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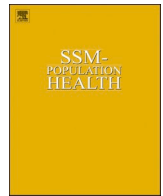
Biosocial medicine: Biology, biography, and the tailored care of the patient

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ABSTRACT

Biosocial Medicine, with its emphasis on the full integration of the person's biology and biography, proposes a strategy for clinical research and the practice of medicine that is transformative for the care of individual patients. In this paper, we argue that Biology is one component of what makes a person unique, but it does not do so alone. Biography, the lived experience of the person, integrates with biology to create a unique signature for each individual and is the foundational concept on which Biosocial Medicine is based. Biosocial Medicine starts with the premise that the individual patient is the focus of clinical care, and that average results for "ideal" patients in population level research cannot substitute for the "real" patient for whom clinical decisions are needed. The paper begins with a description of the case-based method of clinical reasoning, considers the strengths and limitations of Randomized Controlled Trials and Evidence Based Medicine, reviews the increasing focus on precision medicine and then explores the neglected role of biography as part of a new approach to the tailored care of patients. After a review of the analytical challenges in Biosocial Medicine, the paper concludes by linking the physician's commitment to understanding the patient's biography as a critical element in developing trust with the patient.

For most of the history of medicine, clinical decision-making for individual patients was guided by the prevailing theory of disease, the personal experience of the doctor treating similar patients in the past and the authoritative, if sometimes misguided, recommendations of eminent clinicians. In the early 1800s and later, advances in the physical and biological sciences provided much needed explanations for how the body functioned in health and disease.

Scientists such as Claude Bernard developed the concept of internal physiological balance (Bernard, 1878), later named homeostasis by Walter Cannon (Cannon, 1939). Edward Jenner introduced the method of vaccination (Smith, 2011), and Joseph Lister demonstrated the value of antisepsis (Maki, 1976). It was not long before those discoveries and others (e.g., Karl Landsteiner's system of blood compatibility (Landsteiner, 1930), Frederick Banting and insulin for diabetes [6]) fundamentally strengthened our understanding of how the body functions in health and disease.

Today, biological science is progressing rapidly. Nowhere is that more evident than in the stunning ability to sequence the SARS-Cov-2 genome (Kim et al., 2020) and develop highly effective vaccines in a matter of months. That capability was made possible thanks to the advances in genomic and molecular sciences that also underlies the basis for the drive to establish Precision Medicine in the clinical care of the individual patient. Precision Medicine is typically defined as an approach that tailors treatment to patients based on genetic or molecular features of their disease (Ashley, 2016).

Biology is one important component of what makes a person unique and enables precision medicine, but it does not do so alone. Biography, the lived experience of the person, integrates with biology to create a unique signature for each individual. The integration of biology and biography is the foundational concept for Biosocial Medicine that is the focus of this paper.

The paper is organized into distinctive sections. We begin with a description of case based medicine as a form of evidence that was introduced by Cabot (Dodds, 1993) and later refined by Kassirer

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(Kassirer, 1989). Next, we consider the reliance on RCT (Randomized Controlled Trial) and population level evidence (EBM or Evidence-Based Medicine) that has served as the basis for prediction rules and estimates of treatment response using average results for "ideal" patients, rather than the real patients of clinical practice. The following section then looks at the neglected role of biography and its essential consideration as part of a new approach to the tailored care of patients, termed *Biosocial Medicine*. After a review of the analytical challenges in Biosocial Medicine, we conclude by linking the physician's commitment to biography as a critical element in developing trust with the patient.

It is worth noting here that our overarching goal in proposing Biosocial Medicine is to improve the science and practice of Medicine by integrating both biology and biography, and in so doing, improving the diagnosis, prediction, and treatment of *individual* patients. Some may read this essay on Biosocial Medicine and the requirement that we once again learn about the lives of our patients as incompatible with the current business model of Medicine. Where is the time to inquire about our patients' lived experience, even if it improves diagnosis and treatment, when we have just 10 min for a return patient and 20 min for a new one? Perhaps the best answer is to refer to a quote often attributed to Robert Kennedy (although first stated by George Bernard Shaw): "Some men see things as they are, and ask why. I dream of things that never were, and ask why not." (Kennedy, 1968).

In the remainder of this paper we present the reasons for adopting Biosocial Medicine as the basis for the science and practice of Medicine.

Guerir quelquefloils, soulanger souvent, consoler toujours.
(To cure sometimes, to relieve often, to comfort always)

— Louis Pasteur (Louis Pasteur (attributed))

When Louis Pasteur wrote these words, cure was rare. The path breaking science of Lister, Pasteur, and Semmelweiss (Best and Neuhauser, 2004) had not yet led to the antimicrobials that would cure previously lethal infectious diseases; steroids and other immunosuppressive medicines had not yet been discovered to slow the course of inflammatory and immune mediated diseases; anti-hypertensives that would later reduce the risk of stroke, kidney disease and heart attacks were not yet known. In just 100 years after Pasteur's death, all of these medicines and more were in clinical use, the Human Genome Project had written the "book of life", and molecular science was finding new targets for medicines that could prolong survival and improve the quality of life for patients with cancer.

Equally important, remarkable advances occurred concurrently in imaging sciences. Roentgen discovered X-Rays in 1895 and their clinical application was promptly recognized (Chodos, 2015). New technologies such as nuclear scans and later computed tomography, magnetic resonance imaging, high resolution ultrasonography, and more changed the practice of medicine by enabling visual evidence of internal disease while avoiding the morbidity of invasive procedures. So too have the information sciences that created new tools to build the now ubiquitous electronic medical record, and to store, display and analyze vast amounts of data. And the field of artificial intelligence, relying on immense computational advances, has enabled biological and physiological sensors and machines that have fundamentally altered how we monitor individual patients and understand their risk for disease and their response to treatments.

