Bioavailable 5-HT is most commonly believed to be deficient in clinical depression and anxiety and deficient in IBD. 5-HT gets depleted during an attack of UC as the gut is its primary source where it is essentially trapped. As informed as this perspective is in understanding IBDs, it is woefully deficient in acknowledging the causal role that chronic environmental stresses play in provoking IBDs in vulnerable persons where these neurotransmitter effects are playing a mediating role between psychogenic stress, depression, anxiety and UC/IBD . A more holistic view of IBDs includes immunological dysfunctions embracing illnesses such as commonly co-occurring diseases such as asthma and food allergies (Wilczynska-Kwiatek, Bargie-Matusiewitz, and Lapinski, 2009).

Nowakowski, Crobak and Dudek (2016) also noted that mental disorders such as anxiety, depression and bipolar disorders occur more often in IBD. These disorders are probably attributable to unregulated stress resulting in hormonal changes in turn leading to abnormally high levels of Norepinephrine (NE). The present authors argue that in the brain-gut-axis, immunological dysfunctions and vagus nerve dysfunction play a role in IBDs as these problems are also tied in directly with anxiety and stress. Vagus cranial nerve X affects the GI tract. Intriguingly, Tjonneland et al. (2009) found that about 47% of UC is caused by red meat and its inflammatory effects in susceptible individuals. The nexus of addressed IBDs appears to be the inflammatory gut response. Such findings underscore the fact that an in-

terdisciplinary approach to IBDs is advisable with an emphasis on identifying the causal mechanism or mechanisms in the compromised individual's inflammatory response. The present authors argue that psychogenic stress acts as an independent determining variable in these cases.

As indicated, a key contributor to most mental illnesses is excessive, unregulated stress, which is also associated with an inflammatory gut response in vulnerable people. To illustrate, Nowakowski et al. (2016) noted that IBD flare-ups are often accompanied by declining mental health. In their review, they found that the need for surgical interventions and symptom severity were associated with higher levels of depression and the need for immunosuppressant therapies such as corticosteroids. 5HT deficiency is the pharmacological focus of mental illnesses such as depression and anxiety and is the major active target for drugs such as selective serotonin reupake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).) However, it is a leap of faith to think that a defective gut can metabolize SSRIs and TCAs. If the gut were efficient then serotinergic medications would address IBDs. They do not. We argue that the reverse also needs to be considered, that chronic stresses fuel gut-brain disturbances. Meanwhile, the authors posit that this tendency to attempt to reduce symptoms without applying curative intervention—e.g., psychotherapeutic and behavioral intervention—is likely due to ignorance of and omission of the causal psychological factors in addressing these disorders.

One reason given for the use of psychotherapy is that medications are relatively ineffective in IBD is that although the majority (80-90%) of 5-HT is produced in the gut, the form of 5-HT produced in the brain is used by the brain. That is, 5-HT produced in the gut supposedly does not cross the blood brain barrier (BBB) and is therefore unavailable to the brain. For instance, it is not known if and to what extent 5-HT introduced by antidepressants such as SSRIs is released in the brain. This is a hotly debated issue in psychiatry as SSRIs are marginally more effective compared to placebo. (HAM-D study). Thus, in terms of this prevailing wisdom, IBD should have no bearing on mental health treatments when antidepressant medications are deployed. To elaborate, since 5-HT produced by SSRIs attaches to platelet walls, making the division between gut produced and brain produced serotonin not as clear cut as formerly thought. Further complicating the issue is that it is not presently known to what extent 5-HT levels in the bloodstream reflect those levels in the brain (See Nakatani et al., 2000). Furthermore, if a therapeutic approach is taken addressing causal (e.g., psychological and stress) factors, some of these pharmacological dynamics might be of less crucial importance anyway. Psychological stress affects the gut lumen.

As previously discussed, the key underpinnings of a psychosomatic understanding of IBDs are that severe and serious levels of stress result in a depletion of serotonin in the brain and the gut. To illustrate, Scott et al. (2015), using surveys from 17 countries, found that 16 mental disorders predated the onset of 10 physical conditions. For example, a history of mood disorders was associated with subsequent heart disease. The seminal works of Hans Selye (e.g., 1976) attest abundantly to the fact that chronic excessive stress can and does impair and damage bodily tissues. This stress-induced depression in the brain also impinges on the workings of the gut. Not surprisingly, Sajadinejad et al. (2012) in their review found that in almost 75% of patients with irritable bowel disease (IBD) (which includes UC) that stress, or their own personality makeup is a major contributor to the development of this disease, and in more than 90% of cases that it influences their disease activity. On the other hand, these authors felt that, similar to Seligman' s (1992a,b) theory of loss of control and self-efficacy, that the unpredictable and incurable course of the disease impairs the individual's belief about self-control and self-efficacy, causing chronic helplessness and predisposing the patient to depression and anxiety. Accordingly, Sajadinejad et al. recognized that genetic, immune, and environmental factors such as psychological stress trig-

ger immune dysfunction and bowel symptoms. These authors included impairment of body image and fear of sexual inadequacy as likely outcomes of IBD and are consistent with our case illustration above. Perfectionism to be and look perfect is common in such patients and may point to personality variables that contribute to the condition, as though these variables are separate and distinct from the emergent history of the UC problem. Anxiety and depression are heightened during relapse. The implication of excessive stress as a cause of UC stems from the fact that introducing more serotonin alone as a stand-alone treatment is not effective.

At his juncture, it is appropriate to examine how efficacious traditional psychotherapy is with IBDs. Given the high correlation between UC, psychiatric disorders and stress, interventions that directly address emotion and emotional conflict as causal are at face value far more appropriate. These would include interpersonal and relational interventions, e.g., interpersonal psychotherapy and object-relations informed psychodynamic psychotherapy. However, while psychodynamic and psychoanalytically-informed interventions have been explored with a host of other psychogenic and psychosomatic conditions studies of psychological interventions with IBD have mostly been cognitive-behavioral (e.g., Cognitive Behavior Therapy; CBT). Grace et al. (2017) in their systematic review of IBD trials between 1947-2016 showed that randomized control trials showed that patients receiving CBT had an improved quality of life but not a reduction in actual IBD symptoms. McCombie et al. (2013) reviewed eighteen studies of psychotherapy showing minimal effects on depression and anxiety but quality of life, disease progression, relapse rates and hospitalizations were improved.

Antonina et al. (2006) recognized that inflammatory bowel disease (IBD) is incompletely understood and the individual patient's response to treatment is variable. Even though there is a link between the patient’s mental health and the course of this disease, there is no evidence that CBT psychotherapy is effective in spite of the fact that serotonin is increased via psychotherapy (Friedman, 2002). On the other hand, the NHS has found otherwise. In Antonina et al.’s review, the effectiveness of treatment with antidepressants in IBD patients was defined as the remission of the disease activity beyond the usual length of remission. Mental health issues improved somewhat in some studies via SSRI therapy. To clarify, SSRIs were targeted to treat the disease manifestations but not specifically to improve mental health.

The causal direction between mental illness and IBD is indisputably complex, but Kuria et al. (2001) found that anxiety and depression had the greatest linkage to IBD up to five years before symptoms of UC appeared. I.e., Psychological factors are evidently present in the initial causal chain of events . Yet, these endless studies that investigate this disease and its treatment are without any regard for this holistic reality. To illustrate, Antonina et al.’s (2006) systematic review identified 20 IBD patients, with 12 of these in case reports. For example, Kast and Altschuler (2004) presented a medical history of a depressed and anxious patient with Crohn's disease treated with phenelzine (an MAOI) and subsequently achieved remission. Walker, Gelfand, Gelfand et al. (1996) compared IBD patients with and without current psychological disorders and noticed that depressed patients (n = 8) who were given Paroxetine in an open label design showed significant improvement in relation to functional disability. These researchers had expected an improvement only in depression; however, patients' scores on the SF-12 (a health survey) also improved in the area of quality of life. The fact that there is little good quality data in this area does not mean that it is unworthy of further study. In fact, it strongly supports more resources and effort being put into this line of research versus endlessly dumping money into research that is no more likely to result in positive findings than it did the previous hundreds of studies. The present state of knowledge regarding the interaction between psychological co-mor-

bidities and IBD resembles that of our knowledge of the suspected psychosomatic pathogenesis of irritable bowel syndrome twenty years ago. Of particular interest to mental health physicians, Laird et al. (2015) found that family therapy reduces IBD symptoms even after therapy ends. Psychotherapy works and is relevant when it addresses interpersonal-affective dynamics! Thus, rigid distinctions between psychological versus inflammatory mechanisms are more difficult to uphold. In fact, the mind and body are on a continuum and, while these domains may be distinguished academically, they are part of a unity of mind-body. Andrews et al. (1987) showed a connection between Crohn's Disease (CD) and psychiatric illness (50%) vs. well (8%). As one would expect with UC, and the frequent occurrence with body dysmorphic disorder (BDD), this disorder is more likely in patients who experienced child sexual abuse (CSA) or emotional abuse during childhood, as our index case illustrates. The mental health effects of such abuse over the developmental trajectory heighten the risk of mental illnesses and IBDs.

Medical Psychology and Disease

The penultimate attraction of psychotherapy, as opposed to supportive counselling, in the broadest sense, is that it addresses the core element of the disease: Stress and regulation of stress based in relational, developmental histories. Such core determinants cannot be addressed by primary psychoactive medications "treatments." For example, psychotherapy promotes better outcomes after heart surgery (Wayne and Katon, 2009). Psychotherapy even plays an important role in treatment of conventionally "core" medical problems (infections, heart valve defects, broken bones, etc.) as all of these conditions have psychological determinants. Infections are associated with immune functioning which is impacted by stress and modulation of stress, heart defects are associated with behavioral lifestyle choices, self-care and stress and regulation of stress and broken bones and recovery from broken bones are associated with multiple behavioral and psychological factors in terms of risk-taking behavior, impulsivity, ability to tolerate frustration (e.g., keeping the leg still while rehabilitating). In addition to its role as a primary treatment psychotherapy is valuable in terms of an adjunctive treatment in adherence to medical interventions in cases where these are primary, such as taking your antibiotics as prescribed and in alcohol withdrawal. Obviously, since the time of Aristotle, psychotherapy was primarily designed to address mental health problems that medicine—then and now—that medicine could not and cannot address alone. Notably, stress reduction and modulation and a sort of "family milieu" therapy were Aristotle's primary interventions and—in a highly advanced form—are applied effectively today. Moreover, we are now getting a clearer awareness that psychological, behavioral, interpersonal and developmental factors are at the root of many illnesses and their recovery.

References

Andrews, H., Barczak, F., and Allan, R. N. (1987). Psychiatric illness in patients with inflammatory bowel disease. 1987 (Gut, 28(12), 1600-1604.

Antonina, A., Mikocka-Walus, Deborah A Turnbull, D. A. Nicole T Moulding, N. T., Ian G Wilson, Jane M Andrews, J. M., and Gerald J Holtmann, G. J. (2006). Antidepressants and inflammatory bowel disease: a systematic review. *Clinical Practice and Epidemiological| Mental Health*, *20*, Published online 2006 Sep 20. doi: 10.1186/1745-0179-2-24.

Armstrong, E. M., and Abel, E. L. (2000). Fetal alcohol syndrome: The origins of a moral panic. (2000) httpalcalc.oxfordjournals.org/content/35/3/276 DOI: http://dx.doi.org/10.1093/alcalc/35.3.276 276-282 First published online: 1 May 2000. http://alcalc.oxfordjournals.org/content/35/3/276;http://dx.doi.org/10.1093/alcalc/35.3.276 276- 282.

Bagby R. M., Taylor G. J., Parker J. D. A., and Dickens S. E. (2006). The development of the Toronto Structured Interview for Alexithymia: item selection, factor structure, reliability and concurrent validity. Psychotherapy and Psychosomatic Disorders. 75, 25–39. 10.1159/000089224 [PubMed] [Cross Ref]

Bellinger, F.P., Davidson, M.S., Bedi, K.S., and Wilce, P.A. (2002). Neonatal ethanol exposure reduces AMPA but not NMDA receptor levels in the rat neocortex. *Developmental Brain Research, 136,* 77-84.

Bigelow, B. (2006). There's an elephant in the room: The impact of early poverty and neglect on intelligence and common learning disorders in children, adolescents and their parents. *Developmental Disabilities Bulletin*, 2006, *34*, 1-2.

Carrozzino, D, and Porecelli, P. (2018). Alexithymia in gastroenterology: a systematic review. *Frontiers in Psychology*, *9*, 470.

Chang, C. K., Broadbent, H. R., Fernandes, M., Lee, W., , Hotopf, M., Stewart R. (2010). All- cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: A cohort study. *BMC Psychiatry*;*10*:77.

Cole, J. (2019). Emotion as a determining variable in emotion-physiological correlation-causation studies: Commentary. Link to article posted to AMP facebook page

Ebner, K, Muigg, P., Singewald, G., and Singewad, N. (2008). Substance P in stress and anxiety: NK-1 receptor antagonism Interacts with key brain areas of the stress circuitry. *Annals of the New York Academy of Science*, 1144; 61-73.

Fuller-Thomson, E., West, K. J., Sulamn, J., and Baird, S. L. (2015). Childhood maltreatment in associated with ulcerative colitis but not Crohn's Disease. *Inflammatory Bowel Diseases*, *1*, 10, 1097.

Fredrickson, B. L. and Levenson, R. W. (2011), Positive emotions speed recovery from the cardiovascular Sequelae of negative emotions. *Cognition and Emotion*. Xxxxxx

Friedman, R.A. (2002). Behavior; like drugs, talk therapy can change brain chemistry. Behavior, August 27.

Gracie, D. J., Irvine, A., Sood, R., Mikocka-Walus, A., Hamlin, P.J., and Ford, A. C. (2017). Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastro Enterology Hepatology*, *2*(3), 189-199.

Helzer, J. E, Stillings, W. A., Chammas, S, Norland, C. C, and Alpers, D. H. (2012). A controlled study of the association between ulcerative colitis and psychiatric diagnoses. *Gastroenterology Research and Practice.* Volume *2012*, Article ID 106502, 11 pages http://dx.doi.org/10.1155/2012/106502.

Kast, R. E., and Altschuler, E. L. (2004). Bone density loss in Crohn's disease: role of TNF and potential for prevention by bupropion. *Gut*. 53:105.

Kawahito, Y., Sano, H., Mukai, S., Asai, K., Kimura, S., Yamamura, Y., Kato, H., Chrousos, G. P., Wilder, R. L., and Kondo, M. (1995). *Gut*, *37*, 544-551.

Kurina, L. M., Goldacre, M. J., Yeates, M. J., and Gill, L. E. (2001). Depression and anxiety in people with inflammatory bowel disease. *Journal of Epidemiological Community Health*, *55*(10), 716-720.

Kroenke, K., Spitzer, R. L., Williams, J. B., Linzer, M., Hahn, S. R., deGruy, F., V. 3rd, and Brody, D. (1994) Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Archives of Family Medicine*, *3*(9); 774-9.

Mawdsley, J. E., and Rampton, D. S. (2005). Psychological stress in IBD: New Insights into Pathogenic and Therapeutic Implications. Recent Advances in Basic Science. *Gut*, *54(10)*; 1481-1491.

Laird, K. T., Tanner-Smith, E, E., Russell, A. C., Hollon, S. D., and Walker, L. S. (2015). Short-term and Long-term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis, Clinical Gasterenterology and Hepatology. http://dx.doi.org/10.1016/j.cgh.2015.11.020

Magni, G., Bernasconi, G., Mauro, P., D'Odorico, A., Sturniolo, G. C., Canton, A, and Martin, A. (1982). Psychiatric diagnoses in ulcerative colitis: A controlled study. *Digest of Disease Science*, *27*(6); 513-8.

McCombie, A. M.M., Mulder, R. T., and Gearry, R. B. (2013). Psychotherapy for inflam-

matory bowel disease; a review and update. *Journal of Crohn's Colitis*, *7*(12), 935-49.
Nakatani, Y., Sato-Suzuki, I., Tsujino, N., Nakasato. A., Seki, Y., Fumoto, M., and Arita, H. (2000). Augmented brain 5-HT crosses the blood–brain barrier through the 5-HT transporter in rat. *European Journal of Neuroscience*, *27*, 2466–2472.
Nowakowski, J., chrobak, A. A., and Dudek, D. (2016). Psychiatric illnesses in inflammatory bowel diseases – psychiatric comorbidity and biological underpinnings. *Psychiatric Policy*, *50*(6), 1157-1166.
Roshanaei-Moghaddam, B., Katon, W. (2009). Premature mortality from general medical illness among persons with bipolar disorder: A review. *Psychiatric Service. 60*; 147–156. [PubMed*] Clinical Practice and Epidemiological Mental Health* (2006), *2*: 24.Published online 2006 Sep 20. doi: 10.1186/1745-0179-2-24 [PubMed]
Sajadinejad, M. S., Asgari, K., Molavi, I. H., Kalantari, I. M., and Adibi, P. (2012) Psychological Issues in Inflammatory Bowel Disease: An Overview. *Gastroenterology Research and Practice*. http://dx.doi.org/10.1155/2012/106502.
Scott, K. M., Lim, C., ali-Hamzawi, A., Alonso, J., Bruffaerts, R., Caldas-de-Almeida, J., M. Florecu, S., de Girolamo, G., Hu, C., de Jongs, P., Kawasami, N., Medina-Mora, M. E., Moskalewicz, J., Navarrro—Mateu, F., O'Neil, S., Piazza, M., Posada-Villa, J., Torrs, Y., and Kessler, R. C. (2015). Association of mental disorders with subsequent chronic physical conditions: World mental health surveys from 17 countries. *JAMA Psychiatry*, 2688. Published online December 23, 2015.doi:10.100/jamapsychiatry.2015-2688.
Seligman, M. (2002a) *Learned Optimism*. Vintage Books, New York, NY, USA.
Seligman, Martin E.P. (2002b). *Authentic Happiness: Using the New Positive Psychology to Realize Your Potential for Lasting Fulfillment*. New York, NY: Free Press.
Tjonneland, A., Overvad, K., Bergmann, M. M., Nagel, G., Linseisen, J., Hallmans, G., Palmqvist, R., Sjodin, H., Hagglund, G., Berglund, G., Lindgren, S., Grip, O., Palli, D., Day, N. E., Knaw, K. T., Bingham S.,Riboli, E., Kennedy, H., and Hart, A. Linoleic acid, a dietary n-6 polyunstaurated fatty acid, and the aetiology of ulcerative colitis: a nested cass-control study within a European prospective cohort study. *Gut*, 58(12), 1606-11.
Selye H. (1976) *The Stress of Life* (rev. ed.). New York: McGraw-Hill
Stein, A. (2014). http://www.neurosciencemyths.com/Colitis.htm. Retrieved April 23, 2014. *British Journal of Psychiatry* (1991), *158*: 413-5.
Taylor G. J., Ryan D., Bagby R. M. (1985). Toward the development of a new self-alexithymia scale. *Psychotherapy and Psychosomatic Disorders*. *44*, 191–199. 10.1159/000287912 [PubMed] [Cross Ref]
Walker, E. A., Gelfand, M. D., Gelfand, A. N., et al. (1996). The relationship of current psychiatric disorders to functional disability and depression in patients with inflammatory bowel disease. *General Hospital psychiatry*, 18(*4*), 220-229.
Wayne, J., and Katon, W. J. (2009). Psychotherapy Can Ease Post-Surgical Depression - HealthDay. http://consumer.healthday.com/mental-health-information-25/anxiety-news-33/psychotherapy-can-ease-post-surgical-depression-625785.htm.
Wilczynska-Kwiatek, Bargie-Matusiewitz, and Lapinski (2009). Asthmam allergy, mood disorders and nutrition. *European Journal of Medical Research*, *14*, 248-254.

Psycoquulum:
A Relational Mind-Body Containment Model

Jeffrey D. Cole, PhD, FPPR, FICPP, ABMP
Director, Board of Directors, American Board of Medical Psychology

Abstract

A previous paper (Cole, 2017) introduced the idea that a more psychologically-informed understanding of human medicine is needed to address current deficits in healthcare. Given modern medicine's almost exclusive focus on biological processes, and psychology's general eschewal of biology, an alternative understanding of the mind-body continuum is needed to conceive a comprehensive model of health, illness and healing. In the present paper, this relational-biological continuum introduced in the first paper as the *psycoquulum* is addressed as a thing-in-itself. That is, the psycoquulum is a heuristic for an emerging paradigm and it is also a construct. It is a complex construct comprised of sociological, psychological and medical constructs. But, it is *not the biopsychosocial* model by dint of the displacement of the biological substrate in that model with a containing psychological-social infrastructure from which the biological emerges. As such, this complex construct must be understood in terms of the way society at large is represented in individuals and in relationships between individuals, permeating tissue as a determinant in conception and gestational events and then engaged interpersonally-physiologically-cum-interpersonally-affectively in early development. The internalized construct in the young and developing person then interacts with and becomes part of the larger social constructs (institutions, systems, society) and the process repeats. The psycoquulum is a relational, cross-temporal, cross-generational and cross-situational container of mind-body processes that dictate health, illness, healing and response to treatment.

A Third Paradigm and a Heuristic

For decades the trend in medicine has been toward biologization of human health and disease and toward medicalization (Bell & Figert, 2012) and pharmaceuticalization (Abraham, 2010; Joubert, 2015) of the methods by which disease is treated. Biologization is the reduction of illness to its biomedical component with less regard to the psychological, social, environmental, economic and other factors that are part of the illness process (Helman, 2008). Medicalization and pharmaceuticalization are approaches to treatment that reduce target factors largely to these biological or to individual physical and mechanistic components.

Bell and Figert (2012) state with regards to medicalization and pharmaceuticalization:

> One of the most influential definitions of medicalization comes from American sociologist Peter Conrad (2005: 3) who declares that the essential meaning of the term is "defining a problem in medical terms, usually as an illness or disorder, or using a medical intervention to treat it." [emphasis in the original]. Pharmaceuticalization is the term given to "the process by which social, behavioral or bodily conditions are treated, or deemed to be in need of treatment/intervention, with pharmaceuticals by doctors, patients, or both" (Abraham, 2010a: 290)" (pp. 775-776)

Correspondence address: Jeffrey D. Cole, PhD, ABMP, 1121 Upper Front Street, Binghamton, NY 13905, DrJeffDCole@gmail.com, (607) 761-2934

Thus, from medicalization and pharmaceuticalization perspectives an infection is treated with antibiotics with little or passing attention to other contributing factors, e.g., environmental conditions, stress effects on immune system functioning and the associated psychological and relational factors inherent in stress and coping. By the same token, neuroleptic medications are given to a schizophrenic person sometimes resulting in relative improvement in a few symptoms but when the individual stops "complying" with the medications little thought is given to why the individual is rejecting what he or she, in many cases as it turns out, experiences as a weak substitute for developing a relationship that could lead to an understanding of his or her suffering.

All of these trends—biologization, medicalization and pharmaceuticalization—can be thought of as concretization and simplification of complex, interactive, multivariate structures and processes involving developmental, attachment and relationship histories, trauma, environmental antigens and defenses and situational stressors and supports. As concretizations and simplifications these trends create models of disease that are only approximations of reality at best and thus result in treatment and outcomes in many cases which are consistent with approximation, i.e., suboptimal (Beresford, 2010).

Abraham (2010) states:

> The biomedicalism thesis, which claims that expansion of drug treatment reflects advances in biomedical science to meet health needs, is found to be a weak explanatory factor because a significant amount of growth in pharmaceuticalization is inconsistent with scientific evidence, and because drug innovations offering significant therapeutic advance have been declining across the sector, including areas of major health need. Some elements of consumerism have undermined pharmaceuticalization, even causing de-pharmaceuticalization in some therapeutic subfields. However, other aspects of consumerism, together with industry promotion, medicalization, and deregulatory state policies are found to be drivers of increased pharmaceuticalization in ways that are largely outside, or suboptimal for, significant therapeutic advances in the interests of public health (p. 603)

Biologization—as well as pharmaceuticalization—has been particularly notable in psychiatry where the obviousness of other, non-biological variables, e.g., relationships, stressors, interpersonal and emotional conflict and developmental histories make the inadequacy and incompleteness of such unidimensional models self-evident (Helman, 2008). That is, while psychology is many things beyond biology, within contemporary medicine it is largely reduced to a biological medical model.

While most people would deny, for instance, that the most salient aspect—or fundamental meaning—associated with loss or trauma is "changes in neurochemistry" this is increasingly how suffering associated with these experiences is treated in contemporary healthcare (Helman, 2008). Joubert states with regards to the National Institute of Mental Health's (NIMH's) mission:

> The mission of the U.S. National Institute of Mental Health is to transform understanding and treatment of mental disorders. According to its former director, Dr. Thomas Insel, fundamental to its mission is the proposition that "mental illnesses are brain disorders." The aim of this article is to examine this proposition and to argue that it does not make sense. As a scientific proposition, it is based on contentious empirical claims, and as a metaphysical proposition, it is consistent with those who claim that a person is a brain. A conceptual analysis is employed as a tool to show that it is a category mistake to ascribe psychological properties of a person to a brain (2015. p. 185).

The biological paradigm is so embedded at this point that, even when an ostensibly expanded model—one declaring enthusiastic intent for inclusion of non-biological factors along with the biological in psychiatry is introduced—i.e., the Research Domain Criteria (RDoC)—the "non-biological" factors are attached to the biological factors additively, secondarily or, at best, as mediators or moderators rather than as the contexts in which health changes, including biological health changes, emerge. Miller (2012) states:

> We systematically mistreat psychological phenomena, both logically and clinically…. [T]he dominant discourse in modern cognitive, affective, and clinical neuroscience assumes that we know how psychology/biology causation works when we do not; that there are serious intellectual, clinical, and policy costs to pretending we do know; and that crucial scientific and clinical progress will be stymied as long as we frame psychology, biology, and their relationship in currently dominant ways. [These dominant ways are based in] misguided attempts to localize psychological function via neuroimaging, misunderstandings about the role of genetics in psychopathology, and untoward constraints on health-care policy and clinical service delivery. A particular challenge…determining what constitutes adequate explanation in the relationship between psychology and biology" (p. 716)

While, for human existential reasons this lopsidedness is most notable in psychiatry physical medicine is no-less over-biologized. That is, even in physical illnesses there is an over-reliance on biological explanations when, once again, psychological and social factors—development, attachment history and relationship, stress, support, self-care, lifestyle choices and learned health habits—play a clear role. Many articles that are published in medical journals contemporarily do not include any reference to the multiple domains involved in health and illness related processes instead focusing almost entirely on the fractional etiology that is the disease once it has developed internal, biological processes in the individual. That is: proximal causes as opposed to ultimate causes.

