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THOUGHT PROVOKING IDEAS OF THE GLOBAL ESSAY COMPETITION 2022

Addiction in these terms: a new social contract to heal what medicine harms

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Introduction

Losses of human life resulting from drug overdose continue to climb to new maxima in the US, fueled by increased prescribing and use since the late 1990s of analgesic opioids, "a class of drugs that include the illegal drug heroin, synthetic opioids such as fentanyl," and those "available legally by prescription."1,2 Drug overdose deaths "experienced disproportionately among the young" cost "Americans about 3.5 million years of life," in 2020, a year that set multiple records including "the most drug overdose deaths" and "the most deaths from opioid overdoses."3 Among the mortality data used for these analyses, you'll find the February entry for my friend Paul, to whom I dedicate this writing.

The opioid epidemic is often framed as a time-stamped phenomenon, as *having been* a preventable national crisis despite its ongoing time-course and international reach.4,5 To me, it exposes a broader collapse of intergenerational fairness that extends beyond any one nation or drug class. In this essay, I first define drug addiction in terms of justice and introduce epigenetic inheritance as an emerging transgenerational agent while addressing current challenges faced. I then posit solutions constituting a new social contract between present and future generations that prioritizes intergenerational bio-social justice and populist science.

Generational addiction

"Impaired self-control" is a "core clinical symptom" of drug addiction, marked by durable changes in brain circuits underlying normal patterns of human impulse and reward.6 Individuals in active addiction experience "loss of control in drug intake" and continue drug self-administration despite experienced harms.7 The rational psyche collapses as substance replaces self-preservation. It follows that addiction opposes Rawlsian justice by depleting requisite human goods.

Pendlebury defends individual autonomy as a basic Rawlsian good "for which human beings have a deeply rooted, natural drive," and by which I would have us evaluate justice today.8 We can also apply Rawls' fundamental condition of self-respect as "confidence in one's ability, so far as it is within one's power, to fulfill one's intentions."9 Since loss of self-control opposes both autonomy and self-respect, sources of addiction undermine the fundamental human goods, or rights, required of free societies through time.

Though addiction, even if unjust, is not itself time dependent, novelty is precisely defined as not having existed before now. It is at the intersection of these terms where unjust addiction becomes generational. Novel addictive agents, including those produced by modification or combination of existing compounds, result from technological and intellectual advancements unique to the generations that enable them – so too is any prevalent addiction that follows. For example, Purdue Pharma's extended-release oxycodone formulation was introduced to the public in 1995 and, thus, was not a source of addiction for individuals of generations prior.10 Only of then and thereafter.

So, an intergenerational social contract maintains fair and complete jurisdiction here given (1) the direct opposition of addiction to basic human goods – Pendlebury's autonomy and Rawls' self-respect
– via self-control's elimination, and (2) the introduction of new addictive compounds to society as a generational phenomenon.

With transgenerational potential

As our understanding of human genetics increases, so does the recognized potential for behaviors like drug use to have transgenerational impacts via epigenetic mechanisms, or "changes in gene function that are heritable and that are not attributed to alterations of the DNA sequence."11 Essentially, chronic drug exposure can cause chemical changes to a person's *epi*genome, a summation of "epigenetic marks" *atop* or *near* the underlying DNA code.11 If these changes occur in gamete cells, egg or sperm any offspring subsequent their fusion can inherit them.11,12 The result? Biological transmission of parental behavior in one generation to their offspring in the next.

While the impact(s) of parental drug consumption on the epigenome and downstream functional outcomes of their offspring have not been directly assessed in humans, animal studies suggest it is consequential by demonstrating "parental morphine exposure" in rodents could alter offspring "locomotor activity," "morphine tolerance," and "anxiety-like behaviors" with effects on "drug seeking behavior" and "drug tolerance" observed even in the succeeding generation, or the offspring's offspring.12 In review of these findings, Thomas and colleagues of the University of Lausanne addressed their implications directly: "transgenerational effects following drug exposure before pregnancy might generate considerable long-term consequences in the population."12 If so, this would constitute an anterograde, transgenerational unfairness resulting from one current where biological inheritance transmits unjust addiction.