1. The individual patient as the focus of the physician

The advances in pathology, physiology and medical imaging enabled a more robust practice of medicine in which scientific advances could be applied directly to the care of the individual patient. This focus on the individual patient and the case-based process of clinical reasoning that was the underlying basis of clinical practice received its most prominent expression in the development of the Clinico-pathologic conference (CPC) by Richard Cabot in the early 1900s. In the CPC, a presenter (typically a medical resident), describes a patient who is unknown to the discussant of the case and the audience. The presenter gives the history, physical examination, and all relevant investigations, including the results of diagnostic tests and procedures. The discussant, typically an experienced clinician, provides an analysis that accounts for the patient's clinical illness and laboratory abnormalities. Differential diagnoses are put forward and narrowed with an emphasis on the range of possible diagnoses (differential diagnoses) rather than a single diagnosis. At the conclusion of the discussant's analysis, the clinician typically proposes a final diagnosis. In the classic form of the CPC a pathologist then emerges from the audience to reveal the authoritative diagnosis as determined from tissue obtained by biopsy (if the patient is alive) or autopsy (if the patient died).

A modification of the CPC that was intended to illustrate how knowledge is utilized in practice came with the development of a formalized approach to clinical reasoning by Jerry Kassirer (Kassirer, 1989). In this approach, clinical information about the patient's illness (signs, symptoms, laboratory findings), along with limited sociodemographic information (age, sex, ethnic background, work history) is presented in small chunks sequentially to an experienced clinician. This information triggers one or more initial hypotheses in the mind of the clinician based on biological mechanisms (dysfunction in one or more physiological systems) that might have produced the given symptoms and signs. The basis for the initial hypothesis generation is usually the expert knowledge of the physician as well as clinical histories and diagnoses of known patients, the prior experience of the physician, or case reports where the information set of these cases approximately matches the presenting conditions of the patient at hand. With each succeeding chunk of information, the clinician refines her diagnostic considerations. Both the CPC and the Clinical Reasoning format focus on the case-based approach to the individual patient at hand who presents with a clinical problem.

2. The focus shifts from patient to population

When the CPC was introduced, reasoning about the diagnosis was the prominent form of clinical excellence since therapeutics was still in its infancy. Modern therapeutics, however, was poised for its own revolution. For thousands of years natural plant extracts were used to treat disease with varying effects. The modern era of therapeutics began when purified chemicals, rather than crude extracts, became the standard drugs. Morphine, the active ingredient in the plant opium, and digoxin, the chemical purified from the plant Digitalis lanata, were early examples. Penicillin was recognized as the active ingredient in the penicillium mold in 1928, but it took the impetus of World War 2 to accelerate production of the antibiotic. But soon Gertrude Elion and George Hitchings discovered the purine drugs that acted to suppress the immune system, such as Azathioprine (Elion et al., 1951); James Black discovered the beta blockers, such as propranolol (Quirke, 2006); and Sir David Jack developed the first inhaled beta 2 adrenergic agonist for asthma (Cazzola et al., 2012).

How would we know whether these new medicines would do more harm than good for sick patients? To answer these questions, Medicine turned to a method that had been introduced to study the impact of fertilizer on crop yields. The Randomized Controlled Trial (RCT), developed in agriculture by R.A. Fisher (Parolini, 2015), was adapted for medicine by Austin Bradford Hill to assess whether a new treatment was, on average, better than no treatment or the previous standard of care (Hill, 1952). This strategy of estimating average effects in heterogeneous populations using the RCT became popularized as Evidence Based Medicine (Guyatt, 1991). In the process, the RCT became a required method for demonstrating the effectiveness of new medicines and devices. An average reduction of 30% in outcomes as measured in an RCT is well understood for a population but not as well appreciated at the level of the individual where an outcome either occurs for an individual (100%) or does not occur (0%). The rise of EBM was notable too because

it signaled that there were knowledge gaps in medicine that required new ways of thinking.

3. EBM rise and skepticism

Evidence-based medicine claimed to provide objective procedures for evaluating the evidence that supported the effectiveness of a medical drug or device (Guyatt, 1991). The evidence was typically evaluated within a framework of research design hierarchy that placed RCTs at the top and observational studies in a subordinate role (Concato et al., 2000). When multiple RCTs on a single topic (treatment and disease) were available, EBM proposed meta-analyses that employed statistical techniques to summarize the results across studies (Feinstein and Horwitz, 1997).

Even as EBM was proliferating, many of the scientists who had pioneered the methods, including Bradford Hill and John Tukey, were lamenting that RCTs could tell you whether a treatment would work on average, but not whether it would help an individual patient. Indeed, one of the under-appreciated consequences of EBM was to give unprecedented weight in clinical decision-making to population level evidence and to distract the physician's gaze from her individual patient. In his Heberden Oration in 1965, Austin Bradford Hill wrote, "This leads to a related criticism of the present controlled trial that it does not tell the physician what he needs to know. It may be so constituted as to show without any doubt that treatment A is on the average better than treatment B. On the other hand, that result does not answer the practicing doctor's question: what is the most likely outcome when this particular drug is given to a particular patient?" (Hill, 1966).

Like Bradford Hill, the great American statistician John Tukey struggled with how to create knowledge that would help physicians to care for individual patients at the bedside. Despite his role in developing quantitative techniques for the analysis of RCTs, Tukey was skeptical of their value for clinical decision making at the level of the individual patient. In a famous 1979 paper in the journal *Science* in which he considered the statistical problem of multiplicity in RCTs, Tukey referred to what he perceived was an even more intractable problem. He wrote,

> "It is a difficult task to drive the nearly incompatible two horse team: On the one hand, knowledge of a most carefully evaluated kind where in particular questions of multiplicity are faced up to, and on the other, informed professional opinion, where impressions gained from statistically inadequate numbers of cases often, and so far as we can see, should control the treatment of individual patients. The same physician or surgeon must be concerned with both what is his knowledge and what is his informed professional opinion as part of treating a single patient. I wish I understood better how to help in this essentially ambivalent task." (Tukey, 1977).

4. Epistemology in Science and Medicine: New Ways of Knowing

Bradford Hill and Tukey addressed a crucial issue in knowledge generation that is central to how we reason and practice in clinical medicine. When evidence from RCTs or large surveys are used to decide how to treat an individual patient, we reason from the general (the population) to the particular (the patient). But of course, in clinical practice, that is not how we reason. We rely much more on the case-based method introduced by Cabot and further refined by Kassirer. We seek diagnostic clues from knowledge of dysfunctions of physiological systems in the individual patient and we determine treatment course by making longitudinal observations of an individual patient over time. It is a misunderstanding to believe that evidence in clinical care is strictly about decisions in diagnosis and therapy. The care of individual patients requires knowledge that includes diagnosis, prognosis and etiology of disease, along with knowledge about treatment choices. Consider this example.