Consider: Is the core "antigen" where someone is prone to getting colds—where said someone is continuously struggling with trying to hold onto jobs, oppressed with the associated increasing debt, is without time or energy to save failing relationships and, as a result experiences protracted psychogenic stress and a depressed immune system—the rhinovirus? If the cause of an illness are intrapsychic struggles and interpersonal conflict resulting in stress and changes in the body's protective mechanisms should the treatment of choice be antibiotics or antihistamines?

We are long overdue for revamping our meta-model of human health, illness and healing. We are in need of a model that moves relational-affective, developmental and cognitive factors affecting stress, coping, lifestyle and sometimes converting directly into physical illness—e.g., conversion disorders and psychosomatic disorders—much more toward the forefront and into the determinant role in addressing health problems whether physical or psychiatric/psychological in the conventional sense.

Why a heuristic?

Information about health and illness, response to treatment and the recovery process is gained through clinical practice long before it is disentangled, and the relationships defined through controlled research. There is much that practitioners know observationally that runs contrary—or at first look, at least appears to run contrary—to "prescribed" knowledge derived mostly through controlled population-sampling studies. For example, for years evidence-based practices in psychology have emphasized cognitive-behavioral approaches (Johnsen & Friborg, 2015). However, clinical practice shows the fundamental role of relational factors in patient participation and continuity in treatment and treatment

outcome (Ardito & Rabillino, 2015), elements which are emphasized in humanistic, object-relational, interpersonal psychoanalytic and interpersonal psychotherapeutic approaches. Current emphases on managed healthcare, number crunching and pharmaceutically-derived algorithms have gone a long way toward squashing awareness and inclusion of this key element of treatment. That is current dominant trends in healthcare interfere with healing and recovery.

Relational-affective factors largely defy the operationalization, quantification and controls required by randomized controlled trials (RCT's). Yet, their lack of amenability to controlled study neither nullifies their existence nor their core role in healing. At the same time, our current—heavily biologized—paradigm is largely structured around what is amenable to RCT's especially in non-psychiatric medicine but increasingly in psychiatry and mental health care. This structure is reinforced by economic factors. Easily packaged disease and treatment models lend themselves to easily packaged—and readily marketed—"treatments," e.g., pills and potions.

Thus, we have interlocking, mutually-reinforcing disease and treatment paradigms—driven by extrinsic, i.e., pharmacoeconomic factors—which divert our attention from core healing elements. Furthermore, these emphases dissuade development of appropriate research methodologies for developing a paradigm constellated around clinically established core healing elements largely comprised of relational factors. Given the current state of affairs—and, before concerted research and development can commence in a new direction—a guiding concept or organizing principle or archetype for a healthcare paradigm with a truer fit with reality is needed to drive research and development in this new direction.

Thus, a heuristic. A heuristic guides and helps us organize information to make sense of a new idea. A heuristic does not intend to break down all existing elements into their atomic components, investigate these and build a new structure from the outset. It, instead, calls our attention to the observably, logico-deductively coherent, but radically different new model and hints at the steps needed to further explicate and develop this new model into a body of methods and practice consistent with the archetype. And, it gives us an anchor for this new model—a transitional object if you will—to lean on as we emancipate from the old, addictive—but inadequate—model on which we have become problematically dependent.

The Linguistic Construction and Introduction to the Construct

A heuristic, acting as a transitional object (see "Object Relations" section below) to help us transition from the old paradigm to the new itself benefits from a new name to set it apart from the old and familiar. The fundamental distinction from the old mind-body paradigm to the new one is the relative position of the mind in that relationship. Mind—or psyche or relationship—has been treated as a dependent or determined variable in most existing models (Sapolsky, 2016, Porges, 2007; Schore, 2015). But this arrangement does not fit the profound, encompassing role of psychological and social factors, behavior and relationship in human physical, as well as mental, development, health, illness, healing and response to treatment.

As will be articulated and explicated further in the present paper we (human beings) are not only anticipated and conceived, gestated, parented, raised, socialized and enculturated in larger systems—resulting in reiteration of the process in an overall evolutionary movement across time—in an interpersonal-social-relational context. This perpetual entwining of relational expression and experience with the biological processes that make us human results in psychological factors permeating tissue (Cole, 2017). This is a new concept that will be given further attention in the present paper. (To fully grasp this concept requires an un-

derstanding of object relations theory—which will be reviewed below—and how this can be applied to an integrated physiological-affective-interpersonal attunement, containment and internalization process.)

As such, it is helpful to construct a name by which we can identify this new idea and that respects and acknowledges psyche's primacy in the mind-body relationship. As introduced in the previous paper (Cole, 2017) *psycoquulum*, derived from understanding psychological—especially *relational*—factors, "*psych*," as the "cooking vessel," i.e., *coquulum* (Latin)—in which the mental as well as biological emerges and are blended and become yoked domains—or, more accurately qualities of a continuum—captures this psychologically-driven, reciprocal mind-body relationship. Relationship determines procreation and our bonding—bonding as people and bonding of body and mind—at many other levels (as will be described) and, as such, relationship permeates our tissue. Our relational histories—individually and cross-generationally—are expressed in our tissue. As such relational events engage our tissue and biological processes, directly, just as they do our mental and psychological processes. This is the gist of the new model, and of the present heuristic and the focus of this paper. The yoking of the "idea" and "vessel" also, simultaneously captures the idea of "containment" that is central to the notion of the role of relationship in containing affects in object relations theory. Thus, the idea identified by this term *psycoquulum* is a different idea versus those conveyed in other mind-body models (Sapolsky, 2016, Porges, 2007; Schore, 2015) wherein mind and body are recognized as continuously interactive, or even on a continuum but are always related back to a biological substrate or biological primary determinant.

Psycoquulum as Construct

If there is something we are calling the "psycoquulum" but this something is not a tangible—sensorially-perceptually, directly-experienceable—something, and, instead, is known only via its effects on the relationship between other tangible phenomena then this something is a *hypothetical construct* or, simply, a *construct*. Constructs are not directly observable but have effects on observable phenomena.

Hypothetical Constructs: Much of psychology is the study of intangible, not-directly-observable but measurable constructs. Self-esteem, intelligence, optimism/pessimism—and many other objects of study of psychologists—are constructs for which there are well-validated measures with also measurable, though also tangible, directly-observable correlates. Instruments by which constructs are measured are defined by the constructs that they measure. While this sounds tautological, the intent is the construct is defined by its effect on the relationship between observable phenomena, the named construct is that unseen variable that has this effect and measurements of this variable are then named for the variable. For example, intelligence is that component of human personality that predicts the individual's ability to work effectively with (e.g., store, recall, apply) information. Instruments which measure that ability are then called intelligence tests.

Psychological Constructs (with examples):
Trained psychologists are universally familiar with Cronbach and Meehl's (1955) discussion of the construct validity of psychological tests. In their discussion psychological tests are examined in terms of the constructs that they operationalize. And, through this examination the notion that the identity of a construct is defined and operationalized by measures is explicated. Cronbach and Meehl state:

> A construct is some postulated attribute of people, assumed to be reflected in test performance. In test validation the attribute about which we make statements in interpreting a test is a construct. We expect a person at any time to possess or not

> possess a qualitative attribute (amnesia) or structure, or to possess some degree of a quantitative attribute (cheerfulness). A construct has certain associated meanings carried in statements of this general character: Persons who possess this attribute will, in situation X, act in manner Y (with a stated probability). The logic of construct validation is invoked whether the construct is highly systematized or loose, used in ramified theory or a few simple propositions, used in absolute propositions or probability statements (p. 4)

As such, psychological constructs are generally those indirectly observable traits we think of individuals as possessing such as self-esteem, intelligence, optimism-pessimism, surgency, extroversion-introversion, mood lability and complexity, major depression, borderline personality disorder and schizophrenia.

While we also generally think of psychological traits as, in a sense, possessed internally there are cases where the construct is especially tied to the environment or constructs of other people such as when we speak of object representations and internalized self-other object relations. While internalized object representations are internal constructs they are evoked (Stern, 1985). Their full operation is partly dependent on others' internalized object relations. That is, they are a special construct that can be thought of as "partly inside/partly outside" of the individual.

Sociological Constructs (with examples):
Individual object relations—and how these are partly dependent on others' object relations—provide us a segue to those constructs sociologists primarily work with: sociological constructs. Sociological constructs are those indirectly observable characteristics of groups of people.

Berger and Luckmann, in *The Social Construction of Reality* (1967) described how people and groups interacting in social systems co-create and internalize, with the passage of time, mental representations of one another's actions. And, with habituation these internalized interactions become the reciprocal roles played by each member of the group in relationship with one another. This then becomes the sociological parallel of the previously-mentioned object relations theory in psychology which will be discussed in somewhat greater detail in a later section of the present paper. On the social level, this process that Berger and Luckman termed "social construction" extends beyond person-to-person reciprocation of roles to institutionalization of said interactions, such that these role-definitions are available to other members of society to adopt and play out. These institutionalized social constructs then embed meaning in society, such that reality is now reciprocally entwined with people's experiences of and beliefs about human social interaction. Reality itself, then, according to Berger and Luckman is socially constructed.

Sociological constructs include race, gender, young, old, health, illness and healing.

Medical Constructs (with examples):
The field of medicine also depends largely on constructs, primarily the diseases that physicians treat. While specific antigens (e.g., a germ), lesions or mutations might necessarily be present in a disease, any given clinical disease is defined by the cluster of symptoms that comprise that disease. Leukemia is an example of a medical construct. Other examples of medical constructs include arthritis, diabetes, myofascial pain syndrome and chronic fatigue syndrome.

Meanwhile, medical constructs, while seemingly founded in quantifiable physical events also have a socially constructed dimension. Henderson and Henderson (2002) state:

> Cultural construction theory derives from the larger theoretical domain of the cultural construction of reality. Within this theoretical body, cultural constructs exist as cognitive domains subsumed within the realm of total existence. The cultural construction of health and illness may be viewed as a device for categorizing or systematizing symptoms. Illness constructs are organizing frameworks for imposing structure upon the continuum of experience. Illness constructs reflect core cultural values in that they express normative understandings about the nature and causes of anomaly and dysfunction. The meaningfulness of any cultural construction for any particular group is necessarily a function of that group's cultural values (Hunt et al. 1990; Kleinman 1980) (p. 199)

For example, with regards to dementia they state:

> The cultural construction of dementia and attendant explanatory models for the condition may differ between the patient, the patient's family, and the health care provider (cf. Henderson 2002). It is not the case that lay accounts of illness are impoverished biomedical accounts. Professional and lay models are formulated to meet different objectives. A person's model of illness may reflect cultural understandings and personal experiences, including information obtained from interactions with others. Each person's talk about dementia reflects biomedical input as well as shared cultural understandings, framed within the context of each person's unique circumstance and understandings of their experience (Garro & Lang 1994) (Henderson & Henderson, 2002, p. 199)

The psycoquulum is a complex construct. In addition to psychological dimensions it also has dimensions of medical (disease) and sociological (social construction of reality) constructs.

Psycoquulum as Complex Construct:

The concept of complex construct itself is relatively unexplored in the health, psychological and social sciences. While it is understood that elements of one construct in a particular science—say empathy in psychology—overlap with and interact with other constructs in that same science, e.g., openness to experience (Miklikowska, 2012), there is less research into the interaction between constructs of different sciences comprising a third, complex, construct, e.g., a psychological construct like affect lability interacting with immune response to the rhinovirus.

This is not altogether unaddressed, however. The Common Cold Project (Cohen, 2016) at Carnegie Mellon University and at satellite sites at other research institutions looked at multi-factorial causes of the common cold including, in fact (among multiple other variables) state and trait affect lability, exposure to the rhinovirus and socio-economic stressors as interacting determinants of clinical rhinitis.

An example of a complex construct integrating psychological and sociological constructs is socioeconomic position (SEP). SEP differs from the sociological construct of socioeconomic status (SES) in that SEP also assumes the individual's ability to draw on and apply resources associated with his or her SES: the individual's personal agency interacting with SES one might say.

Sankar, Ramanathan and Kutty (2017) state:

> The socioeconomic position (SEP) of an individual represents an important characteristic of the individual, one that is very relevant to determine the health status at a point in time. It has been seen as distinct from socioeconomic status (SES) which represents access to collectively desired resources. SEP is defined as one's

> access to collectively desired resources and control over the resources which are decided by their own life experiences.[1] SEP builds into its construct an understanding that emerges from life experiences and ability to utilize for one's own benefit, which is absent from the former. SEP therefore is a dynamic concept whereas the latter is more static in conceptualization (p. 201)

An example of a complex construct integrating psychological, social and medical constructs is the placebo effect of active medications. That is, certain interpersonal-affective (e.g., attachment-related caregiving responses) and social factors (e.g., enculturated expectations of medications and marketing) contribute to conditioned expectations and conditioned emotional-physiological responses to a drug and its biochemical effects (Kradin, 2008).

> The total effect of a medication is the sum of its drug effect, placebo effect (meaning response), and their possible interaction (Hammami, Eman A Al-Gaai, Alvi & Hammami, 2010, p. 1)

Psycoquulum as Complex Construct: The psycoquulum is a complex construct. It is comprised of psychological (interpersonal-physiological and interpersonal-affective developmental), social (mores and cultural symbols) and medical (disease biological etiology and disease biological healing criteria) constructs. The components and their dynamics are as follows.

Psychological dimension: One's fundamental conceptualization of self, mind and body emerges via early attachment relationships (or lack thereof). Sense of self is founded in interpersonal-physiological and interpersonal-affective experience. That is our sense of self—whether we are speaking of mind, body or mind-body whole—is fundamentally a relational construct. The psychological theory that best explicates this construction is object relations theory as will be expounded at greater depth and in greater detail later in the paper.

Social dimension: Our social engagement and attachments and the social conceptualization on which these are based are co-constructed (Berger and Luckman,1966), as described in *The Social Construction of Reality*.

Medical dimension: Medical constructs include disease criteria as these are laid-out in diagnostic and statistical manuals (e.g., ICD, DSM). In Western society disease is a formalized conglomeration of clinical observation, self-report and laboratory tests. For example, leukemia is the cooccurrence of pallor, enlarged lymph nodes, an enlarged liver or spleen, bleeding, significant infections, fever, significant bruising, fatigue and small pinpoint rash together with labs showing abnormal white cell count; or, as described in the International Classification of Disease, 10th Edition (ICD-10) leukemia is "characterized by the presence of primitive or atypical myeloid or lymphoid cells in the bone marrow and the blood…classified as acute or chronic based on the degree of cellular differentiation and the predominant cell type present….[and is] usually associated with anemia, fever, hemorrhagic episodes, and splenomegaly." Another example of a medical construct is diabetes insipidus which is the co-occurrence of plasma hyperosmolality associated with urine hypoosmolality or urine/plasma osmolality and plyuria (Di Iorgi, Napoli, Allegri, Olivieri, Bertelli, Gallizia, Rossi & Maghnie, 2012).

Medical constructs for healing in the west include a disease antigen and the "antidote." This is often conceived of as an agent that kills an antigen (e.g., antibiotic killing streptococcus bacteria) or chemically counterbalances an imbalance (e.g., injected or ingested or transdermal insulin restoring adequate insulin levels in diabetes).

In Eastern medicine healing constructs include more general balancing of energies (e.g., yin and yang *chi*) that are necessary for proper functioning of organs. Corrective or heal-

ing measures include stimulating the channels (i.e., meridians) that conduct these energies throughout the body. Eastern medicine assumes that mind is intrinsically involved in healing processes. Western medicine has recently begun to look more seriously at the interaction between mind and physical healing agents in treating disease. For instance, there is now a move toward embracing the placebo effect as an intrinsic part of healing with active medications rather than as an artifact or as differentiated from active agents (Thompson, Ritenbaugh & Nichter, 2009).

That is to say, Eastern medicine—as seen from a Western perspective—already approaches health, illness and healing as complex constructs including what in the West would be thought of as psychological elements integrated with what are traditionally seen as, from a Western perspective, medical constructs.

If one takes this concept of medical-psychological constructs and looks at them as contained. perpetuated and carried through time and across space in a larger social construct one begins to approach, conceptually, the psycoquulum: A complex construct made up of social, psychological and medical dimensions holding together across time and space and reiterated in individuals and interpersonal relationships.

Object Relations

After Freud validated the complexity and depth of the inner world, the object relationists immersed the inner world—and, the individual—in a larger, relational world. In fact, the development of object relations theory showed us that the "inner world" is only partly within us. They showed us that it is, in fact, our experience of ourselves *in* the world that is our experience of ourselves *and* the world.

Otherwise stated, object relations theory tells us that our understanding of the world—and ourselves in the world—comes through our relationships and internalization of our relationships with others. From our earliest attachments (e.g., with our parent or parents) we gain a sense of ourselves in relationship with other people that orients us to relationships with people in general (Stern, 1985) and, from there to our relationship with the universe.

Containment of affects: The primary role of parenting in terms of development of healthy interpersonal experience is supporting the child's ability to contain and modulate affects. Failure to supportively contain results in various defenses against emotions including acting-out, reversion to drive, repression and dissociation-based defensive maneuvers (which have the potential to constellate into serious mental health, somatization and physical health disorders).

It is this "containment of affects" associated with interpersonal-affective development and interpersonal-affective experience that is key in the construction of the psycoquulum and psychological and relational determinants of physical and mental health.

Origins of Object Relations Theory:

Freud took an emerging idea—that there were unseen forces within the psyche acting on the individual's behavior, relationships and consciousness (Freud, 1965)—and structured this into a complex and far-reaching theoretical model that has 100 years later permeated most approaches to psychotherapy and been discredited only in terms of some of its details (Blum, 2017). It is now well-established that human beings act outside of their own awareness and even their own self-interests with relative frequency and continuity.

However, some of Freud's admirers and intellectual descendants observed that Freud's nearly exclusive emphasis on the role of instinctual drives and drive-related conflicts were

inadequate to fully capture human experience (Ferenzci, 1995; Klein, 1932; Winnicott, 1971). This awareness led to the development of a school of psychoanalysis that posited that our relational, emotional —i.e., interpersonal-affective—experiences, from birth throughout life are central to our human being. The theoreticians who developed, and who continue to practice from this model are called *object relationists* and their theory is called Object Relations Theory (Guntrip, 1992).

Main proponents, contributors to and developers of the Object Relational approach included Sandor Ferenczi who drew heavily on Freud but emphasized the importance of relationship—and empathy—in the psychoanalytic process, Melanie Klein (who could be called a "prototypical object relationist," still partly wedded to Freud) and who was an analysand of Ferenczi, Ronald Fairbairn and Donald Winnicott.

Sandor Ferenczi was a member of Sigmund Freud's inner circle and adopted much of his theory. However, he rejected some of Freud's psychoanalytic approach with patients seeing Freud's approach as too relationally remote and too focused on neutral observation of biological drives and without enough emphasis on interpersonal mutuality and here-and-now relational response to the analysand. One of Ferenczi's analysands was Melanie Klein and she went on to become an analyst and theoretician herself. Klein developed a more relational psychoanalytic model including internalization of relational elements in early childhood development. Subsequent theoreticians including Ronald Fairbairn, Donald Winnicott, Michael Balint and Harry Guntrip and others increased focus on internally represented object relations—called object representation—and Object Relations Theory was now a school of psychoanalysis in and of itself.

In the 1980's Daniel Stern (1985) took a rigorous scientific approach to examining very early development of object relations and how object relations become represented by the individual starting in infancy. He showed how repeated emotional attunement and containment experiences of baby and mother, over time and in successively increasing intervals, result in the development of an internalized self-other construct upon which the individual begins to base his or her experience of, expectations and response to his or her interactions with others. Stern's findings are very important to the present paper which posits a hypothetical extension of the affective attunement, containment, temporal interval and internalization processes that Stern applied to interpersonal-affective development and applies these principles to *interpersonal-affective-physiological development* where interpersonal-physiological attunement and containment is a precursor, accompaniment and result of interpersonal-affective attunement and containment processes.

Object Relations of the Psycoquulum: Interpersonal Reciprocation and Transmission of Social, Psychological and Medical Constructs: The psycoquulum is a continuous vessel—or *container*—across time and relationships and is also the relationships it contains and with which it reciprocates. In addition to its ontology as a complex construct with psychological, social and medical dimensions the psycoquulum also operates at multiple, interactive, levels: At the societal level it acts as a co-constructed container of psychological, social and medical constructs transmitted across time and space. At the individual psychological level as an internalized representation of socially shared constructs. At the dyadic or group levels as interpersonal-affective and cognitively shared experience. And, at the medical level as a system of interpersonal-affective supports, containment and stressors that affect human stress and immune response and other responses in the biological realm.

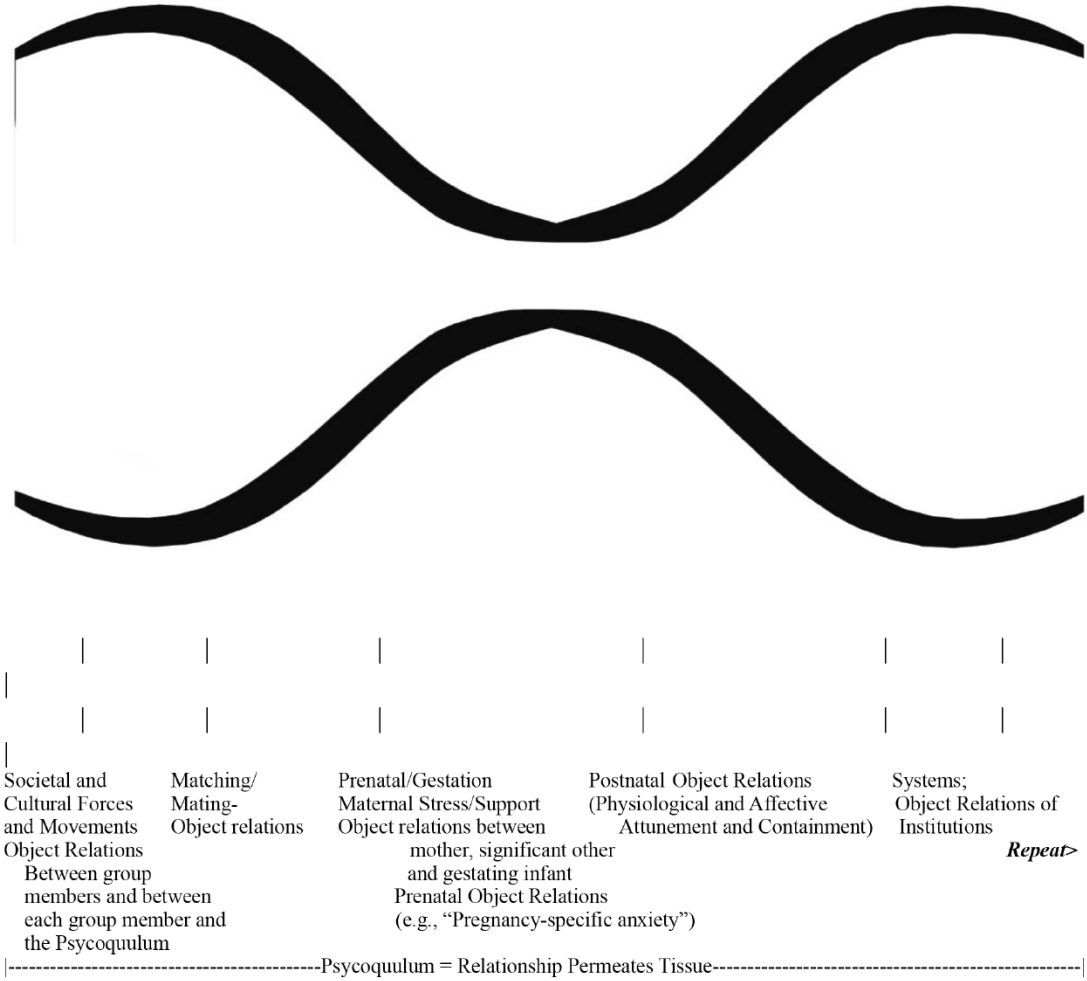
The psycoquulum provides continuity and coherency in the sociological construction of biological, medical and psychological events. Each individual contains a representation of the psycoquulum which is active in every relationship, and there are many individuals and relationships making up the psycoquulum.

Introduction to the Figure

The present paper takes the psycoquulum concept that emerged in Paper 1 and addresses it as "a thing-in-itself." It is a construct. As a construct, the pyscoquulum can be understood in terms of the way society at large is represented in individuals and in relationships between individuals, and—as will be shown—in terms of how these psycho-social constructions permeate tissue through conception and gestation, interpersonal-physiological attunement and containment and interpersonal-affective attunement and engagement especially in early development but also through relationship throughout the lifespan. The internalized construct in the young and developing person interacts with and becomes part of the larger social constructs (institutions, systems, society) as the individual matures and develops and the process repeats.

The present paper develops, further, the psycoquulum model and presents and discusses a figure visually depicting the psycoquulum and highlighting its containing role in social, personal and biological development and evolution.

The proposed model (as represented in the drawn figure) shows that internalized relationship experiences (object representations) tie the individual into larger group and social constructs which are both made from and contain those relationships and their internal



Psycoquulum Figure: Object relations-mediated social support network is the vehicle/container in which the mind-body continuum develops and take place. This is the case through all the phases of the Hourglass Model shown above: Societal Forces and Movements, Matching and Mating Object Relations, Gestation, Birth and Postnatal Object Relations and Development, Maturation and Systems. The sequence—or cycle—repeats

representations. In turn, genetic, epigenetic and biological traits result from these relational events and constructs via multiple mechanisms: 1) Relational and behavioral impact on social migration; 2) social constructs and object relations impact on matching, mating and reproduction; 3) impact of relational supports and stress on gestation, prenatal development and mother-fetus relationship on postnatal development; 4) post-natal object relations reciprocal relationships with social systems (e.g., family, school, work and other institutions) and with mental and physical health, illness and healing throughout life.