Current challenges

State and regional regulatory agencies (Figure 1, below) serve the public by limiting the availability of novel therapies where research demonstrates more harm than clinical benefit.13 To my knowledge, no such agency uses addictive potential for the absolute evaluation – approval versus rejection – of new drugs; rather, addiction's appraisal remains limited to labeling and indication despite causing harm on an epidemic scale. Additionally, these local regulatory bodies increase the international availability of any drugs they approve by

default, particularly if these agents can be redirected for profit. The natural history of fentanyl highlights the global reach an addictive drug can have over its life course; from its creation by Dr. Paul Janssen of Belgium in 1960 and initial dissemination through Western Europe, to its regulation in 2019 by the People's Republic of China in an effort to limit the drug's export into American syringes.14,15

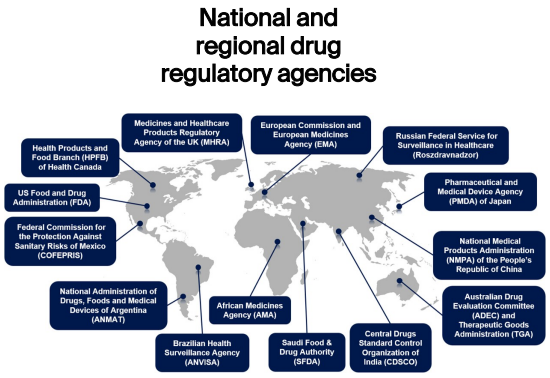

Figure 1: Example drug regulatory bodies of the world. Blank world map from Wikimedia Commons.

Aims to standardize drug regulation and quality globally include the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), though this forum has no enforcement arm.16 Further, the ICH's silence on addictive drug appraisal is unsurprising since it is governed by constituent state groups like the US Food and Drug Administration (FDA), which continued to sponsor new opioid drugs throughout 2021.17 The FDA's contributions to the US opioid epidemic – both its onset and maintenance – have been outlined extensively.10 I will not propose a new intergenerational contract that depends on such agencies for its fulfillment and call it just. The time for demonstrable reform has expired.

The scientific community, on the other hand, stands to serve intergenerational justice as a means to identify and understand the biological processes that shape its course. For example, if we are to increase our understanding of epigenetic inheritance as an intergenerational vehicle for in/justice related to addiction, it will have to be through research, specifically in the human life sciences.

However, this institution grows more compromised by drug profit-related interests each year as research collaborations between academic institutions and pharmaceutical companies regarding their own drug candidates continue to increase (Figure 2, right).18

While these relationships do not assume bias, execution and reporting of drug trial studies sponsored by industry tend to favor product.19 "Simply put, a scientific endeavor that is not trusted by the public cannot adequately contribute to society and will be diminished as a result."20 The following contract addresses these regulatory and interest-related challenges.

A new contract

Medical innovation should not beget epidemic mortality as scientific discovery should not beget social injustice.

To protect and maintain the basic human goods required for justice globally, we should prevent the introduction of novel drugs with high addictive potential to society at large and prioritize our understanding of biological processes that transmit social in/justice across generations. To do so requires the restructuring of human drug policy towards a global centralized body that shares this contract's mission and dedication of scientific communities to the human condition. Taken together, the aims of this contract promote intergenerational bio-social justice. I envisage specific executions of this contract by mid-century below.

A Global Medicines Authority (GMA) for Human Safety and Bio-social Justice

State-based drug regulation and related agencies are replaced by the GMA, combining an enforcement capacity equal to its regional predecessors with an international governing structure based on that of the World Health Organization.

By this scheme, drug candidates undergo initial review at regional GMA centers of Africa, the Americas, Eastern Mediterranean, Europe, South East Asia, and Western Pacific, determined by the drug sponsor's primary operating location. Results and recommendations from initial reviews are taken up by specialized boards populated with basic scientists and medical professionals from GMA member states for secondary and then final evaluation at at a central GMA site with additional recommendations from bio-social justice scholars.

In opposition to current norms and practices, GMA officials have no drug industry appointments and undergo annual review for conflicts of interest.

Importantly, the scoring of harm of candidate drugs against their clinical benefits is based on mandated measurements of addictive potential in addition to historical assessments of physical safety. The former requires measuring and reporting parameters of addictive potential during the pre-clinical and clinical trial study stages. Results are translated into an addictive potential score that dictates absolute drug evaluation. An example scheme is provided in Figure 3 to the right.