> We have a 25-year old female patient in front of us. She tells us that she has frequent urination. We ask whether she has blood in her urine. She says no but reports having pain on urination. We suspect a bladder infection. On further questioning, we inquire about fever, chills or flank pain knowing that these are indications of an upper tract infection that requires a different treatment approach than lower tract infection. The patient reports no signs or symptoms of a complicated infection and a previous episode has been successfully treated with an antibiotic.

This vignette illustrates that we collect information from the patient in clumps of data that are elicited by asking the patient in front of us about her illness. When we consider the choice of an antibiotic to treat her infection, we are guided by knowledge of the organisms that cause simple cystitis, the prevalence of resistant organisms in the community, and the effectiveness of antimicrobials that have activity against those organisms. But we are also guided by knowledge of prognosis in **this** patient, since her illness indicates an uncomplicated lower urinary tract infection, and by **her** report that her previous cystitis was successfully treated with an antibiotic.

Population level evidence from RCTs that generate average estimates of treatment benefit have demonstrated that 79–100% of patients in the trials of antibiotics for lower urinary tract infections were successfully treated. Of course, that doesn't tell us whether our patient will respond positively. To know, we will monitor our patient to determine whether her symptoms have fully resolved within 48–72 h. Should her infection not be eradicated by treatment, we would need to inquire about additional risk factors and her adherence with therapy, always focused on the patient at hand.

This process of longitudinal follow up is characteristic of clinical care and makes the practice of medicine resemble a therapeutic experiment in which the clinician selects the choice of treatment and monitors for the outcomes.

RCTs turned out to be excellent tools for pharmaceutical companies who develop drugs and for regulators who need to license drugs where the question being addressed is whether treatment would do more good than harm overall in the population (Horwitz et al., 1996). But are there ways of knowing that would more closely align with the way physicians care for the individual patient?

5. Personalized/precision medicine

It turned out that help was on the way from unexpected sources. The emphasis on EBM and the RCT was recognized as ignoring an important role for the early phase human research that created new discoveries. These discoveries had suspected clinical applications, but frustration was developing in the biomedical community in the length of time it took for these discoveries to make it into clinical care. This "bench to bedside" lag became the impetus for the emergence of a new term, "translational medicine" that was codified in the NIH Roadmap (Woolf, 2008; Zerhouni, 2003). The translational medicine focus became a metaphor for the difficulty of moving discoveries into clinical practice. But translational medicine as a metaphor was unaccompanied by a set of actual steps or criteria to advance the scientific care of patients.

The more difficult but useful work of integrating new science into clinical care awaited a fresh application of advances in genetic and molecular science. This new translational medicine approach enabled the development of targeted therapies and more accurate prediction of the patient's clinical trajectory with a disease and was ushered in with studies of Diffuse Large B-Cell Lymphoma in which gene expression profiling identified molecular subtypes of the disease with distinct prognoses (Alizadeh et al., 2000). The strategy was initially referred to as personalized medicine, but that term was later replaced with precision medicine. An unexpected benefit of precision medicine was to diminish the emphasis on average results in populations and instead

returned the focus to the patient at hand, reasoning once again about the individual patient using an individually tailored approach.

Indeed, proponents of precision medicine heralded it as rejecting the one size fits all approach of the RCT and evidence-based medicine. Precision medicine offered another under-appreciated but critical innovation in knowledge generation in medicine: it sought to exploit the variability in medicine rather than the average. Rather than designing treatments based on similarities, precision medicine sought to design treatments based on differences. Precision medicine, for example, relied on differences created by disease mutations to develop mutation specific treatments for diverse diseases, from Cystic fibrosis (CFTR gene) (Welsh and Smith, 1993) to lung cancer (EGFR gene) (Pao and Chmielecki, 2010). Today, a major line of research in drug development seeks these mutational and other molecular differences to find treatments that do not necessarily work for everyone with a disease, but work exceptionally well for a subgroup of patients who share the difference in common.

6. But still, something is missing

Evidence based medicine, translational medicine, and precision medicine all heralded an epistemological reckoning in Medicine. The care of patients was limited by gaps in knowledge that were created both by advances in science and especially by the deep understanding of genomic and molecular processes at the level of the individual. When Tukey described the two-horse problem, he distinguished the knowledge gained from scientific studies from the knowledge gained from individual experience. In the course of providing medical care for patients, physicians learn about more than the symptoms of the patient; they learn about the person with those symptoms, including the social and environmental conditions in which they live. As our society has become more heterogeneous, more stratified and more unequal, biography has become as distinctive a signature of an individual as their biology. In recent years, it has become popular to say that a patient's zip code is more important to their health than their genetic code (HuffPost, 2009). Ironically, it took the tragedy of the Covid19 pandemic to remind us just how critical the patient's lived experience is in the development and outcomes of disease.

When Covid-19 appeared in the U.S. in the early months of 2020, it quickly became apparent that Americans were not dying at similar rates. In Louisiana, African-Americans accounted for 33% of the population yet 70% of Covid-19 deaths. In Michigan, African Americans were 14% of the population but were 40% of Covid-19 deaths, and in Chicago, 56% of deaths and 30% of the population. In New York, African Americans were twice as likely to die from the coronavirus as white people. More astonishing, predominantly African American counties in the U.S. were experiencing a three-fold higher infection rate and a six-fold higher death rate than predominantly white counties (Thibault et al., 2020).

Few physicians or social scientists were surprised by these findings. While physicians were aware that comorbidities like hypertension and diabetes were risks for adverse outcomes from Covid-19, and that these comorbidities were more common among African-Americans, most appreciate that the real reason for the disproportional burden of disease in minority communities is attributable to decades of life in a racist society, including racial segregation, unequal access to and treatment within healthcare settings, and the multiplex burdens associated with economic inequalities. As Camara Phyllis Jones, the former President of the American Public Health Association stated, "there is nothing different biologically about race. It is the conditions of our lives." (Hlavinka).