The Stages of the Psycoquulum: An Overview

In the coming pages the major stages of the psycoquulum will be reviewed with an eye to their position and role when looked at as part of a larger, continuous construct that is itself a container for relationships between individuals, couples, groups and society continuous across time as well as space. Here, we are looking at the psycoquulum as a whole structure—a structure that contains the individuals that are the parts of that structure and that make up that structure taken as a whole—such that the whole and the parts are inherent in each other.

Otherwise stated, the structure contains the parts that comprise the structure and structure and parts are represented each in the other. An analogy is an oxygen molecule. An oxygen molecule contains the oxygen atoms that, together, comprise the oxygen molecule. Both the atom and the molecule are oxygen but, as a unit and as a whole made up of units, they are discreet entities.

The general case of the interrelatedness of the parts and the whole is the purview of the area of philosophy known as mereology. From the time of Plato through more recent works in modern philosophy by Stanisław Leśniewski (1916)—and in many fields: biology, mathematics [and others]—mereology has been exquisitely developed at very sophisticated levels of analysis of the given discipline's subject matter. As one of many examples: The relationship between observer and the observed in quantum physics can be thought of as a special case of mereology. In sociology mereology took the form of C. Wright Mill's paradigm-changing "sociological imagination" which examines how individual members of a group understand themselves, and one another in terms of the group and thereby affect the group.

To begin to conceptualize the containing structure of the psycoquulum in relationship to its members (people, couples, groups) we can use another simple analogy, that of a leaf. A leaf is made up of many plant cells held together by cellulose. The leaf provides structure to the community of cells and is a vehicle of nutrients and homeostatic regulation for them. At the same time, the cells are the life of the leaf and are the engines that run the leaf's processes. The individual cells of the leaf are connected to each other and to the leaf as a whole via cellulose.

The relationship between leaf, cells and the cellulose that binds them together is analogous to the relationship between individuals and the larger interpersonal-affective, social container—the psycoquulum—of which the individuals (and sub-groups) are a part, all held together by the object representations (the "cellulose") that inherently bind these. The larger social structure—as well as individual attachment experiences—are internalized in each individual and that "socially-imprinted" individual, in turn, makes up the larger social structure. Society and individual are "contained in" each other.

<u>Object Relations With—and Within—the Psycoquulum</u>:

The present paper posits that, psychologically, at unconscious or relationally innate levels

a mereological understanding of the psycoquulum hinges on object relations. The psycoquulum is the reciprocal relationship between the group members' relationships with each other in the context of the group as whole. The qualities of the group are represented in the individual group members' relationships with one another as special interpersonal schema and scripts known as "object representations." These schema and scripts tell the individual members how to respond to other individual group members interpersonally in the context of the group and reciprocally maintain the continuity of the group structure as the group context of these relationships (parameters, mores, taboos) is inherently represented in these same schema. These representations include the physical and biological events—including those associated with health, illness and healing—that comprise the history of the group and are internalized in the individual. There are specific dynamics determining how psychological and social factors determine events at the biological and tissue level at each stage of the psycoquulum. These are briefly introduced below and will be further expounded upon in subsequent articles in the series.

The Stages of the Psycoquulum

The following are summary introductions to the seven stages labeled in the Psycoquulum Hourglass Figure above. Each stage will be explicated more fully in subsequent articles:

Stage 1: Cultural evolution and social migration: One level of the psycoquulum that can be analyzed in terms of the relationship between the parts and the whole is the society. Societies, such as tribes move from place to place for many reasons. They move in search of more advantageous geographical and climate features for hunting, dwelling, planting, growing and raising families. They move in response to conflicts with other tribes or civilizations. They move for spiritual or religious reasons. They move to acquire land for trade purposes.

Every such migration results in multiple changes in the group. Members die due to the hardship of migration. Others are born in entirely different environments putting markedly different demands on the developing individual members of the group versus the demands his or her ancestors were conceived and raised under. Different predators, competitors and allies are encountered during migration. Different disease antigens and available foodstuffs are encountered. Migrating groups encounter different terrains from those they have known, grown in and developed skills in, skills in navigating and in putting the land and environment to use.

Societies also change, culturally when they stay in one place. Invaders affect cultures. Changes in climate and geological phenomena (e.g., volcanoes, earthquakes, typhoons, hurricanes) affect culture and societies. Changes in animal populations upon which the society depends affect societies that stay in one place and their cultures. Spontaneous creative developments that then affect subsequent generations—e.g., art and architecture created by members of the society —- then affect and influence those offspring exposed to it (Lehman, Chiu & Schaller, 2004). As does use of language.

These societal migratory/horizontal—or cultural/vertical—changes result in modified groups. Yet, the groups, while changed, retain an identity. They are still "the x's" even if they look, act or live relatively differently from their original incarnations.

The feature that allows these transformations while preserving a fundamental identity, that allows continuity during change is object relatedness. It is a feature of human psychology (and, perhaps of other animals) that important relational experiences are internalized and imprinted as templates guiding subsequent relational responding and development. As relational experiences occur in larger group contexts—i.e., in societies (tribes, nations, local

communities)—group attributes are internalized as part of the object relations between its members. As such, the group identity itself is held together by these object relational imprints internalized in each of its members. The group is a determinant in the relational coding of each member and has continuity and coherency as a group because it is coded in each member (Aviram, 2007).

Stage 2: Communities and families: A second level of the psycoquulum that can be explored and analyzed in terms of the relationship between the parts are the sub-groups of society: communities and families. Communities are relatively contained groups with their own identities within societies. They are defined by commonalities shared by multiple societal members that are not shared by the society as a whole (MacQueen, McLellan, Metzger, Kegeles, Strauss, Scotti, Blanchard & Trotter, 2001). Families are biologically or legally related individuals within those communities which may extend beyond the geographic communities into multiple communities (Medalie & Cole-Kelly, 2002). Families have extensive object relatedness and object relations play a powerful role in the identity and cohesion of families.

Stage 3: Couples: Matching and mating factors, coitus and reproduction: The archetypal object-relational situation: the dyad. Object relatedness is what brings two people together and causes them to be “a dyad” rather than “ships passing in the night.” Object representations are specialized scripts and schema for interpersonal relatedness. They inform the individual about what to expect and how to respond when presented with certain cues from another individual.

The intersection between the couples’ object relations and society are matching and mating criteria. Buss, Abbott, Angleitner et al. (1990) tabulated the multiple variables—and their weightedness per a given society—in matching resulting in romantic partnerships. Beyond just resulting in the bringing together of two people and intercourse—potentially resulting in conception—the object relatedness of the involved parties also predicts duration and supportiveness of the relationship.

Stage 4A: Gestation, mother-fetus relationship and prenatal and perinatal development: The preceding stages lead to and converge at the conception and gestation stage of the psycoquulum. Society produces communities that produce families that produce a couple which copulates resulting in the earliest beginnings of the individual. (Thus, the title of the preceding article in the present series: “From Many Two; From Two One,” Cole, 2017).

In the context of the psycoquulum conception is an extraordinary event. The collective relational latticework that comprises this cross-temporal meta-container of interpersonal-affective experience is, suddenly, consolidated: Into sperm and egg. For a moment human being is almost a purely biological event: the only such purely biological event in the entire course and expanse of the psycoquulum, i.e., in the entire progression. From larger societal events through community, family and couples relatedness and—beyond to birth, early and lifespan development—there is one moment, and only one moment, where human—or prototypical-human—experience could feasibly be conceived as a purely biological event: When the man’s sperm is emitted and the woman’s ovum is emitted.

But, this “biological moment” is so transitory—and so transitional—it is questionable whether even this is a purely biological moment. From the moment of emission, the sperm (the one that will achieve conception with the egg), and the ovum are in search of each other. These two—otherwise seemingly biological composites—that are the sperm and the egg that are the person to become are in relationship already at this (pre-joined) moment.

And, as soon as conception occurs—as soon as sperm fertilizes egg—relational events are back in full swing in one of the most complex interactive and mediated ("path model") phases of the progression and container we are calling the psycoquulum. Immediately mother's experience and fertilized egg's experience are on a continuum. Anything happening to the mother affects the zygote. These "happenings" include biological events like the mother's eating, drinking and sleep, emotional events and their correlates in neuroendocrine systems and, mood, stress and anxiety. Duration and supportiveness of the relationship between a gestating mother and her primary other.

What will postnatally become emotional experience and affective expression at the stage of embryo and fetus are physiological events in response to the mother's internal environment which is in response to her external environment. The gestating mother's external environment—including her relationships—affects her internal environment which affects the gestating baby. Postnatally, the mother's attuned affective relationship with the infant will provide the container for the baby's developing emotional self. The parallel of this postnatal affective container, prenatally is the mother's internal state. And, as stated her internal state, which is the gestating fetus's environment, is contained within the mother's external—relational—environment

Stage 4B: Perinatal Development: Another complex juncture in the relationship between biological and relational elements of human development is the perinatal phase. This is the phase of early development where the fetus is metamorphosing from prenatal fetus to postnatal infant and all the systems of survival, growth and development are shifting to accommodate a changing and ultimately very different environment from that it has existed in for the proceeding eight to nine months. Oxygen that was previously provided by the mother-to-fetus blood transfer is now going to come directly from the air. Nutrition, also umbilically delivered up to this point is now going to be via the baby's alimentary system.

Perhaps, most interesting of all, communication between baby and mother, that was previously largely physiologically direct and via physiochemical processes—including affective communication—is going to be bidirectional and largely occurring through vocalizations, para-vocal behavioral and sensory-perceptual apparati.

Stage 5: Postnatal Development: The relationship between infant and mother continues after a shift in the vehicles of communication, nutrition and other physiological and affective support, a shift that started with the perinatal stage of gestation. And, a three-way relationship between mother, infant, father—or mother's significant other—or lack thereof, resumes with the baby in the new environment.

Once born into the world, communication between infant and mother is no longer directly transmitted through a shared physiology (though that shared physiology hypothetically remains embedded in the baby's internalized relational-physiological-affective representations as will be explicated below) but is now mediated by verbal and paraverbal communications and the mother's attunement to the baby's physiological states. Stern (1985) explicated the role of affective attunement in the infant internalizing schemas and scripts for interpersonal-affective relating reinforced by the relief from emotional distress associated with mother's accompaniment of the baby in his or her emotional state.

It is consistent—logico-deductively and given knowledge of mother-infant dyadic regulation of infant's physiological state—that interpersonal-physiological schema and scripts are also internalized. These physiological attunement, containment and internalization processes are likely in motion while the baby is still in utero (e.g., via vagus nerve), as, potentially even are processes of affective attunement and containment in motion in utero (e.g. , as

seen in *pregnancy-specific anxiety*), albeit prenatal affective attunement and containment are necessarily mediated through direct physiological continuum between mother and fetus versus socially mediated interpersonal communication processes (e.g., affective expression and sensory observation) postnatally. As the mother has already shared the infant's physiological processes and response prior to his or her birth, attunement with the processes is probably exquisite after birth even in comparison to affective attunement which is likely following, relatively speaking on physiological attunement. An instance of this is *pregnancy-specific anxiety* wherein the mother is anxious about her own pregnancy and can be differentiated form general anxiety during pregnancy. Physiological attunement potentially also competes with affective attunement for primacy as a joining factor in the mother-infant relationship.

Stage 6: Systems: The group embedded in the individual via matching, mating, coitus and reproduction—and the attendant object relations—re-emerges as the developing child now rejoins systems: the larger family, school, social and peer groups of his or her own, work environments and so on wherein the individual internalizes institutional schemas and scripts and contributes to their modification as well.

Stage 7: Repeat: Systems Become the Cultural Containers of the Society in Which the Whole Process Repeats: The individual in institutions and the institutions themselves become part of the culture that impacts on larger societal traits and dynamics renewing the cycle with resulting effects on communities, families, matching and mating, sexual and reproductive attitudes and behaviors and pre-and-post-natal attitudes toward parenting. The progression from more global to more focal, dyadic and individual object relations—and how these factor into psychological as well as biological development—expands back into more extensive and expanded object relations (which again become part of the container) repeating indefinitely.

Application of the Psycoquulum Heuristic to Healthcare

People's healthcare—which should be dictated primarily by patient need—is instead predicted primarily by the prevailing paradigm. The paradigm can both contribute to care and obstruct it. In a paradigm where biological factors are presumably the basis—or substrate—of what we call health and illness, illness is conceptualized as some change in tissue that needs to be corrected, in most cases by directly acting on tissue.

In a healthcare paradigm that puts health, illness and healing in a relational context, illness is based in an unsustaining or uncontaining relationship with the environment, in particular the interpersonal-affective environment. Internalized physiological unattunement or misattunement can result in poor self-care and internalized unattuned or misattuned interpersonal-affective experiences—particularly those related to early health-related experiences (Kradin, 2008)—will result in problematic provider-patient relationships and generally maladaptive attitudes to health, illness and healing throughout life. Of course, this dynamic could pertain to the provider's early life relationship experiences associated with these matters as well as the patient's.

Incredibly, because if the current "paradigm-centered" approach to healthcare, hospitals specializing in treatment of people with psychological disorders are often run by medical personnel and centered around medical care instead of being run by psychologists and centered around psychological, relational models of care. The role of relational factors in medical health facilities should be revisited as well as these clearly play a bigger role in health, illness and response to treatment than is accounted for.

Systems extend beyond hospital and clinical walls to industries like the pharmaceutical

and medical supply industries. They include institutions like medical schools, schools of pharmacy and even clinical psychology programs that have moved away from relational models over the decades—purportedly because behavioristic and cognitive models are more "scientifically testable"—but arguably because relational models, e.g., psychoanalytic, psychodynamic and humanistic-existential models are of a paradigm at odds with a "biological hegemony." These relational approaches are based in much more fundamental ideas of physics and human attachment and connectedness that pose a fundamental threat to biologically based models.

Beyond this interconnected network of hospitals, other institutions and industries are macro-systems—e.g., our reductionistic economy, marketing and industry-and-profits serving science models—and meta-systems, e.g., impulsivity and short-time extension driven emphases on power and instant gratification systems cultivated by these institutional and macro-systems that benefit from collective emphases on impulsivity, power needs and instant-gratification. And, the role of these in relationship with our lives become internalized, inherent in our internalized object relations.

Questions Going Forward

When the psycoquulum has met its goal of heuristic for an emerging paradigm there is potential for investigating it as a construct with epidemiological, clinical and therapeutic application. At such time it will be necessary to examine theoretical assumptions operationally in terms of the heuristic's validity as an operationalizable construct.

References

Abraham, J. (2010). Pharmaceuticalization of society in context: Theoretical, empirical and health dimensions. *Sociology, Volume 44*(4): 603–622. DOI: 10.1177/0038038510369368

Ardito, R. B. and Rabellino, D. (2011). Therapeutic alliance and outcome of psychotherapy: historical excursus, measurements, and prospects for research. *Frontiers in Psychology, 2*:270. doi: 10.3389/fpsyg.2011.00270 PMCID: PMC3198542 PMID: 22028698

Aviram, R. B. (2007). Object relations and prejudice: from in-group favoritism to out-group hatred. *International Journal of Applied Psychoanalytic Studies, 4*(1), 4-14.

Bell, S. E. and Figert, A. E. (2012). Medicalization and pharmaceuticalization at the intersections: Looking backward, sideways and forward. *Social Science and Medicine, 75*, 775-783.

Beresford, M. J. (2010). Medical reductionism: lessons from the great philosophers. *QJM: An International Journal of Medicine*, 103, 9, 721–724, https://doi.org/10.1093/qjmed/hcq057

Berger, P. L., & Luckmann, T. (1967). *The Social Construction of Reality: A Treatise On the Sociology of Knowledge*. Garden City, N.Y: Doubleday

Blum, H. (2017, May 05). Freud is everywhere. American Psychoanalytic Association: Psychoanalysis Unplugged, Psychology Today. Retrieved from https://www.psychology today.com/us/blog/psychoanalysis-unplugged/201705/freud-is-everwhere?amp

Buss, D.M., Abbott, M., Angleitner, A. and many others. (1990). International preferences in selecting mates: A study of 37 cultures. *Journal of Cross-Cultural Psychology, 21(1)*, 5- 47.

Cohen, S. (2016). The Common Cold Project: 5 Studies of Behavior, Biology, and the Common Cold (ICPSR 36365). Carnegie Mellon University. https://doi.org/10.3886/ICPSR36365.v1 .

Cole, J. (2017). From many two; from two one: Heuristic for an emerging paradigm. *Archives of Medical Psychology, 9*,1, 24- 37.

Cronbach, L.J. and Meehl, P. E. (1955). Construct validity in psychological tests. *Psychological Bulletin, 52*, 281-302.
Di Iorgi, N., Napoli, F., Allegri, A.E., Olivieri, I., Bertelli, E., Gallizia, A., Rossi, A. and Maghnie, M. (2012). Diabetes insipidus—diagnosis and management. *Hormone Research in Paediatrics,77*(2). 69-84. doi: 10.1159/000336333.
Ferenczi, S. (1995). The clinical diary of Sandor Ferenczi. Translator: M. Balint. (J. Dupont Ed). Cambridge: Harvard University Press.
Freud, S. (1965). The psychopathology of everyday life (J. Strachey Ed.). W W Norton & Co.
Hammami, M. M., Al-Gaai, E. A. , Alvi, S. and Hammami, M. B. (2010). Interaction between drug and placebo effects: a cross-over balanced placebo design trial. *Hammami et al. Trials, 11*:110 http://www.trialsjournal.com/content/11/1/110, 1-10.
Healy, D. (2012). *Pharmaggedon*, University of California Press: Berkley.
Henderson, J. N. and Henderson, L. C. (2002). Cultural construction of disease: A "supernormal" construct of dementia in an American Indian tribe. *Journal of Cross-Cultural Gerontology, 17*. 197–212.
Johnsen, T. J. and Friborg, O. (2015). The effects of cognitive behavioral therapy as an anti-depressive treatment is falling: A meta-analysis. *Psychological Bulletin. Advance online publication*. http://dx.doi.org/10.1037/bul0000015 .
Joubert, C. (2015). Are mental disorders brain disorders? *Ethical Human Psychology and Psychiatry, Volume 17*, Number *3, 185-201.*
Klein, M. (1932). The psychoanalysis of children. London: Hogarth.
Kradin, R. (2008). The placebo response and the power of unconscious healing. New York: Routledge.
Lehman, D. R., Chiu, C. and Schaller, M. (2004). Psychology and culture. *Annual Review of Psychology, 55*, 689-714.
MacQueen, K.M., McLellan, E., Metzger, D. S., Kegeles, S., Strauss, R. P., Scotti, R., Blanchard, L., and Trotter II, R. T. (2001). What Is Community? An Evidence-Based Definition for Participatory Public Health. *American Journal of Public Health, 91*, 121928, 1929-1936.
Masyn, K.E., Henderson, C. E. and Greenbaum, P. E. (2010). Exploring the Latent Structures of Psychological Constructs in Social Development Using the Dimensional–Categorical Spectrum. *Social Development, 19*, 3, 470-493.
Medalie, J.H. and Cole-Kelly, K. (2002). The clinical importance of defining family. American Family Physician [Am Fam Physician], ISSN: 0002-838X, 2002). Publisher: American Academy of General Practice. 65 (7), 1277-1279.
Miklikowska, M. (2012). Psychological underpinnings of democracy: Empathy, authoritarianism, self-esteem, interpersonal trust, normative identity style, and openness to experience as predictors of support for democratic values. *Personality and Individual Differences, 53*, 603-608.
Miller, G. A. (2010). Mistreating psychology in the decades of the brain. *Perspectives on-Psychological Science, 5*(6) 716–743. DOI: 10.1177/1745691610388774 .
Pollock, A. and Jones, D. S. (2015). Coronary artery disease and the contours of pharmaceuticalization. *Social Science and Medicine, 131*, 221-227.
Porges, S. W. (2007). The polyvagal perspective. *Biological Psychology, 74*, 116-143.
Sankar, U. V., Ramanathan, M. and Kutty, V. R. (2017). Using qualitative approaches to develop a complex construct: Measuring socioeconomic position. *International Journal of Medical Science and Public Health, 6* , 1, 201-209.
Sapolsky, R. M. (2016). Psychiatric distress in animals versus animal models of psychiatric distress. *Nature Neuroscience, 19*, 11, 1387 -1389.
Schore, A. (2015). *Affect Regulation and the Origin of the Self.* Psychology Press & Routledge Classic Editions.
Thompson, J. J., Ritenbaugh, C. and Nichter (2009). Reconsidering the placebo re-

sponse from a broad anthropological perspective. *Culture, Medicine and Psychiatry, 33* (1), 112-152.

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

Inflammation and Vicissitudes of the Mind: A Holistic Healing Paradigm

Susana A. Galle, PhD, MSCP, ABMP, CTN (ND), CCN, FACN, CCH, RYT500, I-IAYT
Director, The Body-Mind Center, Washington, DC
Medical and Prescribing Psychologist, Albuquerque, NM

*To keep the **body in good health is a duty**... otherwise we shall not be able to keep our mind strong and clear.*

Buddha

*If someone wishes for **good health**, one must first ask oneself if he is **ready to do away with the reasons for his illness**. Only then is it possible to help him.*

Hippocrates

*What you are will show in **what you do**.*

Thomas A. Edison

Abstract

Inflammation is a central topic in 21st century medicine. This article reviews the concept of inflammation, its biology, psychological factors, and health effects, with an emphasis on mental, emotional, and behavioral implications within an interpersonal context. Research highlights the co-morbidity between inflammation and mental factors involved in various psychiatric disorders From an immunological angle, the cytokine theory and supportive evidence are summarized. Autoimmune aspects are described as well. So far depression has been the most widely studied condition. Inflammation and stress are intertwined, and their timing during development is critical. The gut-brain axis and vagal pathways are major aspects of inflammation. They have prime relevance to psycho-therapy and somatic interventions since body and mind make up a functional Gestalt, with the vagus nerve as a key interconnector. Various approaches to inflammation are examined, namely, pharmacological, nutritional, exercise-based, and mind-body methods. From the cellular to the spiritual each modality sustains health. Case examples point to the integrative role of the psychotherapeutic matrix in healing inflammation. The ensuing discussion leads to takeaways for clinical practice and further work.

Key terms: neuroinflammation, cytokines, gut-brain axis, gut-brain-mind connection, vagal pathways, psychobiotics, psychotherapeutic matrix.

Introduction

Mental and emotional status cannot be treated apart from the whole person. Have you ever seen a depressed or anxious individual without physical symptoms? Or someone with a health problem, especially when chronic, that does not influence his/her mind? Bodily complaints reflect states of mind and conversely, with a continuum from transient expressions to full-blown, medically diagnosed diseases. A great deal has been said and written about “stress” since Selye introduced the word[1] Inflammation stands under the umbrella of “distress” vicissitudes. Negative emotions (fear, anger, sadness) and unsustainable life sit-

Correspondence address: e-mail at doctorsusana@gmail.com

uations contribute to inflammatory conditions of varying severity. Conversely, inflammation is often a component of mental and emotional conditions. **THE GUT-BRAIN-MIND AXIS**[2, 3] **IS AT THE HEART OF INFLAMMATION, with overall systemic reverberations modulated by the mind.** This two-way communication occurs through neurological, immune, endocrine and metabolic pathways, being necessary for homeostasis[4, 5]. To be sure, an unfavorable psychosocial context favors the expression of genes trending toward inflammatory processes.

Inflammation anywhere in the body starts out as an adaptive biological process mobilized by the immune system to ***defend the body against pathogens*****, and *preserve our boundaries*.** Proteins known as **cytokines** act as signaling agents that control the direction and duration of immune responses. Their goal is the proliferation of immune cells to be sent wherever needed. However, when inflammation does not turn off properly, it can spawn a lasting inflammatory cascade—a process linked to ill health.

Major Symptoms. Causes, and Biomarkers of Inflammation

The five cardinal symptoms of inflammation include: **heat** (*calor)*, **pain** (*dolor*), **redness** (*rubor*), and **swelling** (*tumor*), according to Celsus (1st century AD). Galen first described a fifth sign of acute inflammation, namely, the **loss or disturbance of function (***functio laesa)***.**

Five major causes of inflammation are grouped here:

1 and 2) Injury and/or infection: the body mounts an attack to fight them;
3 and 4) Stress and emotion: negative feelings and burnout can lead to changes in blood biomarkers such as increased hsCRP (high-sensitivity C-reactive protein), fibrinogen, and homocysteine;
5) Diet: inappropriate food intake and excessive weight are culprits. Fact cells become "inflammation factories." High sugar intake prompts insulin release, which eventually becomes pro-inflammatory. Metabolic syndrome and obesity may ensue.

This work highlights **stress and emotions** (i.e., emotionally-laden thought patterns and interpersonal contexts) **that may "breed and feed" inflammation**. The other three causes contribute to and aggravate the psychosocial factors of inflammatory processes. The complex etiology and effects of inflammation include cell biology, biochemistry, and pathology, among others; i.e., individual cell types, chemical mediators, immunopharmacology, inflammatory diseases, histology, and animal models of inflammation.[6] The causes of soft tissue injury can be traced to physical traumata (strain, sprain, contusion), bacterial or viral infections, heat, and chemical injury.

Physical trauma inflicts direct damage on cells close to the injury, which leads to bleeding. Bleeding, in turn, initiates inflammatory events that promote healing. The progression from acute to chronic inflammation stems from persistent injury or individual factors; eg. diabetes, corticosteroids, etc. Injury management is often linked to outcome.

Important inflammation biomarkers associated with risk of all-cause mortality are:

- Increased hsCRP (high-sensitivity)
- Increased White Blood Cell (WBC) counts
- Decreased Serum Albumin levels

Among the above biomarkers,[7] elevated hsCRP, along with other inflammatory markers were prevalent in patients with bipolar disorder (BD).[8] Other inflammatory biomarkers are drawn from molecular laboratory tests for nutritional assessment. For example, Organic Acids is a first morning urine test that includes measures of the kynurenine pathway, which is relevant to tryptophan degradation and, hence, the serotonergic pathway. Another test

is the GI Effects Profile, based on stool samples, containing a section on the immune system and inflammation. Case examples are given further on.