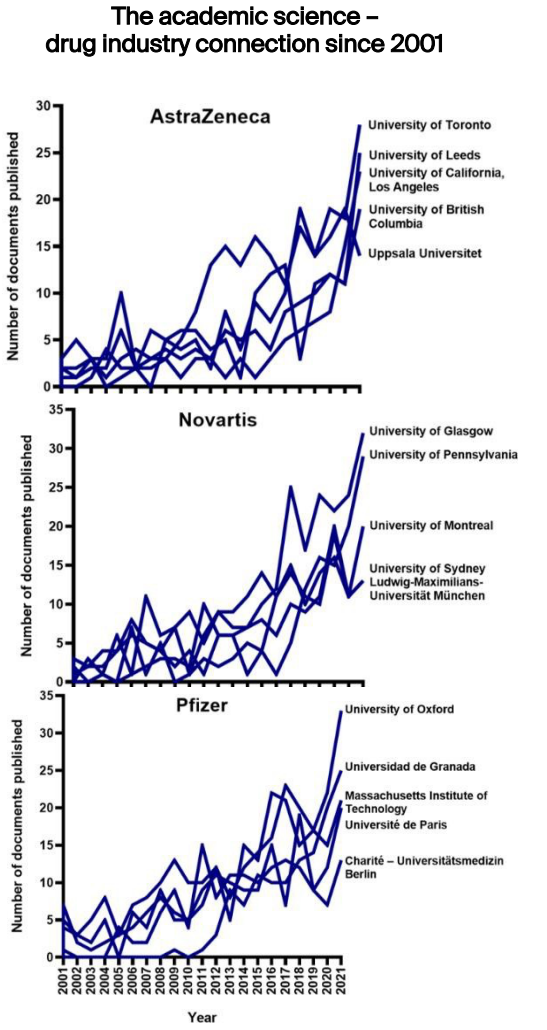

Figure 2: Research outputs with authorships reflecting collaborations between three major pharmaceutical companies (center title) and fifteen universities/academic medical centers (listed to right) since 2001 using Scopus

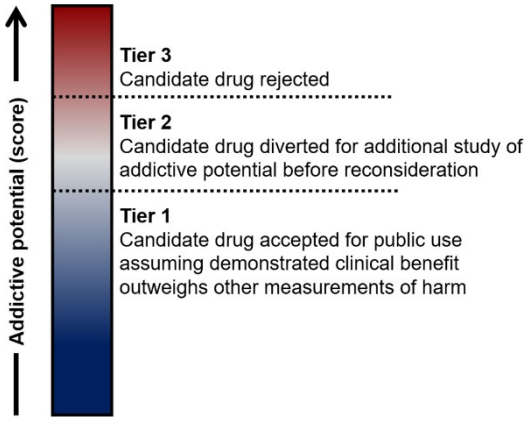

Figure 3: Example drug evalutation model for carrying out new social contract.

Populist science

International centers of scientific research are founded with a core mission to:

I. investigate agents of bio-social justice and its transmission between generations to improve the human condition,
II. free of other interests including those for profit while,
III. maintaining public trust and engagement in these pursuits.

Institutes first recruit senior talent across human medical and life science subdisciplines into faculty- level research positions with decade-term funding where at least 15% of these appointments are dedicated to direct study of human epigenetic inheritance and the remainder to bio-social justice aims in general. Appointments require acceptance of a mission contract maintaining individual intellectual property ownership rights but releasing any claims to profit that would otherwise result from their research endeavors. Trainee recruitment begins after investigator appointments are announced as visibility and public relations (PR) act to prioritize civic engagement from the start.

Thus, such institutes begin with founding generations of mentors and trainees dedicated to scientific discovery for society's betterment or populist science. The intentional norm-busting institutional economies eliminate pressures to produce for the sake of continued funding and needs for outside sponsorship. Given successful recruitment of these parties and public visibility, institutes directly oppose existing norms in academic medicine and research as alternative training sites. At the same time, PR campaigns focus on public citizens' perception of these institutes as merited, trustworthy communities that communicate with them directly and serve their interests. The relationship is mutually beneficial.

Limitations and intended impacts

Opponents to reforms and related operational changes required of drug developers by these aims may cite potential negative impacts of regulation on innovation as companies fear long-term investment losses from late-stage rejections. Fortunately, performing addictive potential measurements at pre-clinical stages of development informs stakeholders to end or proceed study of candidate compounds early in the investment timeline to mitigate these kinds of losses; not to mention, measuring drug-and addiction-related behaviors in animal models are commonplace experiments in many laboratories and can be contracted out if not implemented in-house. Public grants can even supplement or replace industry payments to independent third-party laboratories that take up these efforts.

On the topic of financing, how might the agencies founded by this contract be funded initially? GSA member state or region contributions can be derived from the annual budgets allotted to their pre- existing regulatory bodies over the decade prior, where a member's yearly contribution should be greater than or equal to this ten-year average. Further, membership incentives like standardized drug cost capping should offset local restructuring expenditures. Since this contract may benefit member states with developing manufacturing and regulatory infrastructures the most, it should also attract support from agencies dedicated to equitable drug quality and access across nations.

Whereas the GSA primarily relies on governmental funding, populist science institutes should attract mission-oriented philanthropic donors and non-governmental organization partnerships. Eventually the broader impacts of these institutions, if successful, will change science funding and research priorities to favor their own endurance and that of others who adopt their

founding mission. Over time, populist science as an alternative to current academic research-training program cultures can become the model preferred by citizen and scientist. Accomplishment of this intended norm shift should change the way science is supported and communicated to favor the societal impact over quantity of research output, access over paywall, and the intergenerational mentor-mentee relationship over each party's former self-interests.

Final remarks

Though this contract begins with addiction as its primary motivation, it also evaluates scientific innovation as an institution in terms of intergenerational justice. I believe merging these forums will undoubtedly serve both. More importantly, it will serve humanity

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