These conditions are part of the individual's lived experience, their **biography**, that emerges from the social and environmental conditions in which they live. Biography, with its emphasis on the individual, is distinct from Socioeconomic Status (SES) that creates a hierarchy of social rank among the population (Adler et al., 1994) or the Social Determinants of Health (SDoH)) that identifies the social drivers of health in the population (Marmot, 2005). The CDC organizes the SDoH into

broad categories: healthcare access and quality; education; social and community context; economic stability; and the neighborhood and built environment. In each instance, the SDoH is a population level attribute although it is true that many of the SDoH can be measured at the individual level too. Typically, however, SDoH are used not to characterize an individual but rather an individual's membership in a group within the broader community. Often left unstated, of course, is that any individual in the group may have an experience quite different from the average group experience.

Similarly, SES creates a population level hierarchy based typically on education, income and occupation. The SES hierarchy separates populations into groups whose health outcomes can be described as a monotonic, linear gradient. Groups at the top of the hierarchy have, on average, the best health outcomes while those at the bottom have, on average, the worst. But within each category, there is substantial variation. There are people at the top of the bottom stratum whose health outcomes are the same or worse than some in the top stratum. There are also some individuals in the bottom part of the top stratum whose health outcomes match or exceed people in the bottom stratum. It is this variation that offers an opportunity for a focus on individual biographical difference, just as the development of precision medicine offered an opportunity for a focus on the biological differences that were distinguished by genetic mutations or molecular markers.

7. Biosocial Medicine

Medicine is defined as the science and practice of establishing the diagnosis, prognosis, treatment and prevention of disease. Ordinarily, a definition this encompassing would appear to obviate the need for adjectival modifications of Medicine. And yet, we have already seen that such modifications are increasing in number, including translational medicine, evidence-based medicine, personalized medicine, precision medicine, narrative medicine and more.

All of these modifications of "medicine" are an indication that knowledge gaps are present that are considered necessary to the practice of medicine. Yet, they also imply that there currently is no integrated, coherent theory of Medicine that is sufficiently broad that it captures the whole of the discipline. To fill that gap, we propose **Biosocial Medicine** as a comprehensive theory of medicine that integrates both the biology and biography of the *individual* patient in health and disease. Biosocial Medicine extends across the lifespan, across geographies, across disciplines and critically, across racial and ethnic diversity.

The qualifier 'biosocial' in medicine and life science is not new, and has been referred to in previous work (Summers-Trio, Hayes-Conroy, Singer, & Horwitz, 2019; Engel, 1977; Barr, 2016). The biopsychosocial model proposed by George Engel strongly influenced the approach to clinical care adopted by the specialty of family Medicine. More recently, authors have employed the biosocial model to argue that the key drivers of well-being are the behaviors of smoking, diet, physical activity and alcohol use.

Dorothy Roberts (Roberts, 2016) makes an important distinction between (Bernard, 1878) 'older' biosocial science, which sought biological explanations for perceived social difference and was heavily influenced by eugenicist thinking, and (Cannon, 1939) 'newer' biosocial science, which seeks to understand individual biological differences, including differences in health, through renewed attention to the social dimensions of life. New biosocial science tends to incorporate critical attention to race and racism, stress, inequity, poverty, trauma, and exposures, among other aspects of social structure. Still, we remain vigilant recognizing that, as Roberts cautions, the ethical posture of such an approach is not guaranteed (Roberts, 2016). Our focus on the nuances of individual biography, for example, is chosen in part to move beyond problematic approaches that attach the same biological meaning to the lived experience of social categories of difference.

Biosocial medicine as we present it here is distinct from previous approaches. Biosocial Medicine in this approach seeks to understand the

scientific basis of the intimate relationship between biology and biography. The Biosocial Medicine we propose is focused on the lived experience of the individual and not on social categories per se or social determinants, except as they relate to individual experience. In Biosocial medicine we seek formulations of disease, not disease labels. A formulation can be thought of as a story that describes the illness experience of an individual patient. The formulation gathers and incorporates all of the biological factors to be sure, but also all of the social, experiential, and environmental factors and seeks to understand how these factors interconnect in the patient at hand.

The story of an individual includes her biology, and of course also her genetic predisposition to illness, any trauma occurring during development (e.g., Adverse Childhood Experiences, ACEs) (Felitti et al., 1998), economic circumstances, and experiences of discrimination, as examples. Some of these factors are "in" the biological body, some involve the body's relationship with a social and physical environment, and some entail changes to the biological body due to affective relationships or lived experience. But all of the relevant factors are experienced by the individual, not by a group or population.

The difference between a formulation and a diagnosis can be better understood by an example. The diagnosis "Adult onset diabetes mellitus" is a disease label, a typical diagnosis, that tells you somethings important about a disease but nothing about the person who has the disease, her life circumstances, how her illness developed or, critically, what is needed to treat her successfully.

Rather than a diagnostic label, consider a formulation like this*:*

A 51-year old woman, single mother of two teenage boys, presents with new onset urinary frequency, fatigue and muscle aches. Her current illness was precipitated by a 9-month period of enforced isolation caused by a widespread infectious disease pandemic during which she was unable to work. Required to remain at home while overseeing her boys' home schooling, she had little exercise while eating more than usual. Over the 9-month period, the patient reports gaining 25 pounds, feeling stressed by financial difficulties, and anxious about the future. Three weeks ago, she noted increasing fatigue, awakening at night to urinate and frequent urination during the day. Her blood sugar in the office was 425 mg/dl and her urinary dipstick was 4+ positive for glucose.

Individuals with exactly the same disease label can have completely different formulations. The predisposing and precipitating factors that led to the patient's Type 2 Diabetes Mellitus (T2DM) provides guidance to treatment. A medication to lower her blood sugar will not be sufficient to treat her disease. Her lived experience must be addressed as well: Her excessive eating has been a coping mechanism for underlying stress. Her inactivity related to policies that restricted movement during the pandemic. The need for coping and for movement must be acknowledged and attended to if her T2DM is to be successfully controlled. Rather than prescribing "behavioral" change as one part of treating a disease, we need to carefully consider how she might cope with her changed reality. Doing so targets both the biology and the biography of the patient in addressing the patient's unmet medical needs.