The immune system "subjugates the brain" when an individual transitions from experiencing inflammation, to developing sickness and depression.[9] During peripheral infection, innate immune cells release pro-inflammatory cytokines, namely, interleukin-1 alpha (IL-1α) and IL-1β, tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). These **cytokines act on the brain** and breed **sickness behavior**; i.e., fever and nausea, neglect of food and drinks, reduced interest in physical and social environments, easy fatigue, disrupted sleep, depression, irritability, and mild cognitive impairment (e.g., attention and memory lapses). **Changes in subjective experience and behavior** in the physically ill help them reorganize perceptions and actions to enable better coping with an infection. In cancer or autoimmune diseases, immune signals to the brain result in depression symptoms among vulnerable individuals. Depression was discussed as "an evolutionary strategy to fight inflammation and infection."[10]

Inflammation *itself* increases the risk of major depressive episodes, much like psychosocial factors. Biologically, several mental disorders have been linked to the following processes:

- Chronic, low-grade inflammation and activation of cell-mediated immunity;
- Activation of a compensatory anti-inflammatory reflex system;
- Increased oxidative and nitrosative stress (O&NS).[11]

Conversely, **psychosocial stressors modulate the balance between pro-inflammatory and anti-inflammatory cytokines**. This has major implications for stress-related disorders, including depression and post-traumatic stress disorder (PTSD), but also for anxiety and other mental conditions. Thus for example, negative life events and toxic relationship patterns, especially chronic ones, often antecede clinical depression. **Translational models show that pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα, are both depressogenic and anxiogenic**. These mechanisms may explain why psychosocial stressors and acute psychotrauma may trigger mood disorders in vulnerable individuals; e.g., those with immune gene polymorphisms, lowered levels of proteases (peptidases), and increased inflammatory burden.

Cytokines, Inflammation, and Mental Disorders

Cytokines, also called interleukins (IL), play a role in brain development and function. They can impact neurocircuitry and neurotransmitter (NT) systems, producing behavior changes. Acutely, inflammatory cytokine administration or activation of the innate immune system are conducive to adaptive behaviors fostering energy conservation to fight infection or recover from injury. However, chronically elevated inflammatory cytokines and persistently disrupted NT systems can lead to neuropsychiatric disorders. **Cytokines affect behavior through the activation of brain inflammatory signaling** pathways, which lead to changes in monoamine, glutamate, and neuropeptide systems, and decreases in growth factors such as brain derived neurotrophic factor (BDNF).[12] Moreover, inflammatory cytokines may mediate environmental (e.g. childhood trauma, obesity, stress, insomnia) and genetic (polymorphisms) factors contributing to depression. **Psychoneuroimmunology and psychosomatics** examine **mind-body relationships** to understand and treat inflammation, its causes and persistence. **A** "**Psychophysiology First"** approach is biopsychosocial. It integrates psychotherapy with nutrition, exercise, meditational arts, homeopathy, environmental interventions, and prescription drugs.

The cytokine theory demonstrates the immune system's role in depression among med-

ically ill and healthy individuals. Identifying the intracellular molecular links between inflammation and negative states of mind uncovers treatment options, provided that brain pro-inflammatory cytokine signaling represents the final common pathway to emotional disorders.[13] Personalized nutrition, herbs, and homeopathy offer effective interventions in sync with the tenet "first do no harm." A discussion of cytokine effects, other immune biomarkers, and the pro-inflammatory effects of stress follows. Gut-brain inflammation is also discussed as a link to mental/emotional dysfunction.

Neurochemical and Mental/Behavioral Effects of Inflammatory Cytokines

The mental and behavioral effects of cytokines stem from their following properties:

1) **Signaling pathways** effects, including **p38 mitogen activated protein kinase (MAPK)**, an enzyme mediating inflammation and neurodegeneration. **MAPK impacts the metabolism of NT**s such as serotonin (SE), dopamine (DA), and glutamine (GLU) by affecting synthesis, release and reuptake;
2) **Kynurenine pathway activation,** which depletes tryptophan and generates metabolites that can alter DA and GLU regulation. Animal research suggests that altered brain serotoninergic neurotransmission may not be decisive in inflammation-related depression. Instead, the tryptophan-degrading enzyme indoleamine[2,3] dioxygenase seems a critical factor. For this enzyme produces **potentially neurotoxic** kynurenine metabolites such as **3-hydroxy kynurenine and quinolinic acid.** The relative roles of peripherally versus centrally produced kynurenine and their cellular sources remain unclear. However, such findings suggest new therapeutic targets for inflammation-associated depression and other psychiatric conditions;[14]
3) **Impact on neurocircuits including the basal ganglia and anterior cingulate cortex** through NT system effects**.** Thus can cytokines change motor activity, motivation, anxiety, arousal, and alarm reactions;
4) **Behavioral/immune responses serving evolutionary priorities shunt metabolic resources away from the environment** to fight infection and foster healing while maintaining vigilance against injury and pathogens. However, **chronic activation of this innate behavioral/immune response** may lead to depression and anxiety.[15]

Major psychiatric disorders and suicidal behavior are associated with inflammation biomarkers. Many individuals diagnosed with Major Depressive Disorder (MDD) have high levels of inflammatory markers such as **IL-6.**[16,17] A meta-analysis of cytokine and chemokines showed that suicidal individuals had increased IL-1 and IL-6 in blood and post mortem brain samples ($p = .05$), low *in vitro* IL-2 production by peripheral blood mononuclear cells (PBMC) ($p =<.01$), and decreased IL-8 ($p =.05$) in cerebrospinal fluid (CSF). Thus IL-1 and IL-6 may help differentiate suicidal from non-suicidal patients.[18] Suicidality also coexists with inflammatory conditions such as traumatic brain injury (TBI), vitamin deficits, autoimmune disorders, and infections. Raised inflammatory mediators can dysregulate the kynurenine pathway, overactivate the hypo-thalamic-pituitary-adrenal (HPA) axis, and alter monoamine metabolism. The ensuing changes in emotion and behavior may also increase suicidality in vulnerable individuals. Among the drugs tested with this population, Ketamine, an N-methyl-D-asparte (NMDA) receptor antagonist, may cancel some actions of the kynurenine pathway metabolites but it can also impair cognition.[19] Toll-like receptors (TLR) and the balance between Th1 and Th2-type T cells could also be targeted pharmacologically in suicidal patients.[20]

Interleukin 6 (IL-6) in Depression: Cause, Effect, or Both?

IL-6, a small multifunctional protein, [21] is released from many tissues: BCs, endothelium, epithelium, adipose tissue, astrocytes, microglia and neurons. Primarily **pro-inflamma-**

tory, IL-6 can be also anti-inflammatory. Recent research points to **IL-6's etiological role in depression,** stress-related behavior, and as a therapeutic target.[22,23]

The **clinical depression phenotype impacts IL-6 synthesis**[24], directly affecting brain function and NT production. IL-6 concentration correlates with symptoms of depression, namely, psychomotor retardation, anhedonia, sleep disorders, suicide risk, and anxiety. IL-6's overexpression in MDD is linked to unfavorable prognosis. Further, a strong correlation exists between IL-6 synthesis and the patient's psychosomatic functioning.[25]

Thyroid function is also affected by stress and inflammation, with implications for mental/emotional functioning. N-acetyl-cysteine (NAC), an antioxidant that restores intracellular glutathione (GSH), was found to prevent the IL-6-induced inhibitory effect on the enzymes that convert T4 to T3. This suggests that IL-6 might function by depleting an intracellular sulfur (thiol) cofactor, possibly GSH.[26] Stress-related, pro-inflammatory cytokines (IL-1β, IL-6 and TNF- α) downregulate thyroid related hormones such as TSH, T3, and T4 to T3 conversion. Instead, the body produces reverse T3 (rT3), which is not usable until stress abates. Chronic inflammation also renders thyroid hormone receptors less sensitive to active thyroid hormone ("thyroid resistance"). Sub-clinical hypothyroidism and autoimmune thyroiditis have high prevalence today, particularly among women at middle age and beyond menopause. Their **hypothyroid symptoms often overlap and interact with depressive conditions**; e.g., fatigue, weight gain, low drive, poor digestion, and disrupted sleep. This leads to treatment conundrums.

Neural Markers of Inflammation and Depression in Medical Illnesses

Inflammation has effects on the brain reward center (Striatum). Striatal changes were linked to illness behaviors resembling depression; e.g., fatigue, anhedonia, diminished concentration and motivation. Hepatitis patients (N=23) started on interferon-alpha (IFN-α) manifested an immediate inflammatory response—per blood cytokines. Four hours later, magnetization transfer imaging showed microstructural changes in the striatum compared to pre-treatment. This indicates the striatum's high sensitivity to IFN-α. **IFN-α induced fatigue and depression,** especially between treatment weeks 4 and 12. Early striatal changes predicted later fatigue, but not depression. Some striatal changes were linked to fatigue, but others seemed protective against fatigue. **Inflammation may alter reward and motivation brain regions** in ways that predispose to or protect against fatigue but not depression. Such a varied striatal response may mean that **fatigue and mood are supported by different striatum microcircuits**.[27]

Neuroimmune Development, Inflammation, and Depression

Inflammatory pediatric gastrointestinal (GI) disorders (IBD, IBS, Crohn's, celiac disease, allergies) have been linked to adolescent mental disorders.[28] Pediatric irritable bowel disorder (IBD) decreases growth potential, especially with frequent relapses and poor nutrition linked to repeated steroid use. Such effect can be prevented with early, intensive nutritional support, and the use of steroid-sparing agents. Attaining remission before puberty is important beyond physical growth since a **significant inflammation burden is linked to impaired emotional health**. Further, allergies correlate with high histamine and anxiety disorders. Intestinal permeability ("leaky" gut) makes up a terrain for illness.

The brain yields age-specific behaviors responses to the environment. Adolescence is a unique period of continued brain maturation, with transient needs to take a leap away from parental dependence and towards independence. These needs require immune and brain maturation. Understudied components of adolescent neuroimmune interactions include synaptic pruning, neurite (axon or dendrite) outgrowth, and NT release, all of which

take place via blood-brain barrier (BBB) dynamics and glial activity. During adolescence and early adulthood, mood and psychotic disorders such as MDD, schizophrenia (SZ), and drug addiction rise disproportionately compared to other life stages. Those disorders are associated with **atypical immune activation**, and some are linked to an earlier immune challenge as a risk factor.[29] **Inflammation may increase vulnerability to mental illnesses in adolescence**, also creating room for prevention.

Over the lifespan, **psychological stress can significantly impact various aspects of immune function.**[30,31] Chronic psychosocial stress may accelerate age-related immune dysregulation.[32] Furthermore, age-related disease and impairment may aggravate stress effects or lead to greater clinical impairment among older individuals, particularly those who endured early life stress.[33]

Timing of the Inflammatory Insults and Mental/Emotional Disorders

EARLY LIFE STRESS uniquely contributes to high inflammation in depression. Animal and human research linked childhood inflammation to later depression. Most studies showed increased **depressive disorders** (MDD, PTSD, BD) **risk in adults exposed to inflammation as children**, but not *in utero* nor adolescence.[34,34a] Increased inflammatory tone after early stress was noted among adult female rats.[35,36]

Children exposed to **physical abuse before age 10 and depressed at age 12 had much higher CRP** than those with depression only, maltreatment only, or neither one. Further, **adolescent girls** at risk for depression, with a history of early life stress such as **low socioeconomic status (SES) or parental separation**, had **higher IL-6 and CRP** than depressed counterparts without that history. Adolescents without early life stress showed low CRP as depression lifted. But in those *with* a history of early life stress, high **CRP outlasted depression.** Finally, depressed adults who experienced severe early life stress, such as **maternal rejection, harsh discipline, physical or sexual abuse,** were 1.48 times more likely to have CRP >3 mg/L than depressed adults who did not.[37,38]

The **HPA axis and inflammatory cytokines** are primary effector systems that mediate child maltreatment (CM) outcomes. HPA activation and inflammation can negatively influence SE and BDNF. Moreover, genetic polymorphisms in SE transporter and BDNF genes can aggravate a glucocorticoid (GC) and cytokine-mediated suppression, creating the molecular basis for dysfunction. CM effects in biological hypotheses of depression focus on different aspects, namely, HPA dysfunction, neurotrophic factors, monoamines, cytokines, and structural/behavioral changes in the amygdala and hippocampus. Impaired neurotransmission, decreased neurogenesis and synaptic plasticity, and neuro-degeneration may lead to atrophy in the hippocampus, pre-frontal cortex, and amygdala. These areas mediate emotional and cognitive dysfunction in depression.[39,40,41]

Inflammation in Child and Adolescent Mental Disorders

Immune abnormalities exist in child and adolescent psychiatric conditions and remain understudied but are of great interest. In a subset of **children with PANDAS** (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections), the rapid onset of obsessive-compulsive disorder (OCD) or tic disorders were attributed to group A beta-hemolytic streptococcal (GABHS) infections. An **autoimmune response to GABHS produces antibodies (ABs) interfering with basal ganglia function**, and causes symptom exacerbations. The autoimmune response may lead to neuropsychiatric symptoms (PANS), PANDAS being a subset. **Anti-inflammatories** were successfully given in PANDAS/PANS. The treatment team provided guidelines, including psychiatric medications,

antibiotics, anti-inflammatories, and immunological therapies.[42] The writer treated adolescents with attention and mood disorders co-morbid with PANDAS, who thrived on anti-inflammatory nutrition, classical homeopathy, hypnotherapy, and cognitive-behavioral interventions. Other conditions with significant inflammation are: anti-NMDA receptor encephalitis, psychosis, and autism spectrum disorder (ASD).

Inflammation and Psychosis in Childhood and Adolescence

Intestinal inflammation and dysbiosis were found in ASD and psychosis. **Immune biomarkers, viral and neuronal ABs** were present in adolescent and young adult psychotics.[43,44] NMDA and DA receptor ABs were more prevalent in children and adolescents than adults. A birth cohort study linked **prenatal fever and increased ASD risk.** One research model linked an ASD subset to multisystem inflammation.[45,46]

Pediatric neurodevelopmental disorders are linked to poor nutritional diversity and nutrient deficits. One example is a dearth of essential fatty acids (EFAs), particularly polyunsaturated fatty acids (PUFAs) in ASD children, attention deficit hyperactivity disorder (ADHD) and the schizophrenias. Omega-3 PUFAs act as immunomodulators with anti-inflammatory properties. These factors affect fetal brain development and the microbiota. The **gut microbiome could link inflammatory prenatal environmental insults to neurodevelopmental disorders.**[47,48]

Inflammation and Adolescent Mood Disorders

Brazilian researchers compared serum IL-6 and IL-10 in adolescents with internalizing disorders and those without. Adolescents with internalizing disorders had significantly higher IL-6 while IL-10 differences did not reach significance. Increased IL-6 might be an early biomarker of emotional distress. High levels of inflammatory cytokines may adversely affect general health in the long-term, raising broader public health issues.[49] Another group at UCLA, led by David Miklowitz, PhD, is conducting an ongoing study on Inflammation in Adolescent Mood Disorders.[50]

Autoimmune Conditions and Mental Disorders

There are links between psychiatric symptoms and autoimmune processes in diseases such as lupus, rheumatoid arthritis, Hashimoto's,[51] etc. Similarly, neuroimmunological abnormalities appear in classical psychiatric disorders, such as MDD, BD, SZ, and OCD. Traditionally, the pathophysiology of these mental conditions emphasized dysregulation of the glutamatergic and monoaminergic systems with no clear understanding of the causes of those NT abnormalities. The interplay among psychosocial, genetic, immunological and NT systems can bring to light pathogenic clues, and assist in designing preventive and symptomatic therapies. The area of inflammation, autoimmunity, and mental disorders is thoroughly covered elsewhere.[51a]

Proinflammatory Effects of Stress

Stress-induced priming of neuroinflammatory processes may predispose individuals to a heightened neuroinflammatory response and its neural/behavioral effects when exposed to a subsequent pro-inflammatory insult.[52] Thus stress becomes a risk factor for MDD or other psychiatric disorders in which inflammatory processes are implicated.[53,54] Females are more vulnerable than males, with a higher incidence of emotional and autoimmune illnesses. A study that discussed **psychosocial stress** as one of the main factors **determining microglial activation in patients with psychiatric disorders,** proposed investigating the relevance of such findings for treatment.[55]

During stressful experiences, the quick **increase in pro-inflammatory cytokines and behavioral responses** stems partly from the **activation of brain noradrenergic processes and catecholamines release.**[56] **Norepinephrine** (NE) is **key in the fight/flight response** that modulates physiological reactions to stress, **relaying information to the immune system.** CNS stimulation of beta-adrenergic receptors increases IL-1β mRNA expression in glial cells. Accordingly, peripheral administration of beta-adrenergic receptor antagonists; e.g., propranolol (Inderal) prior to a stressful event prevents subsequent brain cytokine responses and the related behaviors controlled by these cytokines.[57,58,59,60,61] Neuroinflamation upon psychological and physical stressors can lead to depression.[62,63] Conversely, infections stimulate the innate immune system aggravating neuroinflammation and depression-like behavior.[64]

Regarding the influence of positive affect (PA) on inflammation, one study included 25 to 34 year olds. The **Stress-Buffering model** proposes that PA protects health by attenuating noxious stress effects; e.g inflammation.[65] The authors predicted that PA would curtail the effects of perceived psychological stress (PPS) on systemic inflammation, as measured per CRP. **Higher PA was protective against elevated CRP levels** ($p < 0.05$) **but only among participants with greater PPS** levels. Hence, caution is indicated when correlating CRP with PA or PPS.[66]

Sleep Disruption, Inflammation, and the Gut-Brain Connection

Research points to associations among sleep, immune function, and inflammation. A literature review of studies linking sleep, immune function, and gastrointestinal diseases pointed to the interactions between sleep and GI disorders such as IBD, GERD, liver disorders, and colorectal cancer. Different physiologic processes including immune system and inflammatory cytokines modulate sleep. Contributors of sleep disturbances are the inflammatory cytokines such as TNF, IL-1, and IL-6, also implicated in depression and anxiety. Sleep deprivation up-regulates those inflammatory cytokines.[67]

Obesity, Inflammation, and Mental Disorders

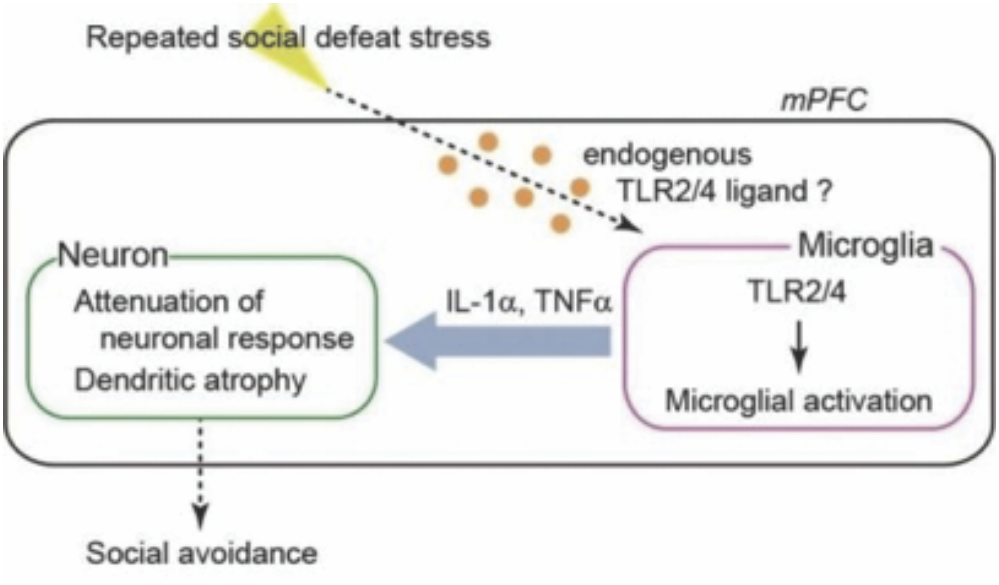
Obesity, due to its connection with high levels of inflammation, was identified as a risk factor for mental disorders. Then again, co-factors such as chronic stressors and lifestyle circumstances may give rise to hormonal and GI issues. **Obesity was associated with increased secretion of proinflammatory hormones and cytokines (leptin, resistin, TNF-*α*, and IL-6) and decreased release of adipokines that downregulate inflammation (adiponectin, IL-10).** Not just the amount but also the type of adipose tissue and the kinds of dietary fats mediate this chronic inflammatory state.[68]

Depression can lead to obesity through increased appetite, poor sleep, and lethargy, while obesity can cause depression due to poor self-esteem, inactivity, and peer rebuff, particularly in females with onset prior to age 14. This shows the significance of incorporating exercise and healthy eating habits in the treatment of depression. The lack of associations between depression and obesity in male adolescents was attributed to developmental differences between the sexes.[69]

Neuroinflammation and Stress-Induced Depression

Japanese researchers (Kobe U.) found that **neural inflammation caused by the innate immune system plays an important role in stress-induced depression**, as follows:

Figure I: Repeated social defeat stress and TLR2/4 immune receptors (Nie X et al, 2018)



TLR2/4 immune receptors mediate repeated social defeat stress-induced social avoidance through **prefrontal microglial activation**. Such stress induces gene expression changes in the brain, increasing a ligand for the innate immune receptors TLR2 and TLR4 (TLR2/4). In normal mice, repeated stress triggered microglia activation in the medial prefrontal cortex, causing impaired responses and neuron atrophy, which led to depression. The TLR2/4-deficient mice did not show social avoidance or extreme anxiety. By selective blockage of TLR2/4 expression in the medial prefrontal cortex microglia through the use of neutralizing ABs for the inflammation-related cytokines (IL-1 and TNF-α), the researchers suppressed depressive behavior.[70]

Neural inflammation caused by the innate immune system for stress-induced depression holds promise for **epigenetic interventions**, pharmacological and nutritional ones. Examples are: a pharmaceutical, the **cannabinoid receptor agonist WIN55,212-2** (non-selective agonist of CB1 & CB2) attenuated social-defeat neuroinflammation,[71] anxiety-like behavior and resistance to fear extinction.[72] On its part, a **nutraceutical based on allicin** (a garlic-derived organosulfur compound) attenuated chronic social defeat stress-induced depressive behaviors through **suppression of NLRP3 inflammasome.**[73,74] Allicin has antioxidant activity and reacts with thiol-containing proteins.

A **social transduction theory** postulated **interpersonal stress and social rejection as risk factors for inflammation and depression** (e.g. MDD).[75] Neural, physiologic, molecular, and genomic mechanisms link social-environmental stress to internal biology. **Social threat and adversity upregulate *proinflammatory cytokines*,** producing behavior changes that lead to depressive symptoms; e.g., sad mood, anhedonia, fatigue, psychomotor retardation, and withdrawal. Critical survival responses during physical threat or injury, also activated by modern-day social, symbolic, or imagined threats result in an **increasingly *proinflammatory phenotype*.** This in turns breeds recurrent depression, overlapping also with somatic conditions such asthma, rheumatoid arthritis (RA), chronic pain, metabolic syndrome, and cardiovascular disease (CVD) such as coronary artery disease (CAD),[76,77] obesity,[78] and neurodegeneration.

Insights into depression, its roots in early life stress, and co-occurrence with anxiety and physical diseases constitute a major task for today's health care. Epigenetic changes linked to childhood stressors increase the risk for mental disorders and chronic physical illnesses. For those patients showing high inflammation, it is crucial to understand their unique psychobiological patterns and lifestyle, in order to offer them effective therapies.

Inflammation, Depression, and Neuroplasticity

Experience-dependent neuroplasticity may stave off depression insofar as **resilience,** an aspect of plasticity**, helps neutralize inflammation**. **Neural markers of resilience** were found among adolescent females at risk for major depression (MDD). In a Stanford University longitudinal study, girls at high depression risk were compared to those with no depression ("resilient") and controls. The high risk group became depressed ("converted"). The resilient group showed greater connectivity between the amygdala and the orbitofrontal cortex, and between the dorsolateral prefrontal cortex and the frontotemporal regions than the converted group. But only the resilient group showed strength of amygdala-orbitofrontal cortex connectivity correlating with positive life events, and higher connectivity within the frontal and limbic networks than controls.[79]

Both high-risk groups had increased salience network connectivity. The converted group had higher intra-network connectivity than the resilient and control groups. The resilient group had higher salience network connectivity with the superior frontal gyrus than the converted group. Thus c**ompensatory functional connectivity patterns in emotion regulatory networks** that correlate with **positive life events led to experience-dependent plasticity and resilience**. Resilience to depression, whether a foundational trait or the outcome of many factors across development, may reflect processes that can be identified, targeted, and enhanced for prevention and treatment.[80,81]

Inflammation and Anxiety

The relationship between inflammation and anxiety has been sparsely examined. One study of 18 to 65 year olds looked into severity, duration, age of onset, anxiety disorder subtype (GAD, social phobia, panic disorder, agoraphobia), and co-morbid depression, versus a group in remission, and healthy controls. Participants were selected from the Netherlands Study of Depression and Anxiety. The **inflammatory markers were CRP, IL-6 & TNF-α**. Upon adjustment for socioeconomic status (SES), lifestyle and disease, the results showed increased CRP in men but not women, with a current anxiety disorder vs controls. No associations were found with IL-6 or TNF-α.

Among persons with a current anxiety disorder, those with social phobia, in particular women, had low CRP & IL-6, whereas high CRP was found among those with an older age of anxiety disorder onset. After 50 years onset age, CRP levels were increased compared with controls. Thus **inflammation** (per high CRP) **occurred in men with current anxiety disorders and immune dysregulation in late-onset anxiety disorder.** This suggests a **specific late-onset anxiety subtype with a distinct etiology**, which could possibly benefit from alternative treatments.[82]

One study connected anxiety, depressive thoughts and inflammation, with implications for psychotherapy. The authors examined inflammatory biomarkers as mediators in a risk model of depressive symptoms secondary to anxiety among "adolescents who ruminate." Over three visits and nine months, the adolescents gave blood samples. They also completed self-report measures of anxiety, depression, and rumination. Higher anxiety predicted increased IL-6, but not CRP for adolescents with high levels of rumination. **Increased anxiety with rumination predicted more inflammation and depressive**

symptoms. The authors concluded that cognitive vulnerabilities to depression as a by-product of anxiety in adolescence may indirectly operate though inflammation. Thus psychotherapies that effectively reduce negative ruminations; e.g., cognitive behavioral therapy (CBT), may entail an "immunocognitive" benefit, namely, biological mechanisms leading up to inflammation reduction.[83]

Neuroinflammation and Obsessive-Compulsive Disorder (OCD)

Neuroinflammation is assessed using positron emission tomography (PET) radoligands that bind to the translocator protein (TSPO). **TSPO density goes up during neuro-inflammation as microglia are activated**. The TSPO distribution volume (V_T) indicates TSPO density. A matched-controls study of individuals diagnosed with OCD aimed to find out whether TSPO V_T is high in the dorsal caudate, orbitofrontal cortex, thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex of OCD patients. All participants were medication and drug-free, and generally healthy. The Yale-Brown Obsessive Compulsive Scale measure of distress associated with preventing compulsive behaviors significantly correlated with elevated TSPO V_T in the orbitofrontal cortex ($p = 0.05$). The authors concluded that autoimmune/neuroinflammatory theories of OCD must go beyond the basal ganglia and include the cortico-striato-thalamo-cortical (CSTC) circuit. They suggested **immunomodulatory therapies** for adults and children.[84]

Gut-Brain Inflammation and the Mind

Inflammation has its roots in the gastrointestinal (GI) tract, the body's first line of defense, removing toxins, bacteria, parasites, and viruses from food before they reach other parts of the body. The GI tract contains about 70% of the body's immune system. Digestive imbalances from **poor nutrition, stress, medications, and environmental toxins** damage GI mucosal structures. The resulting GI immune imbalances ("dysbiosis") breed inflammation. The gut microbiome helps regulate stress and neuroinflammation.