We do not diminish the practice of Medicine by acknowledging that it is an "applied science" where the rules and principles must be figured out in relation to the care of one particular patient. Montgomery has referred to this process as "practical reasoning", borrowing from Aristotle's concept of *phronesis* (Marcum and Montgomery, 2007). We do not currently have a set of rules and principles to guide inference about cause or effect at the level of the individual. Nor do we currently have a systematic approach to the collection of information that defines the medically relevant aspects of a person's biography that is essential to an integrated biological and social understanding of health and disease in the individual person. We propose a Biosocial Medicine that requires a full and equal integration of biology and biography, including a new focus on Biosocial Mechanisms, that forms the basis for this refreshed approach to Biosocial Medicine. In the sections that follow we propose new conceptual elements that are central to the development of Biosocial Medicine: Medical Biography; Biosocial mechanisms; and

person-centered analytics.

8. Medical biography

Biography is a detailed description of a person's life. Critically, it involves more than just the listing of facts such as education, work, relationships and death. Biography portrays a person's experience with these life events. *Medical biography* is the lived experience of a person that is elicited as relevant information in the evaluation and management of a person to assess either their health or disease.

The elements of medical biography are worth mentioning. Although biography is "womb to tomb", medical biography stresses the elements relevant and proximate to the current illness. Biography is an individual attribute and therefore excludes population measures such as socioeconomic status or social rank, except as they are experienced by the individual. Because biography is often measured qualitatively rather than quantitatively like biomarkers or physiological measures, biography is often disparaged as less accurate or precise, or relegated to the vague category of the "Art of Medicine".

The story above of the woman with T2DM caused in part by her lived experience is an illustration of how biography is essential to the treatment of a patient. The biology is well known that links weight gain and obesity to peripheral insulin resistance and dysregulated glucose metabolism. But the link between stress, overeating and disordered glucose regulation is also well known and describes the crucial role of biosocial mechanisms in both leading to disease and identifying approaches to treatment. Neglecting the patient's biography consigns the patient to potential mistreatment.

It is important to point out that the relevant biography in our patient with T2DM was not an exhaustive life history. The lived experience that matters in this example are the events that were proximate to the illness and that require modification if the disease is to be suitably managed. Stress was proximate both to her overeating and to HPA axis dysregulation. The pandemic was the proximate cause of the job loss and financial stress as well as the social isolation and reduced activity. Giving this woman metformin alone without addressing the biosocial contributors to her illness will not adequately treat her diabetes. A pharmacologic treatment course alone may lead to increasing doses and number of oral agents and, when they are unable to control her blood sugar, insulin treatment will be added with the further risk of weight gain and continued elevated measures of glucose excess. Only by addressing her biosocial mechanisms and life circumstances along with medications will her physician effectively manage her disease.

9. Biosocial mechanisms

Biosocial mechanisms connect the patient's lived experience to her biology. The pathway between our experience and our disordered biology has always felt mysterious to many. How does someone's social class get under the skin to affect her biology? How does stress cause hypertension, or even the extraordinary takotsubo syndrome (stress cardiomyopathy)? What is the process that leads from grief to pneumonia, or from grief to a myocardial infarction. Biosocial mechanisms are the roadmaps that describe the pathways connecting the patient's external world to their internal biology. There are numerous biosocial mechanisms, from familiar ones like allostatic load to unfamiliar examples such as the impact of scarcity on mental functioning. To illustrate biosocial mechanisms we will briefly describe two of the more commonly cited processes.

9.1. Stress and allostatic load

Human physiology is attuned to the characteristics of our social environment and interactions with others, and social behavior is similarly affected by biological processes. For many years, this interplay was studied largely in populations by social epidemiologists using large

nationally representative cohorts of individuals with well described social characteristics such as poverty, social isolation, or low education. Interestingly, it took a stress neuroscientist, Bruce McEwen, to focus the study of social processes on individual health and disease. As a result of his work, stress processes are probably the most commonly considered biological mechanisms through which the social environment gets under the skin to affect the risk for disease and the response to treatment.

McEwen and Stellar described a novel understanding of the various ways that adaptation to stress impacts trajectories of health and disease (McEwen and Stellar, 1993). In a landmark paper they wrote, "This article presents a new formulation of the relationship between stress and the processes leading to disease. It emphasizes the hidden costs of chronic stress to the body over long time periods, which act as a predisposing factor for the effects of acute, stressful life events. It also presents a model showing how individual differences in the susceptibility to stress are tiedto individual behavioral responses and to environmental challenges that are coupled to physiological and pathological responses." (McEwen and Stellar, 1993).

The stress leading to the disease model that McEwen proposed was linked to two factors unique to the individual: the way a person perceives a situation, and a person's general health, determined not only by genetic and biological factors but also by behavioral and lifestyle factors (Seeman et al., 1997). Over time, each of us adapts to the life situations we experience in our daily lives and our major physiological systems participate in this process of adaptation. As McEwen noted, "the price of this accommodation to stress has been defined as allostatic load, or the wear and tear that results from chronic over-activity or under-activity of allostatic systems." (McEwen, 1998).

9.2. Epigenetics and health

In September 1944, after a failed attempt to halt the train transport of Nazi troops in the Netherlands, the Nazis punished the country by blocking food supplies and creating the Dutch Winter Famine. The Netherlands were not liberated by the Allies until May 1945 and by that time it is estimated that more than 20,000 people had died of starvation and 4.5 million people were affected.

The Dutch Famine has served as a tragic and unplanned experiment in human health. Pregnant women were especially vulnerable to the effects of food deprivation and the children who were born to these women have had adverse health conditions throughout their lives. When the children became adults, they were heavier than their peers, and had higher rates of numerous medical conditions, including diabetes, obesity, hypertension and neuropsychiatric conditions such as schizophrenia. L.H. Lumey and his colleagues reviewed the death records of hundreds of thousands of Dutch people born in the mid 1940s and found that people who had been in utero during the Dutch Winter famine had a 10 percent greater increase in mortality than people born before or after the famine (Heijmans et al., 2008).

In studying this phenomenon, one of the investigators asked the question we all have, "How on earth can your body remember the environment it was exposed to in the womb—and remember that decades later?", asked Bas Heijmans. The purported answer is stunning: the Dutch Hunger Winter silenced certain genes in unborn children in utero and those genes remained silent throughout their life.

Epigenetics are the changes in an organism caused by the modification of gene expression rather than any change in the genetic code itself. Epigenetics works through DNA methylation by adding a chemical group to DNA that turns genes "on" or "off". Epigenetics also works through Histone modification. Histones are proteins wrapped around DNA. When the histones are very tightly wrapped the DNA cannot be read and genes can again be turned "on" or "off".

When scientists took blood from survivors of the Dutch Famine they observed methylation patterns that were common in the Winter Hunger cohort but missing from their siblings. They also discovered that certain methyl groups were linked both to the famine and later life adverse health states (Heijmans et al., 2008).

We now know that experiences, diet, and environments all affect the patterns of methylation and histones not just in utero but throughout life. Recent research has identified an epigenetic clock that tracks a person's biological age that can either lag behind or ahead of the chronological age. Scientists have recently reported that 9 volunteers who took certain drugs, including growth hormone and two diabetes medications, shed 2.5 years from their biological age as measured using epigenetic assessments. Although work in epigenetics is still in its infancy, the relationship between a person's lived experience, their biography, is profoundly affecting their biology through this biosocial mechanism of epigenetics.

10. Person-centered analytics

We have previously illustrated how reasoning in clinical medicine is a case based process focused on the individual patient in front of the physician and not on some average patient from a population level approach. The average or "ideal" patient is a product of a variable-oriented analytical strategy in which the person is quickly lost. Variable based analytical strategies reify the "ideal" patient. But the "ideal" patient doesn't exist in clinical trials or in clinical practice. Physicians treat the real patient, not the ideal one. Just as case-based reasoning lies at the foundation of clinical practice, so too must the analytical approach be shaped to accommodate a case based design. Our epistemological challenge is how to bring the individual patient into the study of lives as they experience the development, progression and treatment of illness.

The person-centered approach requires analyzing and then aggregating individual patient histories that are collected through longitudinal patient management (Zhao, Brooks-Gunn, & Singer, 2000). The approach we propose depends on a set of underlying principles that are essential to its implementation. One of the core advantages of the patient based strategy is the opportunity to identify multiple trajectories through which individual patients can arrive at similar or different outcomes.

The *first principle* to consider is that any event or characteristic can influence a clinical trajectory differently depending on whether it is present along with another important feature. For instance, we know that mild cognitive impairment in older patients is associated with an increased risk of delirium. However, delirium almost never occurs when the individual is at home in familiar surroundings. When the patient is moved to the hospital, though, and all of her familiar environmental cues are replaced with new and strange surroundings, delirium occurs commonly.

A *second principle* is that features of the patient may either amplify or mitigate risks for certain outcomes. Continuing with the example above, an elderly patient with cognitive impairment who is placed on psychoactive medicines in the hospital is even more likely to experience delirium. Alternatively, designing the hospital environment to more closely resemble a home experience, such as enhanced lighting, avoiding vital signs checks in the middle of the night, etc., may buffer the risk of delirium. Context matters.

A *third principle* that is often overlooked in clinical medicine is that risks are not always the consequence of simple additive effects. A variable based model may identify 5 or 6 risk factors for delirium and it may be tempting to conclude that any 5 risk factors is worse than 4 or 3. However, in actual practice, the way the patient profile is constructed, and the array of features that dominate the patient's experience, may be more important than the number of factors in determining risk or treatment response.

To illustrate the value of person-centered analytics, let's consider the clinical problem of delirium as a physician might. Delirium is an acute state of mental confusion with disorientation, mental impairment and loss of attention (Inouye et al., 1990).

Research using variable based methods has identified a long list of

predisposing and precipitating factors for delirium. Among predisposing factors are older age, male sex, physical and psychiatric co-morbidity, impaired vision and hearing, dehydration and polypharmacy. Precipitating factors include disordered sleep, uncontrolled pain, hospitalization, especially ICU stay, surgery and other concurrent acute illnesses. These risk variables are identified in large cohort studies, often in multivariate analyses, and weights are estimated that correspond to the impact that each feature has on the risk of delirium. A cumulative score is then created that is used to partition patients into different levels of risk.

The difficulty with this approach is that it tells us little about how the patients present with delirium or how to treat them. The case based approach enables a person based analytical approach that is holistic and creates the opportunity for treatment selection.

A 76-year old woman is admitted to hospital with shortness of breath, fever and a cough productive of sputum. Her past medical history included surgery for cataracts, type 2 diabetes controlled with metformin, COPD from a 40-year history of smoking a pack per day of cigarettes treated with inhaled beta agonists and steroids, obesity with a BMI of 30, and diminished hearing and vision. Her CXR suggested evidence of a right lower lobe community acquired pneumonia. She had hypoxemia. Because of her fever and reduced oxygenation, she was admitted to hospital and begun on antibiotics. On the second hospital day the patient's fever spiked, her oxygen level dropped and she was transferred to the ICU. Although she had never previously experienced delirium, on the second night in the ICU the patient became agitated, confused and combative. After repeated efforts to remove her intravenous lines, she was physically restrained. Her agitation increased and she was further restrained with medications.

It is possible to look at this clinical vignette and see the presence of the precipitating and predisposing variables for delirium. A different look, one that is person based, would express the formulation differently. The patient had previous episodes of fever managed at home and exacerbations of her COPD with diminished oxygen levels. Now however, she is acutely ill with fever, infection and hypoxemia. But she is also no longer in the familiar setting of her home. The interaction of her biology and biography (the patient's personal distress created by the move from her familiar home environment to hospital to ICU) has created an illness scenario that also suggests a treatment path. In addition to treating her pneumonia, she needs to be engaged with familiar elements of her home life: family and familiar objects from home.

This scenario emphasizes certain critical principles of person-centered analysis that have been established in previous research. First, relevant determinants of disease or treatment response rarely occur in isolation. You need always to look for multiple features and consider them together. Second, life context may matter. The move from home to hospital interacted with the patient's biology to cause delirium that might not have occurred at home. Thirdly, person-centered analysis recognizes that the experience of the group cannot be substituted for the individual.

The person-centered approach might be considered the "little e" strategy that quantifies the experience of the individual patient. Each of these individual experiences can then be incorporated into what would become a novel "Big e" strategy that is founded on individual patient observations but becomes generalizable from the cumulative descriptions of many patients. In the next section, we show how that might occur with N of 1 trials.