Gut **microbiota** and their metabolites influence immunity and **homeostasis.** Microbial derived-**SCFA** (short-chain fatty acids) and bio-transformed **bile acid** (BA) impact the **immune system,** acting as ligand-specific **cell signaling** receptors (GPRC, TGR5 and FXR), or via **epigenetic** processes. Similarly, intestinal **permeability** ("leaky" gut) and **bacterial translocation** perpetuate systemic inflammation. Without repairing the intestinal barrier, those factors stimulate ongoing inflammation, trigger autoimmune processes, and are likely to contribute to mental and behavioral disorders.

Each person's microbiome is unique yet dynamic and modifiable through diet and life circumstances. Of the 100 trillion estimated microbes, the majority reside in the large intestine. This is 10 times the number of cells in the human body, and 150 times the number of genes in the genome.[85] The 160 species of bacteria in the human gut microbiome can affect body fat stores and, indirectly, inflammation. Two groups of gut microbes (phyla), *Bacteroidetes* (gram-negative, anaerobic) and *Firmicutes* (gram-positive, anaerobic), make up 90% of our microbiome. They serve structural, protective and metabolic functions.

A third important group are *Atinobacteria*, and less abundant ones are Fusobacteria, Proteobacteria, and *Verrucomicrobia.* Each phylus contain several species; e.g.:

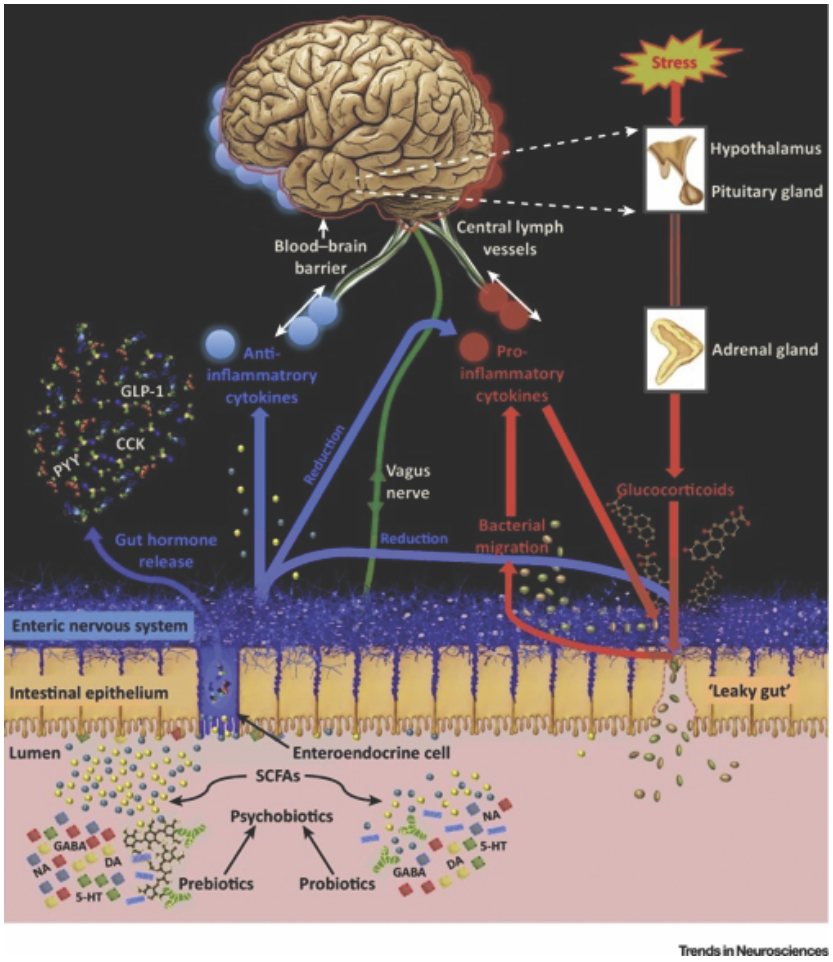


Figure II: In Sarkar A, et al (2016) Psychobiotics and the manipulation of bacteria–gut–brain signals, *Trends Neurosci,* Nov; 39 (11): 763-781

A third important group are *Atinobacteria*, and less abundant ones are Fuso-bacteria, Proteobacteria, and *Verrucomicrobia.* Each phylus contain several species; e.g.:

- ***Bacteroidetes—****Porphyromonas, Prevotella* and *Bacteroides*
- ***Firmicutes—****Ruminococcus, Clostridium, Lactobacillus* and
- ***Actinobacteria—****Bifidobacteria* (the most prevalent type)

Those bacteria displace noxious ones, competing with pathogens for nutrients and producing antimicrobial factors. Studies correlate their imbalance with health conditions (physical and mental). For example, excessive *Bacteroides vulgatus* correlates with inflammation, insulin resistance, and altered metabolism. Certain bacterial strains were high in ASD children, who significantly benefited from nutritional interventions.[86,87]

The beneficial gut bacteria support immune system development, immunoglobulin A (IgA), and the GI mucosal barrier. Metabolic functions include vitamin synthesis (e.g. B) and mineral absorption. The microflora assists in breaking down food, fermenting starch, and forming SCFAs. **Good SCFAs** (e.g. butyric acid) **help modulate inflammation**.

Gut-brain links through the mind/immune-neuroendocrine super highway (MNEI) 88 include **the HPA axis, the sympathoadrenal axis, descending monoaminergic pathways, and the vagus nerve.**[89,90] Bi-directional crosstalk takes place between microbiota and the neuroendocrine system**:** bacteria produce NTs (SE, DA, GABA), hormones (e.g. somatostatin), respond to hormones (e.g. estrogens), and regulate hormonal homeostasis; e.g, by inhibiting gene **prolactin** transcription or converting **glucocorticoids** to androgens.[91] **Psychological stress can mobilize the inflammatory response system and modify the microbiome towards dysbiosis** and gut dysfunction.[92] Those stress-related shifts upregulate pro-inflammatory pathways mediated by the Nod-like receptors family pyrin domain containing **NLRP3 inflammasome—**an intracellular platform (innate immune system) involved in activating inflammatory processes. Such upregulation aggravates depression and compounds gut dysbiosis.[93]

Preclinical and clinical data show that the gut significantly influences mental health through the gut-brain axis, affecting gut barrier integrity, immune regulation, inflammation, and neurotransmission. Psychobiotics are a subclass of probiotics that relieve anxiety and depression.[93a] Although there is a need for further clinical trials, psychobiotics are increasingly used in practice as part of mental health treatment.[94] Evidence favors the use of Lactobacillus and Bifidobacterium strains.[95] According to recent work, gender-specific differences exist in immunity. For the gut microbiome shapes and is shaped by the hormonal milieu governing differences between the sexes.[96]

Histamine, Inflammation, and the Gut-Brain-Mind Axis

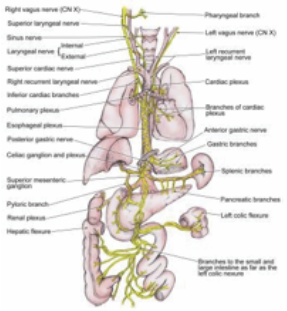
Histamine, central in mediating allergic reactions, gastric acid secretion, and peripheral inflammation, is also a **CNS excitatory NT**. **Histamine-producing bacteria** include ***Lactobacillus casei, Lactobacillus reuteri,*** and ***Lactobacillus bulgaricus***; e.g. in most yogurts and fermented foods. On the other hand, histamine-lowering enzymes (diamine oxide, DAO) also form in gut. The basophil (a granulocyte) is the leukocyte that releases histamine and other mediators of inflammation. The central **histamine** system modulates **arousal** (wake-sleep cycle), **pituitary hormone secretio**n, **suppression of eating, cognitive functions** (learning, memory), **and is involved in anxiety reactions.** Post mortem studies showed histaminergic system alterations in neurological and psychiatric diseases; e.g., elevated brain histamine (histadelia) in Alzheimer's disease-connected seizures, Parkinson's disease (PD), certain patients with SZ, and BD. Since **allergies entail inflammatory reactions, they need to be factored into the diagnostic equation** in order to design effective mental health interventions.[97,98,99]

Vagal Pathways, Inflammation, and Self-Regulation: Where Mind and Body Meet

Vagal functioning is a key link between inflammation and the mind. The Vagus nerve or cranial nerve X (CNX) is the primary parasympathetic cranial nerve (PNS), being both excitatory (E) and inhibitory (I). It functionally connects the brain to the rest of the body, top-down and bottom-up, eliciting output of important NTs, primarily acetylcholine (Ach), but also gamma-aminobutyric acid (GABA) and NE. Ach release is crucial for both CNS and immune function, respectively, attention, learning, memory and **part of the anti-inflammatory pathway**, along with homeostasis after the stress response. CNX **is also very important for DIGESTION. There is vagal dysfunction in neurological and psychological disorders.** In this regard, Porges' polyvagal theory of emotions[100] pivots our understanding and treatment of mental and physical conditions. His work correlated suppressed emotional pain and childhood trauma as unconscious factors of physical illnesses. Uncovering this oft repressed root cause is conducive to healing.

CNX sets the stage for mental state, immune status, and interventions. It interacts with the other cranial nerves, having **functional links to inflammation** and infection. CNX is involved in the cholinergic, anti-inflammatory pathway, essential in controlling the inflammatory response via interaction with peripheral α7 subunit–containing **nicotinic Ach receptors expressed on macrophages.**[101] This hitherto "missing link" in neuroimmunomodulation supports the existence of a **mind-body connection**, with major implications for therapeutic interventions. In the discussion of CNX mental/behavioral effects, one must differentiate between its old and new branches. CNX function is impacted in many health conditions; e.g., trauma, post traumatic stress disorder (PTSD), Adverse Childhood Events (ACE), and infections. Improving **vagal tone** brings about a cascade of positive health effects. The sensory (S) and motor (M) branches of CNX can be unmyelinated (old) or myelinated (new), as seen below.

Figure III: Vagus Nerve Pathways



The Neural-Immune Inferface - Afferent Vagus: The afferent Vagus monitors immune activity. It transmits **information from inflamed peripheral tissues to the brain**, participating in homeostatic and behavioral adaptation, which includes the induction of fever and sickness behavior. Research evidence of this role is the inhibitory effect of subdiaphragmatic vagotomy on fever responses induced by intraperitoneal injection of low doses of IL-1β—a key mediator of inflammatory responses.[102,103]

The Neural-Immune Interface - Efferent Vagus: Pharmacological or electrical stimulation inhibit the release of TNF-α in animals given a lethal dose of endotoxin. They also inhibit pathological effects in animal models of health conditions.[104] The efferent Vagus modulates the activity of immune cells within the spleen indirectly via activation of sympathetic postganglionic neurons in the celiac ganglia. It **possibly modulates IS activity in the spleen indirectly through regulation of NE release from sympathetic nerve endings**.[105]

Vagus Anti-inflammatory Effects
The **Vagus Inflammatory reflex** is a neural mechanism controlling the synthesis and release of cytokines.[106,106a] In response to infection/injury, immune cells produce cytokines. Through their motor arm activation, the **vagal nerve endings release Ach, which in turn inhibits cytokine production by macrophages, protecting peripheral tissues from inflammatory injury.**[107]

The Vagal Paradox and Inflammation: Fear, Trauma, and Reactivity

One major reason for seeking psychotherapeutic help is anxiety/fear of multiple causation (traumata, PTSD). But fear itself may lead to opposite reactions:

1) **Immobilization** or shutdown—an apparent surrender—can be adaptive since it raises pain thresholds; e.g. in abuse, becoming "numb," presumably through dissociative reactions;

2) **Activation** of the Sympathetic Nervous System (SNS), fight/flight reactions, respectively, entail attack versus running away.

The "Vagal paradox" thus refers to two antithetical responses in response to stress or trauma. One response is shutting down, even to the point of syncope (fainting). This involves bradycardia (e.g., reduced oxygen and food demands). In contrast, the activation response is to seek social engagement, which can be calming and sustaining.

"Vagal syncope" entails vagus overstimulation; e.g., upon seeing blood, or emotional shock. Physiological changes include reduced blood pressure (BP) and heart rate (HR), which result in fainting. In extreme syncope, blood flow is restricted to the brain, with a concomitant loss of consciousness. Usually, when the person sits or lays down, things normalize. The evolutionary new vagal circuit, myelinated, can dampen SNS to enable social engagement while optimizing metabolic resources and homeostatic processes. This type of response is conducive to health, growth, and restoration. The two above types of vagal responses are, respectively, **defensive *vs* interactive.**

Vagal disturbances from stress and trauma lead to different clinical pictures depending on which branch of the vagus is affected. The **subdiaphragmatic** branch (old, **unmyelinated**) is involved in **GI inflammation**; e.g., IBS, IBD, etc. The unmyelinated vagus is recruited as an immobilization system. Furthermore, the chronic use of fight/ flight reactions inhibits the unmyelinated vagus. This leads to indigestion, microbiota imbalances, and vulnerability to infections. The **supradiaphragmatic** branch (new, myelinated) has to do with the respiratory and cardiac systems and their dyfunctions. **Regardless of myelination status, vagal pathways disruptions can be linked to inflammation, substantiating a psychosomatic approach to health and illness.**[108]

The following section reviews various therapies for inflammation.

Therapeutic Approaches to Inflammation

Several approaches are considered, namely, pharmacology, nutrition, lifestyle, mind-body methods, and psychotherapy.

I. Pharmacology

1. Psychopharmacotherapy:

1) Antidepressants: SSRIs, SNRIS, and TCAs

Researchers examined the anti-inflammatory effects of different antidepressant classes, namely, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine inhibitors (SNRIs), and tri-cyclic antidepressants (TCAs). Several studies of SSRIs and the innate immune system point to their anti-inflammatory effect,[109] and their up-regulation of *interferon regulatory factor 7* (*IRF7*) gene activity. IRF7 is a transcription regulator of IFN-α. Fewer studies assessed SSRI effects on the adaptive immune system. Earlier work was on lowered natural killer (NK) cell activity in depression. For example, after one year on SSRIs, MDD patients showed increased natural killer (NK) cells and B cells, which was attributed to increased extracellular serotonin.[110,111]

Hypercortisolism and flluctuating cytokine levels characterize MDD. Short-term studies of SSRIs in MDD disclosed changes in cortisol and pro-inflammatory cytokines. In one study, interleukin IL-1β, IL-10, IL-2, IFN-γ, IL-4, IL-13, and 24-h urine cortisol were assessed at weeks (W) 0, 5, 20, 36 and 52. Initially, they found high cortisol, IL-4, IL-10, and IL-13 (Th2) among MDD patients vs healthy controls. At W20 depression inventories (Hamilton, Beck)

indicated remission, which coexisted with increased IL-2 and IL-1β but without cortisol changes. By treatment end (W52), cortisol and Th2 cytokines decreased while IL-1β and IFN-γ increased. These findings meant that **depressed patients only reached a partial reestablishment of HPA axis function after long-term SSRI therapy**.[112] For their part, TCAs were linked to decreased T, CD4+, CD29+, and CD45RA+ lymphocytes and T-cell mitogen responses. SSRIs and SNRIs had similar anti-inflammatory effects.

SSRIs seem to impact the M-1 and M-2 activation of microglia. M1-activated microglia produce proinflammatory cytokines and neurotoxic mediators, contributing to depression. Conversely, M2-activated microglia promote tissue reconstruction by releasing anti-inflammatory cytokines. Ab animal study of fluoxetine and S-citalopram effects on M1 and M2 microglia activation (the murine BV2 cell line and mouse primary microglia cell) indicated that those medications modulated the immune system by inhibiting M1 activation and improving M2 activation of microglia. Such immune modulation was thought in part to mediate SSRI effects.[112a] Antidepressants favorably affect the innate and adaptive immune systems. Those effects are attributable to antidepressant response and also predict antidepressant response. Further work is warranted.

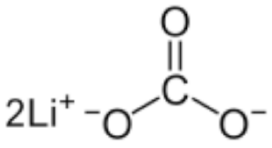
2) Antipsychotics

Genetic studies link SZ with variations in the complement system that regulate microglial synaptic pruning. Genetic and environmental influences conjointly lead to **pathological microglial activation**, conceivably resulting in **excessive synaptic pruning** and **loss of cortical gray matter.** Microglial mediated damage to stress-sensitive regions such as the prefrontal cortex and hippocampus may be implicated in cognitive and negative symptoms, and help explain some structural brain changes in SZ. The loss of cortical control may also produce a disinhibition of subcortical DA, accounting for the positive psychotic symptoms.[113] These studies point up the relevance of neuro-inflammation to psychosis and the **anti-inflammatory potential of antipsychotic drugs**.

One study analyzed blood samples from patients with first-episode SZ (N=12). Cultures from the Peripheral Blood Mononuclear Cells (PBMC) were stimulated with specific substances, and then treated with a typical antipsychotic (haloperidol) or an atypical antipsychotic (clozapine, quetiapine, or risperidone). Proinflammatory (IFN-γ) and anti-inflammatory (IL-4 and IL-10) cytokine levels were measured in the LPS- or poly(I:C)-stimulated PBMC cultures treated with antipsychotics. Haloperidol and quetiapine significantly increased IL-4 ($p<0.05$), while clozapine and quetiapine significantly enhanced the IL-4 levels ($p<0.05$) in poly(I:C)-stimulated PBMC cultures. Only treatment with haloperidol resulted in a significant increase in IL-10 production ($p<0.05$) in LPS-stimulated PBMC cultures, whereas clozapine, quetiapine, and risperidone treatment significantly increased IL-10 production ($p<0.05$) in poly(I:C)-stimulated PBMC cultures. All antipsychotics reduced the IFN-γ level significantly ($p<0.05$) in LPS- and poly(I:C)-stimulated PBMC cultures. Hence, antipsychotics modified immune function by increasing anti-inflammatory cytokines (IL-4 and IL-10) and suppressing pro-inflammatory cytokines (IFN-γ).[113a]

3) Lithium's Anti-inflammatory effects

a) Prescription Lithium (Rx Li carbonate or citrate):



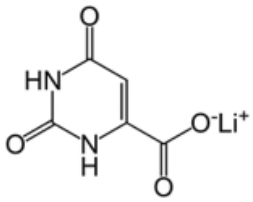
Lithium carbonate

Lithium (Li) therapy for BD, introduced in 1949 by John Cade, remains the gold standard in BD pharmacology. However, its mood stabilizing effects remain barely understood. Pos-

sible Li mechanisms of action (MOA) suggested are: brain inositol depletion, glycogen synthase kinase 3 beta (GSK-3β) inhibition, and Li's impact on NTs and cellular pathways. With regard to NTs, high dose Li was found to depress DA release[114] (flattening elevated moods), while at lower doses it could stimulate SE synthesis[115] (antidepressant effect). **Abnormal GSK-3β has been linked to BD risk**. Li reduces its activity in two ways: directly, and by increasing inhibitory phosphorylation of GSK-3 β. These dual effects act synergistically to enhance Li effects on GSK-3 β-regulated functions such as gene expression, cell structure and survival.[116]

There are data suggesting that **Li carbonate exerts anti-inflammatory effects**; e.g., it suppresses cyclooxygenase-2 (COX-2) expression, inhibits IL-1β and TNF-α production, and enhances IL-2 and IL-10 synthesis. Conversely, under certain experimental conditions Li exhibits proinflammatory properties; e.g., induction of IL-4, IL-6 and other proinflammatory cytokines synthesis. Li's inhibition of inflammatory-associated pathways such as GSK-3β and NF-ϰβ (kappa beta) would lead to reduced inflammatory mediators and inflammation-associated enzymes. But the reviewed studies applied various experimental models, rendering it difficult to draw an unequivocal conclusion regarding Li effects on specific inflammatory mediators. Moreover, pharmacological Li has a very narrow therapeutic window and can produce many side effects; e.g., sodium deficiencies affecting kidney functioning, hypothyroidism since Li blocks iodine absorption (necessary for T4 to T3 conversion), and mental dullness.[117] Prescription (Rx) Li is given in doses up to 1800 mg. qd, which are likely to produce its adverse mental side effects; e.g., dulled emotions, memory loss.

b) Nutritional Lithium: lithium orotate



Lithium orotate

Elemental Li bound to orotic acid yields a more bioavailable molecule than traditional Li carbonate (or citrate), with fewer or negligible side effects. It impacts serum Li levels with a considerably smaller dose than Rx Li, by allowing an efficacious amount to cross BBB while slowing potentially toxic buildup in tissues and organs. Li orotate is five times more potent than Rx Li: 5 mg Li orotate = 100 mg citrate as a 20-fold potency enhancement. Clinical trials involving 150 mg daily doses of Li orotate given 4 to 5 times a week, showed a reduction of manic and depressive symptoms in patients diagnosed with BD.[118,119] A dosage range of 1 to 150 mg daily has been touted as an effective therapeutic strategy for irritability, aggression, BD, ADHD, Parkinson's, and Alzheimer's disease.[120] Further evidence is needed prior to any conclusions about recommending Li orotate (OTC), rather than Rx Li in BD. But it can be considered on an individual basis.

4) Non-psychotropic medications:

Prostaglandins (**PG**) are lipid compounds (eicosanoids) with hormone-like effects, and derived enzymatically from arachidonic acid (AA). These lipid mediators play a major part in regulating physiological and pathological responses, and control key cellular processes. Cyclooxygenase (COX) metabolism converts AA into biologically active compounds. Moreover, the **COX/prostaglandin E (PGE) pathway affects synaptic plasticity** and is implicated in ASD: plasma transferrin, an iron mediator related to eicosanoid signaling, may be related to ASD social impairment. **COX-2 is induced by inflammatory stimuli in most**

tissues and contributes to propagating inflammation. Hence, COX-2 inhibitors are also used in neurodegenerative conditions.[121]

Non-steroidal anti-inflammatory drugs (**NSAID**s), both **selective and non-selective COX-2 inhibitors**, were used as adjuncts to antidepressants. Some studies yielded positive results while others found NSAIDs to decrease SSRI effectiveness. COX-1 mediates proinflammatory microglial activation detrimental to the brain. Moreover, depression correlates with heightened COX-2 activity.[122] The selective COX-2 inhibitor drug celecoxib (Celebrex, 400mg qd) was successfully used as an adjunct in early SZ, BD, and refractory depression.[123] While celecoxib is a helpful adjunct to SSRIs, it may also increase inflammation, Th1 immune reactivity, and glial cell activation.[124] Similarly, aspirin, an NSAID with irreversible inhibition of COX-1 and COX-2, showed inconsistent effects. Such mixed results were attributed to the concomitant use of different antidepressants, doses, selective COX2 and non-selective COX inhibitor NSAIDs, and varying study designs.

Another pharmacological strategy is **TNF-α blockade** since it influences NGF and BDNF. In this medication class, infliximab (Remicade) and etanercept (Enbrel or Benepali) showed usefulness with cognition and depression . However, a better understanding of TNF-α signaling is needed to target specific apoptotic factors in TNF-α rather than a total blockade.[125] *

The evidence of pharmaceuticals exhibiting anti-inflammatory effects is mixed and requires their individualized use to be effective for mental/emotional disorders**. Inflammation is a co-morbidity, a causative factor and a consequence of emotional trauma/ disturbances.** Hence, non-pharmacological approaches supporting psycho-physiological normalization are examined since they constitute the foundations of health. They include: nutrition, botanicals, environmental strategies, and lifestyle interventions.

II. Nutritional and Botanical Therapies

The evidence-based nutrients covered here are: probiotics, omega-3 (ω-3) poly-unsaturated fatty acids (PUFA), taurine, melatonin, D3, and certain botanicals. However, a whole array of vitamins and minerals, herbs, and hormones help check inflammation.

1. Probiotics (psychobiotics)

Diet greatly influences microbiota. Thus a high animal protein, low fiber diet results in fewer *bifidobacteria* and more inflammation. In contrast, the plant-based **Mediterranean diet** has anti-inflammatory **polyphenols** (antioxidant) and correlates with higher levels of **SCFAs.** SCFAs fuel beneficial bacteria and thicken the intestinal mucosa, protecting it from inflammatory compounds, toxins and pathogens; e.g. in ASD.[126] The micro-biome's effects on cognition and emotions has been extensively discussed.[127]

Probiotic bacteria, key to a balanced flora, exist in fermented foods or can be taken as a supplement. Probiotic quality depends on **strains, quantity** (> than 10 billion CFUs) and **state of the bacteria** (alive or "hibernating"). They must be able to resist gastric acid or

* Note on anti-inflammatory medications:
Celecoxib (Celebrex, Onsenal): FDA-approved for pain and inflammation in osteoarthritis, acute adult pain, rheumatoid arthritis, ankylosing spondylitis, dysmenorrhea, and juvenile rheumatoid arthritis. It may also be used to reduce the risk of colorectal adenoma in those with familial adenomatous polyposis.
Infliximab (Remicade): FDA-approved to treat autoimmune diseases; e.g. Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and Behçet's disease.
Etanercept (Enbrel or Benepali): FDA-approved to treat rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis, plaque psoriasis and ankylosing spondylitis.

be encapsulated in enteric-coated capsules. A fiber-rich diet, low in saturated fat, with balanced probiotics is anti- inflammatory and restorative**. Psychobiotics** help improve mental state and mood through g**ut-brain signaling** such as beneficial metaboliteproduction. Gut cytokines communicate with CLV (central lymphatic vessels).