11. Person-centered analysis: N-of-1 trials

Every day, millions of people are prescribed and take medications that will not help them but may cause them harm. It is estimated that of the top ten highest grossing drugs in the US, 1 in 25 to 1 in 4 patients taking those drugs will be helped by them. For some very common treatments, such as statins for elevated cholesterol, as few as 1 patient in 50 may be helped (Schork, 2015).

The reason for this discouraging circumstance is the discrepancy between the population level benefit estimated in large scale randomized controlled trials and the effects in individual patients. In the Beta Blocker Heart Attack Trial, death or recurrent MI occurred in about 10% of placebo patients and 7.5% of patients who were assigned propranolol. This 25% proportional reduction in risk is also a 2.5% absolute difference, leading to a number needed to treat of 40. That is, forty patients need to be treated to prevent one patient from experiencing death or MI, leaving 39 others to experience the risks of treatment but none of the benefits (BHAT Trial Group, 1982).

This discrepancy is a hallmark of clinical circumstances in which the outcome of treatment occurs uncommonly or over long-time periods, or both. Yet for many clinical problems in medicine, the interval between treatment and response is brief and the outcome occurs frequently. A patient with pneumonia treated with an antibiotic will see benefits within days, as is true for most infections. Pain relief may come quickly after medications are started or joints injected. Shortness of breath from asthma may respond quickly to beta adrenergic agents, and blood pressure will decrease soon after an appropriate therapy is started.

This process of treatment and response is a hallmark of every physician's experience. That is why it is possible to appreciate that a physician carries out therapeutic trials in their individual patients every day in routine clinical practice. A patient with asthma may return with worsening symptoms of wheezing and breathlessness occurring more frequently and interfering with daily activities. The physician decides it is necessary to add a new agent to the patient's medication regimen. In this circumstance, the physician determines the patient's eligibility for the added therapy, controls the assignment of treatment, including frequency and dosing, and monitors and measures the patient's response to treatment. All of the elements that we typically associate with a therapeutic trial have been implemented under the control of the physician.

More recently, clinical investigators recognized that the physician was conducting clinical trials in customary practice, but had not formalized the conduct of these studies. Single patient studies, N of 1 trials, were developed as a formalized approach to the informal process of judging response to treatment in clinical care. The physician who may give a patient with asthma that is not well controlled a leukotriene inhibitor to see if that leads to fewer exacerbations and better clinical function could test the benefits of that additional treatment in an N of 1 trial. Or a patient with hypertension uncontrolled with current medications may be given a trial of a different class of anti-hypertensive drug and then followed for their treatment response not as an informal effort but as a more rigorous approach to clinical care.

Like so much in clinical medicine, everything old is new again. In 1953, Hogben and Sim published a paper with the uninspiring title, "The Self-Controlled and Self-Recorded Clinical Trial for Low-Grade Morbidity". (Hogben and Sim, 1953). Hogben and Sim proposed a brilliant innovation that was motivated by a profound insight, stated as follows: "The now current recipe for a clinical trial based on group comparison sets out a balance sheet in which individual variability with respect *both to nature and to previous nurture* (italics added) does not appear as an explicit item in the final statement of the account, but such variability of response to treatment may be of paramount interest in clinical practice."

In this single sentence, Hogben and Sim defined the fundamental basis of Biosocial Medicine, the critical importance of both biology (nature) and biography (nurture), and the central role of human variation in the practice of medicine. It is particularly noteworthy to recognize the nature and nurture reference that was mentioned in this paper. Previously, no attention was paid to the non-biological influences on treatment response. But Hogben and Sim did not stop at this profound challenge in improving clinical care. They went further recognizing that their approach would be disparaged for lacking the statistical precision that would be achievable in a large study where group averages could be calculated and compared. They wrote the following:

"If, as we so often hear, statistics is the science of the averages, …the statistician has a special claim to our attention when the end in view is to record averages, as is true of demographic studies and administrative inquiries which do not concern themselves with individuals as such; but it is for the biologist and the clinician themselves to decide whether the average can be a satisfactory answer to questions they ask about the individual organism." (Hogben and Sim, 1953).

The observation that Hogben and Sim made regarding evidence for the care of the individual patient, and the inadequacies of RCTs, is similar to the concerns raised by Bradford Hill and later Tukey. We do not wish to discard the hard-earned advances in clinical therapeutics that have occurred as a result of the application of population level clinical trials. But we also cannot ignore the limits of those data to the care of the patient at hand. What we can do is to further develop and refine the conduct of N of 1 trials pioneered by Hogben and Sim and make them better suited to current clinical science and practice.

N of 1 trials formalize clinical practice. As currently practiced, the N-of-1 trial is a randomized crossover trial in a single patient. The goal of the N-of-1 trial is to determine the best intervention for an individual patient using data-driven evidence. A frequently mentioned advantage of these trials is that they leverage study design and statistical techniques commonly employed in group-based randomized controlled trials. N-of-1 trials have been popular in educational settings, but have been used sparingly in medicine (Schork, 2015).

N-of-1 trials have been disparaged in part because they frequently lack generalizability. N-of-1 trials that focus exclusively on the individual patient are relevant to the care of patients in clinical practice, but are less likely to create a database that supports the use of an intervention in other patients unless the trials are repeated often to build a library of clinical experience.

12. Biography and the foundation of trust in medical practice

"It is the province of knowledge to speak, and it is the privilege of wisdom to listen." With those words, Oliver Wendell Holmes, Sr. encapsulated the two-horse problem that John Tukey articulated in his Science paper in 1977. Knowledge comes in one form from the carefully curated studies that generate one type of evidence base for clinical medicine. Wisdom comes from a different evidence base for Medicine that is accumulated from the irreplaceable experience of being present with patients, both well patients in the clinic and sick patients in the hospital.

Yet, there is a deluge of papers and testimonials from patients and physicians alike that physicians are not present with their patients and are not acquiring the wisdom embodied in the famous quote by Francis Peabody, "The secret to the care of the patient is caring for the patient." (Peabody, 1927).

No medical student or medical resident strives to enter the profession of Medicine hoping to spend 6 h of their 8–10 h in the hospital each day in front of a computer checking data and entering more data into the electronic medical record of the patient. Yet, numerous surveys document that is the experience of many of our trainees.