Probiotics confer several benefits with implications for mental/emotional well-being:

- **NT production and delivery**; e.g. GABA, SE, DA, and NE modulating neurotransmission in the enteric nervous system (ENS) proximal synapses.
- **Impact ion transport** controlled by cyclic adenosine monophosphate (cAMP), a second messenger important in many biological processes. A derivative of adenosine triphosphate (ATP), cAMP is used for intracellular signal transduction in different organisms. This influences **mitochondrial** function.
- **Vagal links**: Anti-depressant effects mediated via vagus nerve, spinal cord, or neuroendocrine systems.
- **Anti-inflammatory effects:** gut barrier function restoration and enhancement by reducing circulating concentrations of GCs and pro-inflammatory cytokines.
- **Decrease HPA axis** activity.
- **Increase BDNF**.
- **Displace pathogenic** bacteria.
- Support the **development and homeostasis of gut's glial populations**.
- **Improve digestion**, leading to better nutrient production and absorption; hence, support healing IBS and chronic fatigue (CFS) among other conditions.[127a]

2. Omega 3 (ω-3) Polyunsaturated Fatty Acids (PUFAs)

Dietary fats consist of a chain of hydrocarbons with an acid group on the end. Omega-3s are essential fatty acids (EFA) that fall into the PUFAs. An **ω-3 fatty acid** has its first **double bond** between the third and fourth **carbon** atoms from the end of the **carbon** atom chain. The ω-3s fatty acids (FA) have **potent anti-inflammatory** effects. In the body, they produce natural cannabinoids comparable to those in *Cannabis sativa* (mari-juana). An animal tissue study found several chemical reactions **converting ω-3 into anti-inflammatory cannabinoids.** Receptor **C1** in the nervous system **(NS) and C2** in the immune system **(IS**) entail **active metabolites** derived from crosstalk between the endocannabinoid and CYP450 epoxygenase metabolic pathways. The ω-3 endo-cannabinoid epoxides derived from ω-3's (DHA and EPA) form EEQ-EA (epoxyeicosa-tetraenoic acid-ethanolamide) and EDP-EA (epoxydocosapentaenoic acid-ethanolamide). The **ω-3's have anxiolytic and antidepressant effects through the endocannabinoid** receptors.[128]

Food sources of ω-3 include: wild-caught fish, grass-fed organic meat and eggs, nuts and seeds. Omega-6s (ω-6), also found in those foods and others, promote the formation of pro-inflammatory prostaglandins. Both ω-3 and ω-6 FAs produce the endocannabinoids. A diet **rich in ω-3 FA has cardiovascular (CV), neurological, and anti-inflammatory benefits**, through oxidative and non-oxidative pathways. Cannabinoids (both marijuana and endocannabinoids) support IS and have anti-inflammatory effects, but ω-3 derived ones have no psychotropic effects—only THC does. There is evidence of ω-3 FA's usefulness in the treatment of mental disorders.[129]

3. Taurine

Taurine, a semi-essential sulfur-containing β-amino acid (2-aminoethanesulfonic acid) is abundant in the majority of human cells, formed from methionine and cysteine metabolism via hypotaurine in the liver. Taurine is a powerful cell antioxidan**t** since it enhances the expression and activities of superoxide dismutase (SOD), catalase and GSH. *In vitro* and *in vivo* studies, as well as clinical trials support using taurine in chronic inflammatory

diseases.[130] Furthermore, a derivative of **taurine reduced glial cell activation** in an animal model of neuroinflammation.[131]

In the brain, taurine acts as an inhibitory NT, moderately sedative. It assists sodium, potassium, calcium and magnesium transport in and out of cells. Involved in neuron firing, it supports cell membrane stability; hence, its uses in seizure disorders, agitation, anxiety, restlessness, and stress. By slowing down adrenaline release, taurine helps check the fight-flight response. Taurine's anti-inflammatory benefits are: direct, **antioxidant,** and indirect since it **modulates stressful states and their proinflammatory effects**. Two chemical bonds away from taurine, the FDA-approved drug acamprosate (Campral) or **N-acetyl homotaurine** acts as a GABAA agonist and NMDA antagonist, and is used in 300mg tabs to treat alcohol abuse.

4. Flavonoids: Quercitin and Luteolin

Polyphenolic compounds containing anti-inflammatory flavonoids are used in psychiatric and cognitive disorders. Quercetin is a flavonol, and luteolin is a structurally related flavone. Both are abundant in onions, tea, apples, and broccoli. Luteolin is plentiful in olive fruit extract, chamomile, celery, spinach, and oregano. Luteolin reduces amyloid- β peptide production in human transgenic-bearing neuronlike cells and primary neurons. Both quercitin and luteolin seem safe, and were found helpful in ASD.[131a]

5. Melatonin (*N*-acetyl-5-methoxy tryptamine)

Melatonin is a hormone released from the pineal gland. It modulates the sleep-wake cycle. It is produced two steps after SE, upon the consecutive actions of two enzymes, as follows:

SE- N-acetyl transferase —> **N-acetyl 5-HT** —> 5-hydroxyindole-O-methylransferase (5HT) —> **Melatonin**

Experimental and clinical data indicate that melatonin reduces adhesion molecules and pro-inflammatory cytokines, modifying serum inflammatory parameters. Melatonin thus improves the clinical course of inflammatory illnesses. Its antioxidant effects entail scavenging free radicals, stimulating antioxidant enzymes, enhancing the activities of other antioxidants, and protecting antioxidant enzymes from oxidative damage. In one study, **melatonin reduced microglial activation and neuroinflammation**, pointing to the mTOR pathway involvement. Hence, melatonin is **neuroprotective**.[131b,131c]

Many of melatonin's effects occur through activation of the melatonin receptors. Moreover, through its **anti-inflammatory and antioxidant** properties, the adjunctive use of **melatonin in SZ may augment antipsychotics' efficacy and reduce their side effects**; e.g., tardive dyskinesia (TD), metabolic syndrome, and hypertension. Melatonin also influences the tryptophan catabolic pathway via its effect on the stress response and cortisol secretion. Melatonin thus benefits cortex associated cognition, amygdala associated affect, and striatal motivational processing.[131d]

Melatonin is sold as an OTC supplement. It is also known as the prescription drug ramelteon (Rozerem), FDA-approved for insomnia, with no long-term side effects. It selectively binds to the MT1 and MT2 receptors in the suprachiasmatic nucleus (SCN), rather than binding to GABAA receptors (e.g., zolpidem). The usual adult dose range is from two tenths of 1 milligram (mg) to 5 mg, one hour before bedtime. Melatonin undergoes liver biotransformation via CYP1A2. Much caution is indicated with the co-administration of drugs that are strong CYP1A2 and CYP3A4 inhibitors.

6. Vitamin D3 (cholecalciferol)

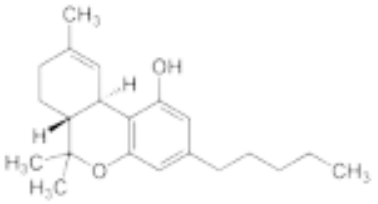
Cholecalciferol is made in the skin exposed to UVB light. In the liver it is converted to calcifediol (or calcidiol, 25-hydroxyvitamin D) and after that, the kidneys form calcitriol (25-dihydroxyvitamin D). D3 increases calcium uptake in the small intestine. It is found in fish, cheese, and eggs. Certain countries have D3-fortified milk.

A meta-analysis of randomized controlled trials evaluated the effects of vitamin D3 supplementation on mental health, assessing biomarkers of inflammation and oxidative stress in patients with psychiatric disorders. The findings included: a significant reduction in Beck Depression Inventory (BDI) scores, along with increase in both GSH and total antioxidant capacity (TAC). Combining data from five studies, they also noted a significant CRP reduction.[131e] Vitamin D3 and melatonin have synergistic effects.

Hyperglycemia is pro-inflammatory. In animal studies with mice, vitamin D3 deficits exacerbated the diabetogenic side effects of atypical antipsychotics.[131f] Moreover, co-administration of vitamin D3 and quietapine (Seroquel) protected against its insulin-lowering effects, as Vitamin D stopped quetiapine from lowering PI3K production—a key enzyme linked to insulin.[131g]

7. Botanicals with Anti-Inflammatory Properties

a) Cannabidiol (CBD) (from *Cannabis sativa*)*:*



Cannabis sativa is made up of two major components: cannabidiol (CBD) and tetra-hydrocannabinol (Δ9-tetrahydrocannabinol, THC). THC, its main psychoactive constituent, acts on CNS. A cannabinoid partial receptor agonist, THC promotes the "cerebral high." The pharmaceutical dronabinol (Rx: Marinol, Syndros) is synthetic THC with no CBD. It is FDA-approved for serious diseases as an appetite stimulant, antiemetic (HIV, cancer chemotherapy), and it can also decrease agitation in some terminally ill patients (the author's personal communication, 2012).

In contrast, CBD, the non-psychoactive portion of *Cannabis sativa*, blocks THC effects in CNS. CBD is highly touted for the treatment of **inflammatory conditions, anxiety, and pain**. CBD is a **cannabinoid antagonist, 5-HT1A (SE) agonist, and anxiolytic.** In one study, a single dose CBD for psychotic symptoms, normalized brain function in the parahippocampus, striatum, and midbrain, per fMRI.[132,133] **CBD has proven anti-inflammatory effects in the gut:** the 30-day trial of a probiotic mix activated endo-cannabinoids and enhanced immune regulation, by inducing gene expression of TLRs and related molecules.[134]

Cannabidiol modulates serotonergic transmission. It reversed allodynia and anxiety-like behavior in a model of neuropathic pain.[135] CBD does not act on the CB1 cannabinoid receptors like THC, but through binding receptors involved in anxiety (SE 5HT1A) and pain (vanilloid TRPV1). CBD increases 5HT firing through desensitization of 5HT1A receptors. Researchers were able to extrapolate the exact dosage of CBD with analgesic and anti-anxiety effects without the addiction and euphoria risk stemming from THC. In fact, low CBD doses (5 mg/kg/qd, s.c.) for seven days alleviated pain and anxiety, two symptoms often associated.

In a CBD/THC combination, the **mixture of phytocannabinoids, terpenes and other active components in a cannabis product ultimately determines the therapeutic effects and side effects.** CBD affects THC absorption and tolerance, potentiating some THC benefits as it reduces psychoactive effects and could thus improve tolerability**.** CBD may counteract some functional consequences of CB1 receptor activation in the brain. This effect has been used to explain why high CBD:THC cannabis use is less associated with psychotic symptoms compared to low CBD:THC cannabis. CBD interacts with the cytochrome (CYP450) enzymes that metabolize THC (2C9 & 3A4) and may alter its effects. THC and CBD act synergistically in therapeutic use.

b) Other anti-inflammatory botanicals

Major botanicals with anti-inflammatory properties, also anxiolytic and antidepressant, comprise:

Aschwagandha (*Withania somnifera*)
Berberine (*Berberis vulgaris, Berberis coptis*)
Curcumin (*Curcuma longa*)
Gotu kola (*Centella asiatica)*
Pink rose (*Rhodiola rosea*)
Saffron (*Crocus sativus*)
St John's Wort (*Hypericum perforatum*)
Resveratrol (in *Vitis vinifera* [grape] & other fruit skins)

The problem of neuroinflammation, in relation to depression, anxiety, and neurodegeneration, led to dedicated research into "**neuroprotectants**." Research on curcumin *(*CUR*),* berberine (BBR) and resveratrol (RES) found them to **act on the 3K/PTEN/Akt/mTORC1/GSK-3 pathway, with a special focus on GSK-3.** Those natural substances may regulate such pathway via mechanisms including: reactive oxygen species (ROS), cytokine receptors, mirco-RNAs (miRs), and numerous others.

1) **CUR** is the main curcuminoid in the turmeric (*Curcuma longa*) root. CUR is used for many disorders, especially those involving inflammatory processes**.**[136]

2) **BBR**, isolated from various plants (*Berberis coptis, vulgaris,* etc), is used in traditional medicine to treat multiple diseases/conditions.[136a,136b,136c,136d]

3) **RES** is a natural, non-flavonoid polyphenol antioxidant (3, 4′, 5-trihydroxy-trans-stilbene). It is extracted from red grapes (*(Vitis vinifera*) in wine making, but it is also found in other fruit skins (blueberries, raspberries). It inhibits microglial activation. CUR, BBR, and RES, which are natural anti-inflammatories, have shown promise in relieving depression and anxiety, as well as being anti-proliferative agents.[137]

4) **RHOS**, "Rose root" or "golden rose" (*Rhodiola rosea*), an herb with mild MAO-I inhibiting properties, was widely studied and used in Russia. A well-known adaptogen, RHOS has anti-inflammatory and anti-nociceptive effects.[138,139,140]

Detailed consideration of the anti-inflammatory properties of botanicals is beyond the scope of this article*.*

III. Environmental Enrichment Strategies vs Anti-Inflammatory Pharmaceuticals

Animal research on environmental enrichment (EE) revealed decreased anxiety and depression-like behavior in mice with early nerve injury, which was associated with CNS inflammation.

- **Infant spared nerve injury (SNI)** led to delayed adolescent neuropathic pain and possibly, psychiatric illness;
- EE fostered social communication and activity.

The SNI study consisted of an open field and an elevated plus maze. Pain behaviors (paw withdrawal threshold, spontaneous guarding score, and cold response to acetone) were measured in SNI rats. An enzyme-linked assay of cytokines evaluated the brain's inflammatory response. The researchers compared a pharmaceutical (**Rx**) with environmental enrichment (**EE**): Rx consisted of the intracerebro-ventricular (ICV) injection of a **microglia inhibitor** (**minocycline**, MIN), while EE involved a free**-running wheel, a staircase, a plastic tunnel, a raised platform, colored balls** designed to reverse infant SNI effects on behaviors.

SNI led to adolescent anxiety- and depression-like behaviors. In the brain, the medial prefrontal cortex, basolateral amygdala, and ventral hippocampus skewed to a **pro-inflammatory profile**. **Both Rx and EE treatments decreased anxiety and depression but only EE also affected pain behaviors.** Cytokine re-testing post EE showed increased brain IL-10 but reduced IL-1β and TNF-α, which means that **EE alone neutralized brain inflammation**.[141]

IV. Natural Health Care and Inflammation Reduction

Below is a template to stimulate internal anti-inflammatory responses and immune modulation, working with metabolic and immune processes in a mind-body framework.

1. Diet
   a) Anti-inflammatory Diet

This regimen favors nutrient-dense, whole foods, fiber-rich, the elimination of foods and environmental factors that provoke immune reactions for a period of time, food rotations, and individualized supplementation.[142,143] The **Mediterranean diet** is one prototype of a balanced diet (Mediterranean Diet Score or Healthy Eating Index). A review of evidence on the links between dietary patterns and inflammation biomarkers indicated that **meat-based or "Western-like" patterns tended to correlate with inflammation**, especially CRP, while colorful, plant-based (vegetables and fruit) or "healthy" patterns tended to be inversely associated. Interventions with healthy diets led to reductions of almost all the researched inflammatory biomarkers.[144]

RECOMMEND:

- **ω-3 FA rich foods**: salmon (preferably fresh wild caught, or frozen, canned), sardines (in water, no salt), herring, anchovies, hemp seeds, flaxseeds (fresh ground); mercury-free or lowest mercury fish.
- **Anti-inflammatory foods**: avocados and nuts, especially walnuts, cashews, almonds, pecans, and their nut butters.
- **High-alkaline diet:** greens, dark-leafy vegetables, rainbow (vegetables and fruit).
- Cruciferous (cabbage-family, steamed) vegetables, brightly colored fruits, pomegranate;
- **Green tea**: anti-oxidant, calming;
- **Whole grains**: organic (ideally **sprouted**) non-gluten grains such as brown rice, wild rice, buckwheat, quinoa, and amaranth. Gluten grains such as wheat varieties (spelt, kamut), rye, and barley may be used only if an individual is non-reactive to them. In many instances, it is best to start gluten-free (GF);
- Good **HYDRATION**: Drink plenty of high quality water (mineral or reverse osmosis, RO) between meals, throughout the day;
- **Organic produce** or at a minimum, free of synthetic pesticides (e.g. glyphosate);
- **Small portions of organic, grass-fed meats or fowl**, once a week each.

AVOID:

- Animal saturated fats, except in small quantities
- ω-6 oils: safflower, sunflower, corn, cottonseed, and mixed vegetable oils
- Margarine, vegetable shortening, and products listing them as ingredients
- Canola oil
- Partially hydrogenated oils
- Trans fats (deep fried foods, potato chips)
- Bleached (white flour) products
- Refined foods, added sugars, convenience foods, or refined carbohydrates
- Hormone- and pesticide-laden red meats and fowl
- Mercury-laden fish
- Artificial sweeteners (sucralose = Splenda, aspartame)

CONSUME **Anti-inflammatory supplements:**

- High quality, balanced multivitamin
- Buffered vitamin C
- Balanced probiotics
- Bioflavonoids (quercitin, oligoproanthocyanidins = OPC)
- ω-3 (EPA/DHA). If reactive, may use plankton-based DHA
- Herbal anti-inflammatories (boswellia, saffron, turmeric, ginger, parsley)
- Herbal detoxifiers (milk thistle, dandelion)
- Taurine, or in certain instances, NAC (N-acetylcysteine), a precursor in the production of the major antioxidant enzyme glutathione (GSH).
- Anti-inflammatory powder drinks and herbal, digestive teas (ginger, mint)

b. Alkalinization:

Alkalinization helps reverse inflammation and restores physiological resilience through improved repair.[144a] This entails progressive changes in diet, thinking, and activity patterns, which contribute 92% to our quality of life (RNA, epigenetic). Only 8% comes from genetics (DNA). A program of 80% alkaline foods and up to 20% acid ones supports pH normalization (80-20). In a healthy person, the alkaline/acid food ratio may shift to 60-40. A daily log of the first daily urine pH is used to monitor alkaline/acid balance. The desired, normal pH range is between 6.5 -7.5 as measured with a pH strip.

2. Lifestyle:

This includes active engagement, fulfilling work or retirement pursuits, the cultivation of nurturing relationships, a form of continued learning at any age, and community affiliations as desired. **Several lifestyle aspects that support the body's own anti-inflammatory processes** are:

- **Exercise**: individualized and moderate. Exercise has a profound effect on the functioning of the immune system. It is generally accepted that prolonged periods of intensive exercise training can depress immunity, while regular, moderate-intensity exercise is beneficial.[145,146] Research found that a high-intensity interval walking protocol in older adults with stable rheumatoid arthritis was associated with reduced disease activity, improved cardiovascular fitness, and improved innate immune functions, indicative of reduced infection risk and inflammatory potential.[147] Another recent study provides evidence to suggest that cytotoxic T cells become transiently reductive (stressed) in healthy individuals following a single bout of cycling.148
- **"Non-action" moments or periodic pauses** help recharge one's reserves, also improving alertness, attention, and mood.

- **Sleep:** refuels the system and detoxifies. Dreams can help work through psychological issues.
- **Mind-body practices:** relaxation (deep breathing, autogenic training, the relaxation response), Oriental healing practices based on personal preferences (Yoga, Tai Qi, Qi Gong), and, in certain instances, martial arts (Tai kwondo, Aikido, Judo).
- **Mindfulness-based cognitive therapy**: programs implemented in various countries.

Brain, Mind, and Psychotherapeutic Communication: Vagal tone and the inflammation connection

Our perception and understanding of ourselves and the world, the actions we take, and our relationships play a role in producing, aggravating, or curbing inflammation. Freud placed our mental life in the context of a whole person. In Mind and Brain, he stated that the brain processes cognition in a parallel and dynamic fashion—a departure from the neuroscientific "brain-based" reference frame. He viewed **Mind from a psychological perspective—** a starting point for psychosocial interventions with beneficial physiological and metabolic effects. Insight oriented-psychotherapies such as psychoanalysis are transformative. There is evidence of the neurophysiological changes brought about by transference interpretations,[149,150] and the modification of imprints in analytic hypnotherapy.[151,152] Those changes constitute novel learning within a relational context; hence, **new protein formation, including those that modulate inflammation**.[153]

Looking at the development of neurocognitive and emotional dysfunction relative to neuroinflammation markers is needed towards designing effective interventions. Studies of pediatric depression point to neurocognitive dysfunction, including the processing of affects, reward processing, and cognitive control, all of them interrelated domains.[154,155,156] In contrast, neuroimaging research shows measurable improvements in brain function after cognitive behavioral therapy (CBT), Interpersonal Psychotherapy (IP), and psychodynamic psychotherapy including psychoanalysis proper (PP). Neuroscientists and clinicians need to interpret those results collaboratively, and their relevance to inflammation.

The available data, notably with GI symptoms, fatigue, and stress-related disorders, point to the **usefulness of CBT, mind-body methods, and psychodynamic approaches in reducing inflammatory burden as well as improving emotional conditions**.157 For example, one study of two psychotherapies for youths with a severe GI inflammatory disease, Crohn' (CD), showed that both CBT and supportive non-directive therapy helped relieve depression and disease activity among those who were not on high dose steroids.[158] However, psychiatric co-morbidities in patients with inflammatory bowel disorders (IBD) call for interdisciplinary work. While psychotherapies alleviate inflammation, psychiatric medications have side effects that may worsen IBD, thus necessitating coordination with internal medicine specialists.159

Neuroinflammation may negatively impact any brain region. While the whole brain is instrumental to mental processes, certain regions are critical for affective and higher-order mental functions; e.g., fear conditioning, affective valence, emotional regulation, motivation, reward, memory, prediction, behavioral inhibition/response control, and imagery. Those regions include: the amygdala, hippocampus, and medial prefrontal cortex (mPFC), which are highly interconnected. They also connect with other limbic, subcortical and neocortical regions. All these brain regions play a part at the interface of sensory, cognitive, affective, and behavioral processing.

The Interpersonal Synchrony Model of Psychotherapy (" In-Sync") proposes that the psychotherapeutic alliance emerges from coupling the neural activity of the patient and therapist. This coupling can be achieved through the mutual coordination of the patient and therapist's behavior and experiences. Synchrony supports that alliance, which is conducive to the patient's adaptive emotion regulation and, hence, produces good therapeutic outcomes, including inflammation reduction.[160]

The psychotherapeutic dialogue, impacting our thoughts, feelings, and behaviors, produces structural, functional, and metabolic brain changes, with significant effects on inflammatory processes. Porges proposed that "**positive neuroception**" in psychotherapy can potentially restore and/or build basic trust, and has a cascade of beneficial health effects. This extends to neuroinflammation and its impact on mental/emotional functioning. It would be worth **systematically examining inflammation biomarkers and clinical symptoms pre- and post- psychotherapies of various persuasions**.

Clinical Illustrations of MNEI Approaches within the Psychotherapeutic Matrix:**
Specific cases illustrate the gut-brain axis per GI Effects Profiles[161] based on stool samples from patients with various emotional conditions, who experienced a MNEI approach to psychotherapy. Those individuals shared biomarkers of immune involvement, namely, abnormal (high or low) secretory IgA (sIgA) reflecting the status of the intestinal lining, and microflora imbalances (dysbiosis). With intestinal permeability ("leaky" gut) or autoimmune processes, immune function is compromised to various degrees. In several cases, sIgA was at Borderline High or High levels, suggesting that the system was under an inflammatory challenge. Financial considerations precluded re-testing but outcomes were assessed on the basis of clinical responses. The patients reported improved digestion, energy, sleep, and motivation, and reduction/elimination of pain. Those physiological indicators of inflammation reduction and restoration of function coexisted with improved thought patterns and mood, constructive actions, and interpersonal engagement, pointing to good treatment responses.

Bob: 10 year-old boy with multiple diagnoses: ASD, ADHD, BD, dyslexia, and Tourette's syndrome. Major problems were: mood swings, irritability, insomnia, "meltdowns," rigidity, tics, muscle spasms, overweight, anxiety, and "unusual" or repetitive behaviors. His GI keynote was severe constipation. Bob was socially isolated. His medication regimen included: Trileptal 450 mg *bid*, Buspar 22.5 mg *bid*, Trazodone 50 mg *qhs*, and OTC Melatonin 5 mg *qhs*. The parents also gave him probiotics, calcium, and a "kid" multivitamin. The GI Stool Profile showed evidence of dysbiosis, inflammation, and suggested autoimmune processes. Bob started an individualized gluten-free, dairy-free, sugar-free (GFDFSF) diet—challenging due to his age and eating habits. The new vitamin program was simple, i.e., a multivitamin, probiotics, fish oils, buffered C powder, and taurine. He also took a daily solution of the homeopathic remedy *Zincum metallicum*, in progressively higher potencies. Psychotherapy focused on strengthening cognition, behavior, and interpersonal skills. Medications were tapered off. His cognitive development, behavior, and social adaptation improved exponentially. He reads and writes fluently, remembers his friends' names and enjoys their company, and has a restful night sleep. No tics are noticed anymore.

Doris: A 17 year-old girl, high school junior, with a history of dyslexia and attention deficits (ADHD) successfully managed in public school with a suitable IEP. She had been diagnosed as having Acute Paranoid Schizophrenia. Her condition appeared suddenly only months after recovery from mononucleosis. Doris was exposed to Lyme disease three

** The patients' names and certain demographics were changed to protect their privacy.

years prior to intake. She presented with florid hallucinations (auditory and visual) and extreme agitation. Moreover, she suffered from constipation and abdominal pain. The child psychiatrist prescribed a starting dose of Risperdal (1mg *qd*), which was increased up to 3 mg *qd*. Doris primarily experienced risperidone's side effects: some sedation and amenorrhea (from prolactin stimulation). Her delusional thinking persisted and worsened. The parents discontinued that care. A second psychiatrist gave Beth antibiotics on the assumption that Lyme was the culprit. Doris ended up hospitalized with a toxic reaction. At that point, the parents refused anything other than "natural care."

An Individualized Optimum Nutritional (ION) profile (blood and urine) revealed nutritional deficits and metabolic pathways abnormalities. Among her deficits was methylmalonate — active B12 metabolite —, which is essential for methylation and, hence, NT formation. Doris also showed GI inflammation and dysbiosis. Nutrition replenished deficits and rebalanced metabolism. Conversational psychotherapy was challenging as Doris was not a talker. She also resented her parents and this writer for "withholding a pill" that would "make the problems go away." However, hypnotherapy helped reduce the "nasty voices" from several to one. Anti-inflammatory nutrition, supplementation, and rebuilding the GI microbiome helped. But ultimately, the homeopathic bowel nosodes (extracts of noxious bacteria) exerted profound catalytic effects by rebalancing her dysbiotic microbiome. Thereafter the patient was free of disturbed thinking and her affect normalized. Doris graduated from high school and enrolled in a junior college. All the interventions, but particularly the immune support impacting Doris' neuroinflammatory state, were deemed responsible for her recovery.

Frances: Aged 28, single, female, and a physician's assistant diagnosed with BD. She refused pharmacotherapy and sought alternatives. She experienced irritable bowel (alternating diarrhea and constipation, flatulence), insomnia, career doubts, and concerns about finding a suitable mate. She presented as intense and anxious, having made impulsive decisions in the past. Yet the BD label remained unclear based on the writer's evaluation. GI Stool Profile revealed high inflammation and intestinal dysbiosis, including yeast overgrowth. Frances committed to a structured regimen that included a Yeast Elimination Diet, nutraceuticals, and homeopathy, in addition to regular psychotherapy for three months. She quickly established rapport and complied with treatment. Psychotherapy uncovered issues of trust based on her dysfunctional family of origin, and a low self image. Frances made quick strides, simultaneously working on her digestive health and clarifying issues of self-confidence and boundary-setting. She redefined her plans, moved abroad, and became romantically involved. She requested occasional follow ups but her life was now on course, with improved total health.

Oliver: Aged 44, male, a successful lawyer, and married with two young children. He sought help with unrelenting, pervasive stress. His presenting complaints were: GI symptoms (bloating, diarrhea/constipation, gas), insomnia, exhaustion, with anxious and depressed features. The background included: a guilt-producing, secret affair secondary to major marital problems, a very demanding job load, and hectic travel schedules. Treatment entailed relaxation training (autogenics), hypnosis, and psychodynamic psychotherapy. He adopted an anti-inflammatory diet, and took nutritional supplements with an emphasis on adaptogens, probiotics, and fish oils. Within one month, he reported improved GI function and mood, along with stress relief. By treatment end, after 5 months, Oliver had modified self-perception and attitudes, benefiting him and his family.

Peter: A 47 year old male, working as a writer, and in a live-in relationship. Over the years his diagnoses included GAD, dysthymic disorder, insomnia, and IBS. He had one psychiatric hospitalization triggered by mourning. Peter complained of allergies, mental fog,

constipation, and poor sleep. For years he took SSRIs and benzodiazepines (BZDs). On intake, he was still on klonazepam, and on a statin drug to reduce his high cholesterol. He also went through decades of psychotherapy. He traced his problems to extreme infant constipation and allergies (rhinitis, rashes). Peter attributed chronic GI issues to his mother's "intrusiveness" in the bathroom. The GI Effects Profile showed an elevated sIgA and inflammation. Individualized treatment included a GFDFSF diet including bio-compatible foods, and a homeopathic remedy covering his high anxiety, perfectionism, and chemical sensitivities (*Arsenicum album)*. Peter had experiential and cognitive psychotherapy with occasional hypnosis, and practiced mindfulness. Within six months, his symptoms improved markedly, he ended his "codependent" relationship, and moved on. He is medication free, no longer suffers from GI inflammation, sleeps regularly, and boosted his creative career. He was followed seasonally until a year ago.

Rita: Aged 65 and a childless widow, with a supportive network. Rita presented with a chronic stress-related disorder and "burn-out" symptoms brewing over five years . She experienced fatigue, insomnia, pain, GI symptoms (gas, constipation), arthritic pains, crying spells, anxieties, and despair. GI Stool testing showed immune dysfunction (high sIgA, dysbiosis, and yeast overgrowth). Her physician prescribed Wellbutrin, 450mg *bid*, and referred Rita for psychotherapy. It took several months to begin tapering off the medication. An empath with poor boundaries, Rita was overcommitted, loyal, and drawn into others' conflicts. Treatment consisted of cognitive and interpersonal therapy, diet, nutrition, and lifestyle rearrangements. She built a strong psychotherapeutic alliance. She started a Candida elimination diet combined with anti-inflammatory choices, gluten-free and sugar free (GFSF) with limited cultured dairy. Nutritional supplementation included probiotics, a multivitamin, fish oils, liver support, an adaptogen herb (*Rhodiola rosea)*, and selected homeopathic remedies Within months she felt better, and her joint pains also decreased. With improved boundaries, self-esteem and self-care, she released her self-sacrificing behaviors, and her latent anger dissipated. She gradually reduced the Wellbutrin, and discontinued it after one year. Her resilient self emerged, and she continues with good self-care.

Wendy: A case with mixed outcome. Wendy, aged 26, was single and a talented journalist dissatisfied with her job. The diagnoses were: IBS with considerable pain and GAD. She suffered from generalized anxiety, insomnia, indigestion, and constipation. She desired natural treatment, and was eager to learn how to use the mind-body connection for healing. Initially enthusiastic, she established rapport and became more hopeful. She followed a combination of psychotherapy, GI- focused hypnosis, and nutritional interventions. A central issue was her pessimism about young men, which had to do with a disturbed psychosexual history. While her physical symptoms improved, Wendy did not address the psychological roots of her problem: poor body-image, guilt-laden sexual experimentation condemned by an excessively repressive mother, and her fears of intimacy. Instead, she quit psychotherapy. Wendy expected that GI improvement would suffice for her to heal otherwise, when underlying her pain and stresses were self-defeating patterns of relating that invariably led to disappointment.

The above cases show the central role of the gut-brain-mind connection in mental health conditions. The resolution of GI inflammation worked synergistically with psychotherapy in all but one case, Wendy. She showed that GI intervention alone is insufficient in holistic healing. Psychotherapy is strongly indicated whenever psychological conflicts fuel somatic dysfunction, which is often a co-morbidity. The above cases point to pervasive low-grade inflammation (or worse) among younger individuals with emotional disorders, although signs of inflammation are often more apparent among older patients. In that context, nutritional and pharmacological interventions lend biological support. The psychotherapeutic matrix, a prime learning context, is conducive to lasting health gains.

Discussion

The links between inflammation and mental disorders have received increasing attention in psychiatry and psychology. Inflammation affects sleep, mood, and energy metabolism (mitochondria). Conversely, stress mobilizes the HPA axis and modifies gut-brain-mind interactions, producing inflammation since vagal pathways are disrupted. These mutual influences warrant addressing various aspects of causation. Antidepressants, anti-psychotics when indicated, and anti-inflammatories showed anti-inflammatory effects, per cytokine, CRP, and TNF-α measures. However, antidepressants and antipsychotics carry side effects across body systems, along with the potential for aggression and suicide. Antipsychotics have extra-pyramidal, anticholinergic and metabolic side effects. Anti-inflammatory drugs—helpful adjuncts —, have shown mixed results.

Approximately over 7% of adults in the U.S.A. went through at least one major depressive episode in 2017. The 18 to 25 age group showed the highest depression rates. Based on the monoamine theory of depression, several medications were sequentially hailed as the treatment of choice, from TCAs to SSRIs and SNRIs. As reports grew of undesirable side effects, long-term health deterioration, and treatment resistance, psychiatrists and psychologists began to look elsewhere. The interest in inflammation coincided with the ascent of natural medicine and nutrition, along with growing awareness of regular physical activity and meditational practices benefiting mood.

Non-pharmacological options include health-building strategies, such as balanced nutrition, diet, and exercise. Moreover, mind-body methods include those derived from the Oriental healing arts (yoga, tai chi, qi gong), and applied psychophysiology (e.g. peripheral biofeedback and neurofeedback), autogenic training, and hypnotherapy. Finally, varied psychotherapeutic approaches (CBT, IT, PP) with a good track record for mental conditions, can be helpful adjuncts in somatic disorders such as IBS and IBD, cardiovascular conditions (e.g. the relaxation response), and asthma (e.g. autogenic training). In many instances, inflammation, stress, and trauma are common denominators.

Practice Implications

With a focus on inflammation, this article reviewed treatment options to restore mind-body balance using the psychotherapeutic matrix. Major sources of inflammation stem from the gut-brain axis via vagal links, and the cumulative effects of miscarried adaptation to complex stressors. Through reciprocal influences, thought patterns, emotional engagement and involvement, and styles of relating to others significantly shape physiology and illness, physical and mental. This area was heavily studied during the zenith years of psychoanalysis and psychosomatic medicine. Those times preceded the explosion of molecular biology with its wealth of data and resources for treating mental/emotional disorders and their somatoform expressions, specifically, inflammation.

What have we learned from the cytokine theory of depression, consideration of the gut-brain axis, and the examination of vagal connections? We can include all those aspects within the MNEI model of mental/emotional disorders, which also applies to physical conditions, especially chronic ones of multiple etiologies. Translational exchanges between basic science and clinical practice can foster productive interventions.

The author's work proposes guidelines for medical and prescribing psychologists to perform personalized diagnosis and treatment—N of 1. Medical psychologists of the future, with their unique education and training, can spearhead multidisciplinary teams for the integrative treatment of mental/emotional disorders, as follows:

I. Evaluation and diagnosis:

1) Biopsychosocial history and physical assessment;
2) Psychological, psychophysiological, neuropsychological testing, and/or Quantitative Electroencephalogram (QEEG) as indicated;
3) Laboratory tests for integrative practice (GI Effects, Organic Acids, Hormone profiles, etc), which include biomarkers of inflammation;
4) Complete Blood Chemistries (CBC) panel and identification of allergies;
5) Physical activity patterns;
6) Interpersonal connectedness;
7) Work adaptation/satisfaction (school, with children, adolescents, and youths)
8) Exposure to environmental toxins and hormone disruptors implicated in neuro-inflammation.

II. Treatment:

1) The **psychotherapeutic matrix**: Psychotherapy can be problem-focused or broad-based. Either way, this is a place for acceptance, empathy, mindfulness, trust, and active participation. In this **non-judgmental** learning context can the patient's self-exploration and awareness sustain behaviors that reshape health.
2) **Vagal tone normalization** takes place through cognitive, physiological, and behavior changes that accompany the formation of a therapeutic alliance. Among other factors, "positive neuroception" reduces stress and can help heal inflammation.
3) A **psychosomatic approach to inflammation** tackles personal patterns that shape identity and interpersonal adaptations (family, friends, etc), psychosexual factors, school/work related issues within a developmental framework. Guiding this work, Erikson's model of identity formation adeptly defines tasks against which to assess psychotherapeutic progress.[162,163]
4) **Pharmacotherapy**: Whenever possible consider **targeted monotherapy** within a time-frame, and taper off gently with the help of natural and complementary approaches;
5) **Lifestyle**: personalized nutrition, exercise, meditational practices, socialization, etc.
6) **Interdisciplinary collaboration** with primary care physicians and other health care specialists whenever psychiatric disorders involve medical co-morbidities.

III. Takeaways:

1) The brain and the gut contain three systems that mirror each other: nervous, immune, and endocrine; hence, the intricate **interconnections of the gut-brain-mind axis**;
2) **Sustaining inflammation is gut-brain "dissociation,"** which also reflects a disconnect between the central and autonomous nervous systems (CNS and ANS);
3) **Minding the gut within the psychotherapeutic matrix entails bi-directional brain- gut communication** through biopsychosocial strategies that help decrease inflammation and rebuild health;
4) The **stress-inflammation connection goes beyond the HPA axis. It includes other hormonal systems**, most notably the thyroid, a key regulator of metabolism and mood. This is a connection to explore carefully before thyroid medication alone is given to normalize mood. Once the context and causes are established, an appropriate integration of approaches can be implemented.
5) **Neuroinflammation is linked to mental disorders**. In view of the enhanced role of certain brain areas in cognitive and emotional processing, work is being done to pinpoint zones of network specificity and multi-network integration in the basal ganglia and thalamus of individuals. Such data could help create personalized and more ef-

fective brain stimulation therapies for neuropsychiatric disorders.[164]

6) Elucidating the **metabolic and cellular mechanisms and pathways through which nutrition promotes neuron resilience, resolves neuroinflammation, and improves mental fitness**, can substantiate a diet composition supporting mental health individually, with variations throughout life and changing circumstances.
7) **Pharmaceuticals, nutraceuticals, botanicals, and homeopathy have their place** in the treatment plan. While pharmaceuticals can give an edge in the healing process, natural products help fill the gaps in nutrient pathways for improved metabolism. **Beneficial drug-nutrient-herb interactions** can facilitate and enhance treatment.
8) The **psychotherapeutic interaction is conducive to inflammation reduction.** Hence, it is an invaluable tool in overall health care, not just for mental disorders. This unique interpersonal context provides an opportunity to remediate interoceptive impairments associated with illness, physical and mental.[165,166]
9) The **cultivation of self-awareness and learning sustainable coping methods promote adaptations critical to healing inflammation**. For these will deeply impact the **actions that sustain or undermine self-care**, and influence the mind favorably.

Concluding Remarks

Different approaches can be used to treat inflammation: pharmacological, nutritional, homeopathic, exercise-based, and mind-body methods as integrators of the healing process that potentiate self-help. Other treatment approaches such as acupuncture, massage, osteopathy, and chiropractic work, may be indicated as well. Finally, while being cognizant of genetic predisposition, this work aims to optimize epigenetics.

A holistic paradigm posits inflammation resolution, or at least reduction, as one of the desirable goals of psychotherapy. The constant back and forth between psychological changes and improved health markers is part and parcel of measuring psychotherapeutic progress today. The **gut-brain axis and vagal pathways are two major biological pillars of mind-body integration**. Translational work to connect psyche and soma is of the utmost importance. The author's MNEI model endeavors to include major expressions of mental/emotional struggles via inflammation, and enlist multiple resources to support the complex processes of dealing with the mind's vicissitudes and healing its wounds.

References

1. Szabo S, Tache Y, & Somogyi A (2012) The legacy of Hans Selye and the origins of stress research:A retrospective 75 years after his landmark brief "Letter" to the Editor of Nature, *Stress*, September, 15(5): 472-478
2. Mayer EA (2016) The Mind-Gut Connection: How the Hidden Conversation Within Our Bodies Impacts our Mood, Our Choices, and Our Overall Health, Harper Collins, NY, NY.
3. Mayer EA (2011) Gut Feelings: the emerging biology of brain-gut communication, *Nature Rev Neurosci,* 12 (8), 453-466**.**
4. Carabotti M, Scirocco A, Maselli MA, & Severi C (2015) The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems, *Annals of Gastroenterol,* 28(2):203
5. Cryan JF & O'Mahony S (2011) The microbiome-gut-brain axis: from bowel to behavior, *Neurogastroenterol and Motility* , 23(3): 187-192.
6. C. N. Serhan (2014) Novel Pro-Resolving Lipid Mediators in Inflammation Are Leads for Resolution Physiology, *Nature,* Jun 5; 510(7503): 92–101.
7. Kabagambe EK, Judd SE, Howard VJ, Zakai NA, Jenny NS, Hsieh M, Warnock DG, & Cushman M (2011) Inflammation biomarkers and risk of all-cause mortality in the Reasons for Geographic And Racial Differences in Stroke cohort, *Amer J*

Epidemiol, 16 Jun, 174(3):284-292.
8. Goldstein BI, Lotrich F, Axelson DA, Gill MK, Hower H, Goldstein TR, Fan J, Yen S, Diler R, Dickstein D, Strober MA, Iyengar S, Ryan ND, Keller MB, Birmaher B (2015) Inflammatory markers among adolescents and young adults with bipolar spectrum disorders, *J Clin Psychiat* Nov ;76(11):1556-63.
9. Dantzer R (2009) Cytokine, sickness behavior, and depression, *Immunol Allergy Clin North Am*, May; 29(2): 247-264.
10. Anders S , Tanaka M, Kinney DK. (2013) Depression as an evolutionary strategy for defense against infection, *Brain Behav Immun.* Jul;31:9-22.
11. Berk, M., Williams, L.J., Jacka, F.N. O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, & Maes M (2013) So depression is an inflammatory disease, but where does the inflammation come from?. *BMC (Bio Med Central Ltd) Med* 11, 200.
12. Felger JC & Lotrich FE (2013) Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications, *Neurosci*, Aug 29; 246:199-229.
13. Almeida PGC, Nani JV, Oses JP, Brietzke E, & Hayashi MA (2019) Neuroinflammation and glial cell activation in mental disorders, *Brain, Behav Immun, Health* xxx (xxxx) xxx, Dec. (Elsevier)
14. Dantzer R, O'Connor JC, Lawson MA, & Kelley KW (2011) Inflammation-associated depression: From serotonin to kynurenine, *Psychoneuroendocrinol,* Apr; 36(3): 426-436.
15. Miller AH, Haroon , Raison CL, Felger JC (2013) Cytokine targets in the brain: Impact on neurotransmitters and neurocircuits, *Depress Anxiety*. April; 30(4): 297-306.
16. Maes M, Bosman E, De Jongh R, Kenis G et al (1997) Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression, *Cytokine,* 9 (11): 853-858.
17. Savitz J & Harrison NA (2018) Interoception and inflammation in psychiatric disorders, *Biol Psychiatry Cogn Neurosci Neuroimaging*, June 2014, 3(6): 514-524.
18. Black C & Miller BJ (2015) Meta-analysis of cytokines and chemokines in suicidality: Distinguishing suicidal versus nonsuicidal patients, *Biol Psychiat,* Jul 1;78(1):28-37.
19. Yanning Li Y, Ruipeng Shen R, Wen G, Ding R, Ao Du, Zhou J, Dong Z, Ren X, Yao H, Zhao R, Zhang G, Lu Y & Wu X (2017) Effects of ketamine on levels of inflammatory cytokines IL-6, IL-1β, and TNF-α in the hippocampus of mice following acute or chronic administration, *Front. Pharmacol*., 20 March.
20. Brundin L. , Bryleva EY, & Rajamani KT (2017) Role of inflammation in suicide: From mechanisms to treatment, *Neuropsychopharm,* 42:271-283.
21. Tanaka T & Kishimoto T (2014) The biology and medical implications of interleukin-6, *Cancer Immunol. Res*., 2: 288-294.
22. Hodes GH, Kana V, Mnard C, Merad M & Russo SJ (2015) Neuroimmune mechanisms of depression, *Nat Neurosci* Oct. 18(10: 1386-1393.
23. Hodes GE, Menard C, & Russo SJ (2016) Integrating interleukin-6 into depression diagnosis and treatment, *Neurobiol of Stress*, Oct., 4:15-22.
24. Zadka L, Dziegiel P, Kulus M, & Olajossy M (2017) Clinical phenotype of depression affects interleukin-6 synthesis, *J Interferon Cytokine Res.,*Jun;37(6):231-245,
25. Gregg LP, Carmody T, Le D, Martins G, Trivedi M, & Hedayati S (2020) A systematic review and meta-analysis of depression and protein-energy wasting in kidney disease, *Kidney Intl Reports,* Jan.
26. Wajner SM, Goemann IM, Bueno AL, Larsen PR, Maia AL (2011) IL-6 promotes nonthyroidal illness syndrome by blocking thyroxine activation while promoting thyroid hormone inactivation in human cells, *J Clin Invest,* May;121(5):1834-1845.

27. Dowell NG, Cooper EA, Tibble J, Voon V, Critchley HD, Cercignani M, & Harrison NA (2016) Acute changes in striatal microstructure predict the development of interferon-alpha induced fatigue, *Biol Psychiat,* Feb 1.
28. Diefenbach KA & Breuer CK (2006) Pediatric inflammatory bowel disease , *World J gastroenterol.* May 28: 12(20): 3204-3212.
29. Galle SA (2016) Neuroplasticity in the vortex of adolescence: Mind and matter*,* *Arch Med Psych*, Fall issue, Nov, 8: 33-53.
30. Graham JE, Christian LM, & Kiecolt-Glaser JK (2006) Stress, age, and immune function: Toward a lifespan approach, *J Behav Med*, Aug, 29 (4): 389-400.
31. Kiecolt-Glaser JK, Glaser R (2001) Stress and immunity: Age enhances the risks. *Curr Dir Psychol Sci,* 10:18–21.
32. Kiecolt-Glaser JK, Glaser R, Cacioppo JT, MacCallum RC, Snydersmith M, Kim C, Malarkey WB (1997) Marital conflict in older adults: Endocrinological and immunological correlates, *Psychosom Med,* 59:339–349.
33. Sapolsky R (1992) Stress, the Aging Brain, and the Mechanisms of Neuron Death, Bradford Books.
34. Morris G, Berk M, Maes M, Carvalho AF, & Puri BK (2019) Socioeconomic deprivation, adverse childhood experiences and medical disorders in adulthood: mechanisms and associations, *Mol Neurobiol;* Jan.; 56(8): 5866–5890.

34a. Du Preez A, Leveson J, Zunszain PA, & Pariante CM, Inflammatory insults and mental health consequences: does timing matter when it comes to depression (2016) *Psychol Med,* Jul; 46(10): 2041–2057.

35. Cavigelli SA, McClintock MK (2003) Fear of novelty in infant rats predicts adult corticosterone dynamics and an early death, *Proc. Natl. Acad. Sci*. USA. 100:16131–16136.
36. Cavigelli SA, Yee JR & McClintock MK (2006) Infant temperament predicts life span in female rats that develop spontaneous tumors. *Horm. Behav.* 2006;50:454–4562.
37. Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J, Arseneault L. (2011) Biological embedding of stress through inflammation processes in childhood*. Molecular Psychiatry*. 2011;16:244–246.
38. Danese A & McEwen BS (2012) Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & Behavior*, 106:29–39.
39. Baune BT (Ed) (2018) Inflammation and Immunity in Depression: Basic Science and Clinical Applications, Academic Press, London, UK.
40. Jawahar MC & Baune BT (2018) Ch 17: Biological Embedding of Childhood Maltreatment in Adult Depression, in Baune BT (2018) pp 301-314.
41. Gonzalez A (2013) The impact of childhood maltreatment on biological systems: implications for clinical interventions, *Pediatrics & Child Health,* 18(8), 415-418.
42. Swedo SE, Frankovich J, & Murphy TK (2017) Treatment of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS): Diagnosis and treatment guidelines for PANDAS/PANS, *J of Child and Adol Psychopharm (JCAP)*, July 20, 3 articles.
43. Struneka A, Blaylock RL, Patocka J, & Strunecka O 2018) Immunoexcitotoxicity as the central mechanism of etiopathology and treatment of autism spectrum disorders: A possible role of fluoride and aluminum, *Surgical Neurology Internationa,* 9:74.
44. Delaney S, Hornig M, et al (2018) Environmental exposures and neuropsychiatric disorders: What role does the gut-immune-brain axis play? *Curr Environ Health Rep,* Feb 8.
45. Siniscalco D, Schultz S, Brigida AL, & Antonucci N (2018) Inflammation and neuro-immune dysregulations in autism spectrum disorders, *Pharmaceuticals,* Jun; 11(2): 56.
46. Thom RP, Keary CJ, Palumbo ML, Ravichandran CT, Mullett JE, Hazen EP,

Neumeyer AM, & McDougle CJ (2019) Beyond the brain: A multi-system inflammatory subtype of autism spectrum disorder**,** *Psychopharmacol.,* 236: 3045–3061.
47. Madore C, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, & Laye S (2016) Neuroinflammation in autism: Plausible role of maternal inflammation, dietary omega 3, and microbiota, *Neural Plast*; 2016: 3597209.
48. Tonhazerova I, Ondrejka I, & Mestanik M (2015) Inflammatory activity in autism spectrum disorder, *A*dvances *in Exper Med & Biol*, 861.
49. Tschiedel Belem da Silva C, Abreu Costa M, Kapczinski F, Wollenhaptde Aguiar B, Abrahao Salum G, & Gus Manfro G. (2017), Inflammation and internalizing disorders in adolescents**,** *Prog Neuro-Psychopharmacol and Biol Psychiat*,3 July, 77: 133-137].).
50. Another group at the UCLA Semel Institute for Neuroscience and Human Behavior, David Miklowitz, PhD has an ongoing study on Inflammation in Adolescent Mood Disorders [UCLA].
51. Siegmann EM, Müller HHO, Luecke C, Philipsen A, Kornhuber J, & Grömer TW (2018) Association of depression and anxiety disorders with autoimmune thyroiditis: A systematic review and meta-analysis, *JAMA Psychiatry*; 75(6):577-584.

51a. Najjar S, Pearlman DM, Alper K, Najjar A, & Devinsky O (2013) Neuroinflammation and psychiatric illness, *J Neuroinflammation,* 10: 43.

52. Frank MG, Weber MD , Watkins LR, Maier SF (2016) Stress-induced neuroinflammatory priming: A liability factor in the etiology of psychiatric disorders, Neurobiol of Stress, 4: 62-70. Müller,
53. Cohen S, Janicki-Deverts, Doyle WJ, Miller GE, Frank E, Rabin BS, & Turner RB (2012) Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk, *Proc Natl Acad Sci USA,* Apr 17; 109(16): 5995–5999.
54. Jones KA & Thomsen C (2013) The role of the innate immune system in psychiatric disorders, *Mol Cell Neurosci 53:52-62.*
55. Vernon AC, Turkheimer F, Dazzan P, & Pariante CM (2017) Brain microglia in psychiatric disorders, *The Lancet Psychiat*, 4, 7: 563-572.
56. Bierhaus A, Wolf J, Andrasy M, Rohleder N, Humpert PM, Pettov D et al (2003) A mechanism converting psychosocial stress into mononuclear cell activation, *Proc Natl Acad Sci USA,* 100(4), 1920-1925.
57. P. Blandino Jr., C.J. Barnum, L.G. Solomon, Y. Larish, B.S. Lankow, T. Deak (2009) Gene expression changes in the hypothalamus provide evidence for regionally-selective changes in IL-1 and microglial markers after acute stress, *Brain Behav. Immun*., 23: 958-968.
58. Hanke ML, Powell ND, Stiner LM, Bailey MT, & Sheridan JF (2012) Beta adrenergic blockade decreases the immunomodulatory effects of social disruption stress, *Brain Behav. Immun*., 26: 1150-1159.
59. Johnson JD, Campisi J, Sharkey CM, Kennedy SL, Nickerson M, Greenwood BN, & Fleshner M (2005) Catecholamines mediate stress-induced increases in peripheral and central inflammatory cytokines, *Neurosci*, 135: 1295-1307.
60. Wohleb ES, Hanke ML, Corona AW, Powell ND, Stiner LM, Bailey MT, Nelson RJ, Godbout JP, & Sheridan JF (2011**)** Beta-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat, *J. Neurosci*., 31: 6277-6288.
61. Weber MD, Watkins LR, & Maier SF (2016) Stress-induced neuroinflammatory priming: A liability factor in the etiology of psychiatric disorders, *Neurobiol of Stress*, Oct., 4: 62-70.
62. Brites D & Fernandes A (2015) Neuroinflammation and depression: microglia activation, extracellular microvessicles, and microRNA dysregulation, *Front Cell Neurosci,* 9, 476).