A neglected role for biography is its importance in building trust between the patient and physician even as we enrich the experience of physicians who practice medicine. Empowering patients is a major, albeit undervalued, component to most effective medical and psychological treatments. If patients believe that they have no role in getting better, and that their health outcomes will be determined by their medical treatments, they will experience an increase in loss of control and learned helplessness.

Biography, the parts of the patient's life that is directly relevant to their care, can only come from being present with the patient in the messy process that is so characteristic of clinical care. The 72 year-old man sitting in front of us with heart failure is different from the 72 year-old man with heart failure waiting to see the physician next. They each have rich stories that are completely different yet those stories will directly affect the treatment and outcome of their disease. One patient will have repeated episodes of heart failure because he lacks the funds to purchase his medicine; the other may have a stressful job that causes poorly controlled hypertension and repeated episodes of flash pulmonary edema.

The loss of trust in Medicine has been studied extensively, especially since the debacle of the Tuskegee Syphilis Study and its violations of the medical principle to always put the well-being of individual patients ahead of competing considerations (Brandt, 1978). The erosion of trust has been growing, however, as physicians navigate a complex medical business environment in which health systems often put economic considerations ahead of patient concerns.

If we consider Medicine as a profession built on trust, then biography becomes an essential element of the trusting relationship between patient and physician. We do not believe that the physician can reliably fulfill these conditions of a trust-based profession without a suitable understanding of the patient's biography. Lived experience, with all of its inspiration and indignity, does more than just determine disease risk and treatment response. Lived experience, as appreciated by the physician, can create the bond of trust that is fundamental to practice. Extensive research establishes that trust in the healer is essential to healing itself (Birkhäuer, Gaab, & Kossowsky, 2017). Yet there are many forces working to undermine that trust.

An important factor that makes trust in physicians more difficult to achieve is the extraordinary role of technology in Medicine. Previously, it was the patient's story that was the basis for understanding the patient's illness, augmented by information from the clinical examination. Now it is not just the technology of the laboratory and imaging tests, but also the information technologies that create electronic medical records that distract the physician's gaze away from the patient and to the machine. The patient knows when the physician is more focused on the computer screen than on their personal story.

13. Concluding comments

In its December 5, 2019 issue, just weeks before the emergence of the Coronavirus pandemic, Nature Medicine asked 11 experts to imagine the future of Medicine. Perhaps unsurprisingly, the experts saw the world through the lens of genomics and computational advances. Representative comments were as follows: "For many years, biology and disease appeared "too big" to tackle on a broad scale … But now we are on the cusp of an inflection point, where the bigness of biomedicine turns into an advantage."; "By using precision medicine technologies, genetic vulnerabilities to chronic and deadly diseases at the individual level can now be identified …". One expert anticipated a cataclysmic global pandemic, but called out advances in genomics and information sciences as capable of transforming our fight against viral threats. The patient's biography was nowhere to be found (Looking forward 25 years:, 2019).

Not a single expert could imagine that in just a few weeks, the most effective weapon we would have in the fight against a global pandemic would be social distancing and mask wearing. No one could anticipate that the greatest threat to our efforts to control the pandemic would be misinformation and a disregard for truth. Even while science has achieved a notable triumph in the rapid development of a vaccine that is highly protective against the constantly mutating virus, it remains behavioral and cognitive interventions that are essential to the control of the epidemic. Biography, the patient's lived experience, was not mentioned by a single expert even though biography is core to the successful implementation of vaccination and mask-wearing.

Our paper benefitted greatly from several insightful, anonymous reviews. One of the reviewers, after reflecting on our argument for the better integration of biology and biography, wrote a trenchant commentary. The reviewer asked, "How do we use this to shape the next generation of providers and scientists. We are already training physicians in listening and communications skills, cultural humility, shared

decision making, and the social determinants of health as it relates to individual experience, among others. We routinely have medical students visit patients in the community or their homes to see how they live and interact with their environments. And we combine these doctoring skills with the latest in clinical treatments and technology. "

We acknowledge these and other programs that have been introduced into the doctoring curriculum of our medical schools and training programs. Yet, the compelling strength of these programs expose their more compelling weakness. Too much of the focus on the "biography" of the patient is assigned to the "Art of Medicine" when what is needed is to treat biography as an essential component of the "Science of Medicine". Our patients' biography (lived experiences) is part of their biology and the effect of each on the other accounts for the expression of health and disease at the level of the individual. Our vision is for a Biosocial Medicine that is rooted in a new science of human experience that is the foundation for the tailored care of the individual patient.

It is important to point out that this new science of human experience is not equivalent to counting life events or to identifying sources of social support. Life events such as divorce, or job loss, may be experienced differently by different people. For some, the loss of a job might be experienced as a devastating event that leads to economic distress; for others, the experience may be construed as an opportunity to develop a new career. *What is needed is a new approach to a person's biography that links the perception of lived experience to a rigorous integration with individual biology.* Much new work is required to develop the best strategies for collecting these data and understanding how to incorporate the information into meaningful analyses that are linked to clinical management.

Biosocial Medicine is not intended to make physicians culturally sensitive or humanistic, although both developments would be welcome. Biosocial Medicine is intended to improve the practice of medicine, in disease etiology, diagnosis, prediction of clinical course and response to treatment. Medical research needs evidence generation that includes both biography and biology, just as medical practice needs both. If a clinical scientist does not include biography in the design, analysis, and implementation of research, and if a clinical trialist continues to ignore biography in testing new medicines or devices, we will fail to generate the evidence base essential to a Biosocial Medicine tailored to the individual patient. If a physician does not ask a patient with new onset asthma about her work environment, the physician may miss airways disease caused by a toxic exposure. If a physician does not ask a patient with resistant hypertension about her stress at home, the physician may miss the opportunity to improve her outcome of treatment.

Ever since the initiative to sequence the human genome that resulted in a spectacular success of human ingenuity, there has been a rush to understand the biology of individual difference. What is needed now, however, is a complementary process, the biography of individual differences, that integrates completely with biological measurement.

No one denies that the scientific advances of the past decade herald new advances that are beyond our ability to imagine. The challenge for medical practice is to balance advances in biological science with advances in social science and that transforms the care of patients. Biosocial Medicine, with its emphasis on biology and biography, offers a future for medicine that can make the care of individual patients transformative.

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