63. Kim Y.-K., Na, K.-S., Myint, A.-M, & Leonard, B.E. (2016) The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis, and the neuroendocrine system in major depression, *Prog Neuro-Psychopharm & Biol Psychiat,* 64, 277-284.
64. Goldbout, J.O., Moreau, M., Lestage, J., Chen, J., Sparkman, N.L., O'Connor J. et al, (2008) Aging exacerbates depressive-like behavior in response to activation of the peripheral innate immune system, *Neuropsychopharm,* 33 (10): 2341-2351.
65. Cohen S & Pressman S, The Stress-Buffering Hypothesis (2004). In Encyclopedia of Health and Behavior 2, NB Anderson, Ph.D. (Editor) Amer Psychol Assoc, Sage Publications, Thousand Oaks, CA, pp. 780-782.
66. Blevins CL, Sagui SJ, & Bennet JM (2017) Inflammation and positive affect: Examining the stress-buffering hypothesis with data from the National Longitudinal Study of Adolescent to Adult Health, *Brain Behav Immun* March, 61: 21-26.
67. Ali T, Choe J, Awab A, Wagener TL, & Orr WC (2013) Sleep, immunity and inflammation in gastrointestinal disorders, *World J Gastroenterol*, Dec 28; 19(48): 9231–9239.
68. Mancini A, Di Segni C, Raimondo S, Olivieri G, Silvestrini A, Meucci E, and Curro D (2016) Thyroid hormones, oxidative stress, and inflammation, *Mediators Inflamm.*: 6757154.
69. Marmorstein NR, Iacono WG, Legrand L (2014). Obesity and depression in adolescence and beyond: Reciprocal risks, *Intl J of Obesity*.
70. Nie X, Kitaoka S, Tanaka K, Segi-Nishida E, Imoto Y, Ogawa A, Nakano F, tomohiro A, Nakayama K, taaniguchi M, Mimori-Kiyosue Y, Kakizuka A, Narumiya S, & Furuyashiki T (2018) The innate immune receptors TLR2/4 mediate repeated social defeat stress-induced social avoidance through prefrontal microglial activation, *Neuron,* Aug 8: 99 (3): 464-479.
71. Dedovic K, Slavich GM, Muscatell KA, Irwin MR, & Eisenberger NI (2016) Dorsal Anterior Cingulate Cortex Responses to Repeated Social Evaluative Feedback in Young Women with and without a History of Depression, *Front Behav Neurosci,* 10: 64.
72. Lisboa SF, Niraula A, Barbosa Resstel L, Silveira Guimaraes FS, Godbout JP, & Sheridan JF (2018) Repeated social defeat-induced neuroinflammation, anxiety-like behavior and resistance to fear extinction were attenuated by the cannabinoid receptor agonist WIN55,212-2, *Neuropsychopharm,* 43, 1924–1933.
73. Pellegrini C, Fornai M, Antonioli L, Blandizzi C, & Calderone V (2019) Phytochemicals as novel therapeutic strategies for NLRP3 inflammasome-related neurological, metabolic, and inflammatory diseases, *Int J Mol Sci,* Jun; 20(12): 2876
74. Gao W, Wang W, Liu G, Zhang J, & Yang J (2019) Allicin attenuated chronic social defeat stress induced depressive-like behaviors through suppression of NLRP3 inflammasome, *Metabolic Brain Disease,* 34: 319-329.
75. Slavich GM & Irwin MR (2014) From stress to inflammation and major depressive disorder: A social transduction theory of depression, *Psychol Bull,* May; 140(3): 774-815.
76. Joergens S & Arolt V (2018) Does Inflammation Link Clinical Depression and Coronary Artery Disease? In Baune BT, pp 393-410.
77. Esselstyn CB (2011) Resolving the coronary artery disease epidemic through plant-based nutrition, *Prevent Cardiol,* 2001; 4: 171-177.
78. Gregory JM, Mak M, & McIntyre RS (2018) Inflammation and Depression in Patients with Autoimmune Disease, Diabetes, & Obesity (In Baune BT, Ch. 21, 2018).
79. Camara E, Rodriguez-Fornells A, and Münte TF (2009) Functional connectivity of reward processing in the brain, *Front Human Neurosci*, 2, 1-14.
80. Fischer AS, Camacho MC, Ho TC, Whitfield-Gabrieli S, & Gotlib IH (2018) Neural markers of resilience in adolescent females at familial risk for major depressive

disorder, *JAMA Psychiat,* May;75(5):493-502.
81. McEwen BS, Gray JD, & Nasca C (2015) Redefining neuroendocrionology: Stress, sex and cognitive and emotional regulation, *J Endocrinol,* Aug 226(2): T67-T83.
82. Vogelzangs N, Beekman ATF, de Jonge P, & Penninx BWJH (2013) Anxiety disorders and inflammation in a large adult cohort, *Transl Psychiat,* Apr, 3(4): e249.
83. Moriarity DP, McArthur BA, Ellman LM, Coe CL, Abramson LY, Alloy LB, Immunocognitive model of depression secondary to anxiety in adolescents, *J of Youth & Adol*, Dec, 47(12): 2625-2636.
84. Attwells S, Setiawan E, Wilson AA, Rusjan PM, Mizrahi R, Miler L, Xu C, Richtr MA, Kahn A, Kish SJ, Houle S, Ravindran L, & Meyer JH (2017) Inflammation in the neurocircuitry of obsessive-compulsive disorder, *JAMA Psychiat*, 74(8):833-840.
85. Allen AP, Dinan TG, Clarke G, & Cryan JF (2017) A psychology of the human brain-gut-microbiome axis, *Soc Personal Psychol Compass,* Apr; 11(4): e12309.
86. Vuong HE & Hsiao EY (2017) Emerging roles for the gut microbiome in autism spectrum disorder, *Biol Psychiat,* Mar 1;81(5):411-423.
87. MacFabe DF, Cain NE, Boon F, Ossenkopp KP, Cain DP (2011) Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: relevance to autism spectrum disorder, *Behav Brain Res*, Feb 2; 217 (1): 47-54
88. Galle SA (2014) Minding the mitochondria from cell to psyche, *Arch Med Psych,* Fall issue, Dec.; 6: 10-35.
89. Mayer EA, Knight A, Mazmanian SF, Cryan JF, and Tillisch K, 2011, Gut microbes and the brain: paradigm shift in neuroscience, *J. Neurosci,* 34 (46), 15490-15496.
90. Chiang JJ, Ko A, Bower JE, Taylor SE, Irwin MR & Fuligni AJ (2018) Stress, psychological resources, and HPA and inflammatory reactivity during late adolescence, *Develop & Psychopathol,* 31 (2): 1-14.
91. Rea K, Dinan TG, & Cryan JF (2016) The microbiome: A key regulator of stress and neuroinflammation, Neurobiol of Stress, Oct.: 23-33.
92. Bailey MT, Dowd SE, Galley JD, Hufnagle FR, Allen RG, and Lyte M (2011) Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation, *Brain Behav Immun*, 25 (3), 397-407.
93. Inserra A, Rogers GB, Licinio J, & Wong ML (2018) The Microbiota -Inflammasome Hypothesis of Major Depression, *BioEssays*, July 13.
93a. Dinan TG, Stanton C, & Cryan JF (2013) Psychobiotics: a novel class of psychotropic, *Biol Psychiat,* Nov 15;74(10):720-6.
94. Romjin AR & Rucklidge JJ (2015) Systematic review of evidence to support the theory of psychobiotics, *NutrRev*, 73(10), 675-693.
95. Sanders ME, Impact of probiotics on colonizing microbiota of the gut (2011) *J Clin Gastroenterol*, 45: S115-S119.
96. Rizzetto L, Kieran FF, Tuohy M, Selmi C (2018) Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex, J. of Autoimmunity, August, 92: 12-34.
97. Xie H & He SH (2005) Roles of histamine and its receptors in allergic and inflammatory bowel diseases, *World J Gastroenterol,* May 21; 11(19): 2851–2857.
98. Theoharides TC (2014) Brain inflammation, neuropsychiatric disorders, and immunoendocrine effects of luteolin, J Clin Psychopharm, April, 34 (2): 187-189.
99. Silva Moura D, Sultan S, Georgin-Lavialle S, Pillet N, Montestruc F, Gineste P, Barete S, Damaj G, Moussy A, Lortholary O, & Hermine O (2011) Depression in patients with mastocytosis: prevalence features and effects of Masitinib therapy, *PLOSOne*; 6(10): e26375.
100. Porges, SW (2011) The Polyvagal Theory: Neurophysiological Foundations of

Emotions, Attachment, Communication, and Self-Regulation, WW Norton, NY, NY.
101. Pavlov VA, Wang H, Czura CJ, Friedman SG, & Tracey KJ (2003) The cholinergic anti-inflammatory pathway: A missing link in neuroimmunomodulation, *Mol Med,* May-Aug; 9(5-8): 125–134.
102. Tracey KJ. (2002) The inflammatory reflex, *Nature*; 420:853–9.
103. Wieczorek M & Dunn AJ (2006) Effect of subdiaphragmatic vagotomy on the noradrenergic and HPA axis activation induced by intraperitoneal interleukin-1 administration in rats, *Brain Res,* 1101 (1): 73-84]
104. Ondicova K, Mravec B (2010) Multilevel interactions between the sympathetic and parasympathetic nervous systems: a minireview. *Endocr Regul,* 44(2):69–75
105. Rosas-Ballina M, Tracey KJ. (2009) Cholinergic control of inflammation, *J Int Med*.; 265:663–679.
106. Thayer JF & Sternberg EM (2010) Neural aspects of immunomodulation: Focus on the vagus nerve, *Brain Behav Immun*, Nov.; 24(8): 1223-1228.
106a. Huston JM & Fritz JR (2018) The inflammatory reflex and neural tourniquet: harnessing the healing power of the vagus nerve, *Bioelectron in Med*, 1(1): 29-38.
107. Johnston GR & Webster NR (2009). Cytokines and the immunomodulatory function of the vagus nerve, *Br J Anaesth*, 102: 453–462.
108. Bonaz B, Sinniger V, & Pellissier S (2016) Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation, *Physiol*, Oct 15; 594(20): 5781-5790.
109. Baune BT (2018) Modulation of Inflammation by Antidepressants, Ch. 31: pp 539-549 (In Baune BT, 2018).
110. Kook IA, Mizruchin A, Odnopozov N, Gershon H, & Segev Y (1995) Depression and immunity: The biochemical interrelationship between the central nervous system and the immune system, *Biol Psychiat,* June, 37 (11): 817-819.
111. Hernandez ME, Martinez-Fong D, Perez-Tapia M, Estrada-Garcia I, Estrada-Parra S, and Pavón L (2010) Evaluation of the effect of selective serotonin-reuptake inhibitors on lymphocyte subsets in patients with a major depressive disorder, *Eur Neuropsychopharm*, 20: 88–95.
112. Pavon L, Hernandez ME, Mendieta D, Martinez-Fong D, Loria F, Moreno J, Estrada I, and Bojalil R (2008) Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder, *Eur Neuropsychopharm*. 18: 917–924.
112a. Su F, Yi H, Xu L, & Zhang Z (2015) Fluoxetine and S-citalopram inhibit M1 activation and promote M2 activation of microglia *in vitro, Neurosci*, May 21, 294: 60-68.
113. Al-Amin MM, Uddin MMN, & Reza HM (2013) Effects of antipsychotics on the inflammatory response system of patients with schizophrenia in peripheral blood mononuclear cell cultures, *Clin Psychopharmacol Neurosci* Dec 24; 11(3): 144-151.
113a. Howes OD & McCutcheon R (2017) Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization, *Translational Psychiat,* **7:** e1024.
114. Dziedzicka-Wasylewska M, Mackowiak M, Fijat K, Wedzony K. (1996) Adaptive changes in the rat dopaminergic transmission following repeated lithium administration. *J Neural Transm Gen Sect.* 103(7):765-76.
115. Perez-Cruet J, Tagliamonte A, Tagliamonte P, Gessa GL. (1971) Stimulation of serotonin synthesis by lithium, *J Pharmacol Exp Ther,* 178 (2): 325-3.
116. Jope RS (2003), Lithium and GSK-3: one inhibitor, two inhibitory actions, multiple outcomes, *Trends Pharmacol Sci,* Sept, 24 (9): 441-443.
117. Nassar A & Azab AN (2014) Effects of lithium on inflammation, ACS Chem. *Neurosci*., Jun 18; 5(6): 451–458.

118. Nieper HA.(1973) The clinical applications of lithium orotate: A two year study, *Agressologie*, 14(6): 407-11 (Available as article #CM12 from the A. Keith Brewer International Science Library at (608) 647-6513 or on the Web)
119. Sartori HE (1986). Lithium orotate in the treatment of alcoholism and related conditions. *Alcohol*., 3:97–100.
120. Greenblatt JM & Grossman K (2016) Nutritional Lithium: A Cinderella Story: The Untold Tale of a Mineral That Transforms Lives and Heals the Brain, Feb 23.
121. Yui K, Imataka G, Nakamura H, Ohara N, & Naito Y (2015) Eicosanoids derived from arachidonic acid and their family prostaglandins and cyclooxygenase in psychiatric disorders, *Curr Neuropharmacol,* 13 (6): 776–785.
122. Galecki P, Galecka E, Maes M, Chamiliec M, Orzechowska A, Bobinska K et al (2012) The expression of genes encoding for COX-2, MPO, iNOS, and sPLA2-IIA in patients with recurrent depressive disorder, *J Affective Disorders,* 138(3): 360-366.
123. Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, Krogh J (2014) , Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: A systematic review and meta-analysis of randomized clinical trials, *JAMA Psychiat*, 71(12):1381-1391.
124. Aid S & Bossetti F (2011) Targeting cyclooxygenases-1 and 2 in neuroinflammation: therapeutic implications, *Biochimie,* 93(1): 46-51.
125. Baune BT (2018) Future Perspectives on Immune-Related Treatments, Ch. 35 pp.589-604 (In Baune BT, 2018).
126. MacFabe DF (2012) Short-chain fatty acid fermentation products of the gut micro biome: implications in autism spectrum disorders, *Microb Ecol Health Dis*, Aug 24; 23: 1-24.
127. Sarkar A, Harty S, Lehto SM, Moeller AH, Dinan TG, Dunbar RIM, Cryan JF, & Burnet PWJ (2018) The microbiome in psychology and cognitive neuroscience, *Trends in Cogn Sci,* 22(7): 611-636]
127a. Bull M& , Plummer NT. (2014) Part 1: The human gut microbiome in health and disease. *Integr Med*; 13(6):17–22.
128. McDougle DR, Watson JE, Abdeen AA, Adili R, Caputo MP, Krapf JE, Johnson RW, Kilian KA, Holinstat M, & Das A (2017). Anti-inflammatory ω-3 endocannabinoid epoxides**.** *Proc Natl Acad Sci (PNAS)*.
129. Latif A, Sajad W, Bhat A, & Ara A (2015 Omega-3 fatty acids and the treatment of depression: a review of scientific evidence, *Integr Med Res*, Sept. 4 (3): 132-141.
130. Zuardi AW, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, Mc Guire PK, & Guimaraes FS (2012) A critical review of antipsychotics effects of cannabidiol: 30 years of a translational investigation, *Curr Pharmacol Des*. 18 (32): 5131-5140.
131. Davies C & Bhattacharyya S (2019) Cannabidiol as a potential treatment for psychosis, *Ther Adv Psychopharmacol,* Nov. 8, 9: 2045125319881916
131a. Taliou A, Zintzaras E, Lykouras L, & Francis K (2013) An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders, *Clin Ther*, May; 35(5): 592-602.
131b. Ding K, Wang H, Xu J, & Zhu L (2014) Melatonin reduced microglial activation and alleviated neuroinflammation induced neuron degeneration in experimental traumatic brain injury, *Neurochem Intl*, 76.
131c. Esposito E & Cuzzocrea S (2010) Anti-inflammatory activity of melatonin in central nervous system, *Curr Neuropharmacol* Sep; 8 (3): 228–242.
131d. Anderson G & Maes M (2012) Melatonin: an overlooked factor in schizophrenia and in the inhibition of anti-psychotic side effects, June, 27 (1): 113-119.
131e. Jamilian H, Amirani E, Milajerdi A, Kolahdooz F, Mirzaei H, Zaroudi M, Ghaderi A,

& Asemi Z (2019) The effects of vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: A systematic review and meta-analysis of randomized controlled trials, Progr Neuro-Psychopharmacol Biol Psychiat, Aug, 94: 109651.

131f. Dang R, Jiang P, Cai HL, Li H, Guo R, Wu Y, Zhang L, Zhu W, Xin H, Liu Y, & Xu P (2015) Vitamin D deficiency exacerbates atypical antipsychotic-induced metabolic side effects in rats: Involvement of the INSIG/SREBP pathway, *Eur neuropsychopharm,* (European College of Neuropsychopharmacology), May, 25(8).

131g. Nagashima T, Shirakawa H, Nakagawa T & Kaneko S (2016) Prevention of antipsychotic-induced hyperglycaemia by vitamin D: a data mining prediction followed by experimental exploration of the molecular mechanism, *Scientific Reports,* 6: Article number 26375

132. Marcinkiewicz J & Kontny E (2014) Taurine and inflammatory diseases, *Amino Acids*, 46 (1): 7–20.

133. Yanguas-Casas N, Barreda-Manso M A, Nieto-Sampedro M & Romero-Ramirez L (2014) Tauroursodeoxycholic acid reduced glial cell activation in an animal model of neuroinflammation, *J of Neuroinflamm,* 11 (50).

134. Gioacchini, G., Rossi, G., Carnevali, O. (2017) Host-probiotic interaction: new insight into the role of the endocannabinoid system by in vivo and ex vivo approaches, *Scientific Report,* 7; 1261.

135. De Gregorio D, McLaughlin RJ, Posa L, Ochoa-Sanchez R, Enns J, Lopez-Canul M, Aboud M, Maione S, Comai S, & Gobbi G (2019) Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain, *Pain,* Jan; 160(1): 136–150.

136. Hurley LL & Tizabi Y (2013) Neuroinflammation, neurodegeneration and depression, *Neurotox Res,* Feb; 23(2): 131-144.

136a. Kulkarni SK & Dhir A (2008) On the mechanism of antidepressant-like action of berberine chloride. *European J of Pharmacol*. 589 (1-3):163-172.

136b. Liu YM, Niu L, Wang LL, Bai L, Fang XY, *et al.* 2017. Berberine attenuates depressive-like behaviors by suppressing neuro-inflammation in stressed mice. *Brain Res Bull*, 134: 220-227.

136c. Shen JD, Ma LG, Pei YY, Jin SL, Fang XY, *et al.* 2016. Berberine up-regulates the BDNF expression in hippocampus and attenuates corticosterone-induced depressive-like behavior in mice, *Neurosci Letters*. 614:77-82.

136d. Zhu X, Sun Y, Zhang C, and Liu H. 2017. Effects of berberine on a rat model of chronic stress and depression via gastrointestinal tract pathology and gastrointestinal flora profile assays. *Mol Med Reports*, 15(5):3161-3171.

137. Lertpiriyapong K, Steelman LS, Abrams SL, Corro L, Ratti S, Martelli AM, Candido S, Libra M, Montalto G, Cervello M, Gizak A, Rakus D (2017) Regulation of GSK-3 activity by curcumin, berberine, and resveratrol: Potential effects on multiple diseases, *Adv Biol Regul*, 65: 77-88.

138. Lee Y, Jung JC, Jang S, Kim J, Ali Z, Khan IA, & Oh S (2013) Anti-inflammatory and neuroprotective effects of constituents isolated from Rhodiola rosea, *Evid Based Complement Alternat Med*, Apr, 16: 514049.

139. Doncheva ND, Mihaylova AS, & Getova DP, Antinociceptive and anti-inflammatory effects of Rhodiola Rosea L. extract in rats, *Folia Med,* 55 (3-4): 70-75.

140. Li WH, Yu YL, Zhang Y, Song L, Wang ZX, Peng YF, Shi H, Zhou K, & Li TX (2020) Anti-inflammatory effects of Rhodiola rosea: A review, *Biomed & Pharmacother*, Jan.; 121: 109552.

141. Gong X, Chen Y, Chang J, Huang Y, Cai M, & Zhang M (2018) Environmental enrichment reduces adolescent anxiety- and depression-like behaviors of rats sub-

jected to infant nerve injury, J Neuroinflamm, 15:262-275.
142. Lakhan SE & Vieira KF (2008) Nutritional therapies for mental disorders, Nutr. J., Jan 21; 7 (2).
143. Adan RAH, van deer Beek EM, Buitelaar JK, Cryan JF, Hebebrand J, Higgs S, Schellekens H, & Dickson SL (2019) Nutritional psychiatry: Towards improving mental health by what you eat, Eur Neuropsychopharm, 29: 1321-1332.
144. Barbaresko J, Koch M, Schulze M, & Noethlings U (2013) Dietary pattern analysis and biomarkers of low-grade inflammation: A systematic literature review, July, *Nutrition Reviews*, 71 (8): 511-527.
144a. Schwalfenberg GK (2012) The Alkaline Diet: Is There Evidence That an Alkaline pH Diet Benefits Health? *J Environ Pub Health*; 727630.
145. Simpson RJ, Kunz H, Agha N, Graff R (2015) Exercise and the regulation of immune functions. *Prog Mol Biol Transl Sci*. 2015; 135: 355-380
146. Ratey JJ, with Hagerman E (2008) Spark: The Revolutionary New Science of Exercise and the Brain, Little, Brown & Co, NY, NY.
147. Bartlett DB, Willis LH, Slenz CA, et al (2018) Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis: a pilot study, *Arthritis Res Ther*, 20 (1):127.
148. Wadley AJ, Holliday A, Morgan RG, et al (2018) Preliminary evidence of reductive stress in human cytotoxic T cells following exercise, *J Appl Physiol,* 125 (2): 586-595.
149. Galle SA (2015) The fire within: A perspective on pain, *Acad Med Psych* (AMP) *Newsletter*, March, 4, 1:3.150.
150. Levin FM (1997) Integrating Some Mind and Brain Views of Transference: the Phenomena, Aug. 1, *J Amer Psychoanal Assoc***.**
151. Cheek DB & LeCron L (1994) Clinical Hypnotherapy, WW Norton & Co., NY, NY.(2nd, revised edition).
152. Cheek DB & Rossi EL (1988) Mind-Body Therapy: Methods of Ideodynamic Healing in Hypnosis, WW Norton & Co, New York, NY.
153. Kandel ER (2006) In Search of Memory: the Emergence of a New Science of Mind, WW Norton & Co., New York, NY.
154. Protopopescu X, Gerber AJ (2013) Bridging the gap between neuroscientific and psychodynamic models in child and adolescent psychiatry, Clinical Review Articles, Child & Adolescent Psychiatric Clinics of North America, *Psychodynamic Approaches to Psychopathology, Vol 1.*Editors: Ritvo RZ & Henderson SW., Consulting Editor, Trivedi HK, Jan.
155. C-J Boraxbekk et al. (2016**)** Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder**.** *Translat Psychiat*, Feb.
156. Britton JC, Kennedy SM, Seager I, Quen AH, Hernandez MV, Spiro CN, Ehrenreich May J (2015) Ch. 8: Pediatric Depression: Neurocognitive function and treatment implications. In Mohlman J, Deckersbach T, & Weissman A (Eds.) "From Symptom to Synapse: A Neurocognitive Perspective on Clinical Psychology," Routledge, Abingdon, Oxfordshire, UK.
157. Pearlstein JG, Staudenmaier PJ, West AE, Geraghty S, & Cosgrove VE (2019) Immune response to stress induction as a predictor of cognitive-behavioral therapy outcomes in adolescent mood disorders: a pilot study, *J Psychiatr Res,* 20: 56-63.
158. Szigethy E, Youk AO, Gonzalez-Heydrich J, Bujoreanu SI, Weisz J, Fairclough D, Ducharme P, Jones N, Lotrich F, Keljo D, Srinath A, Bousvaros A, Kupfer D, & DeMaso DR (2015) Effect of two psychotherapies on depression and disease activity in pediatric Crohn's disease, *Inflamm Bowel Dis,* Jun; 21 (6): 1321–1328.

159. Filipovic BR & Filipovic BF (2014) Psychiatric comorbidity in the treatment of patients with inflammatory bowel disease, *World J Gastroenterol*, Apr 7; 20 (13): 3552–3563.
160. Koole SL & Tschacher W (2016) Synchrony in psychotherapy: A review and an integrative framework for the therapeutic alliance, *Fron. Psychol*, 14 June.
161. Lord RS & Bralley JA (Eds. 2nd Edition) (2008) Laboratory Evaluations for Integrative and Functional Medicine, Metametrix Institute, Duluth, GA.
162. Erikson, E. H. (1950). Childhood and Society, W Norton, New York, NY.
163. Gross, R. D., & Humphreys, P. (1992). Psychology: The Science of Mind and Behaviour, Hodder & Stoughton, London.
164. Greene DJ, Marek S, Gordon EM, Siegel JS, Gratton C, Laumann TO, Gilmore AW, Berg JJ, Nguyen AL, Dierker D et al (2020) Integrative and Network-Specific Connectivity of the Basal Ganglia and Thalamus Defined in Individuals, *Neuron,* 105: 742-758.
165. Quadt, Lisa, Critchley, Hugo D and Garfinkel, Sarah N (2018) The neurobiology of interoception in health and disease. *Annals New York Acad Sci*, 1428 (1): 112-128.
166. Critchley HD (2004) The human cortex responds to an interoceptive challenge, *Proc Natl Acad Sci USA*, Apr 27; 101 (17): 6333–6334.