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Tackling the Unknown: Medical Semiotics of Inflammation and their Legal-Epistemological Boundaries in Brazil

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ABSTRACT

Do different medico-scientific understandings of autoimmune inflammation, whose carriers disobediently promote the therapeutic use of immunostimulants, have the potential to destabilize the hegemony of the standard palliative treatment based on immunosuppression? Here I explore whether and how medical paradigms in Brazil develop and expand around immunopathologies through practices of exclusion and inclusion in the context of global circulation of knowledges, therapies, and regulatory frameworks. While focusing on concurrent immunotherapeutic models *within* biomedicine, I discuss aspects of legal-epistemological frictions that animate controversies in which distinct ways of co-producing medical evidence affect and are affected by the biomedical establishment.

RESUMO

Será que diferentes entendimentos médico-científicos a respeito de inflamações autoimunes, cujos porta-vozes promovem desobedientemente o uso terapêutico de imunoestimulantes, têm o potencial de desestabilizar a hegemonia do tratamento paliativo padrão baseado na imunossupressão? Neste artigo, exploro se e como os paradigmas médicos no Brasil se desenvolvem e se expandem em torno de imunopatologias através de práticas de exclusão e inclusão no contexto da circulação global de conhecimentos, terapias e diretrizes regulatórias. Ao focar em modelos imunoterapêuticos concorrentes *dentro* do campo da biomedicina, discuto aspectos de fricções jurídico-epistemológicas que animam controvérsias nas quais formas distintas de coprodução de evidências médicas afetam e são afetadas pelas elites biomédicas.

KEYWORDS

Biotechnological innovations; Brazil; immunotherapies; legal-epistemological boundaries; medical semiotics; regenerative medicine; regulatory science

Autoimmune diseases are among the greatest causes of disability in the world. An autoimmune disorder is normally characterized as the immune system's loss of capacity to distinguish between healthy cells (self) and antigen (non-self) and the consequent self-destruction of one's own tissue. Immunologists and physicians in general, notably rheumatologists as clinical experts, sometimes encounter difficulties in providing unambiguous diagnoses of an indefinite number of immunopathologies, including arthritis, lupus, diabetes, and multiple sclerosis. While inflammation, often followed by pain, remains a common medical sign, the symptoms of such diseases sometimes overlap (Delves et al. 2017 [1971]). Their clinical course is unpredictable and their causes remain mostly unknown. Despite that, autoimmune diseases officially do not have a cure and are seen by global biomedical authorities as chronic. Consequently, physicians normally advise patients that they must learn to live

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with their condition. However, there is disagreement amongst physicians, medical scientists, and other health professionals about the cause and treatment of autoimmune phenomena, with some questioning the standard palliative therapies based on immunosuppression to relieve autoimmune symptoms (e.g. Chandrashekara 2012; CRC 1160 IMPATH 2021; Ludwig et al. 2017). Given that, do different medico-scientific understandings of autoimmune inflammation, particularly those whose carriers disobediently promote the therapeutic use of immunostimulants, have the potential to destabilize the hegemonic use of immunosuppressants?

In this article, I report on findings about whether and how distinct medical semiotics in Brazil develop and expand around immunopathologies through practices of exclusion and inclusion in the context of global circulation of knowledge, therapies, and regulatory frameworks. I focus on practices and knowledges related to competing immunotherapeutic models *within* allopathic medicine (or biomedicine). I discuss aspects of legal-epistemological frictions that animate controversies in which distinct practices among medico-scientific professionals, including the co-production of valid medical evidence (Jasanoff 2004), affect and are affected by the biomedical establishment.

The present analysis is part of a broader project that seeks to understand how medico-legal regimes are negotiated in Brazil, as some physicians and patients advocate that immunostimulant therapies offer a promissory biomedical future for the treatment of immunopathologies. I analyze the legal difficulties that stand in the way of immunostimulant therapies becoming authorized by Brazilian regulatory institutions and which stand in clear contrast to the legal status of conventional immunosuppressive therapies. In doing so, I situate related controversies, mainly from the perspective of the users of immunostimulants as parts of the debate on what counts as proof in science and medicine, and for whom.

My main case study comprises the controversy around the "anti-brucellic vaccine" (VAB), a biotechnological promise for the treatment of autoimmune diseases such as arthritis and ankylosing spondylitis. VAB is an immunostimulant drug used since the 1980s, which the Brazilian Health Regulatory Agency (ANVISA) prohibited in 2005. In the 10 years after VAB prohibition, its regulatory status changed back and forth. It eventually become available again under new labels as a "manipulated medicament;" i.e., as legally produced and commercialized for individual use on a small scale without needing to be registered with ANVISA, and available from manipulation pharmacies with a prescription. Originally designed to become a pharmaceutical before the Evidence Based Medicine movement found its way in Brazil, VAB nowadays has a status comparable to that of homeopathic drugs. VAB's path is not exceptional.

As I learned, in order for new drugs to be legally authorized as biotechnological innovation, and therefore as pharmaceuticals that can be produced and commercialized at a large scale, they must first be subject to a set of researches, clinical trials, and meet standards of safety and efficacy. If, for any reason, they are impeded of moving throughout this regulatory path, then they can be either abandoned or circulated outside of established biomedicine. Thus, these disallowed *moléculas*, as medico-scientists might call them before they receive some drug status, can move between and through diverse bodies (scientific research, laboratories, medical and academic institutions, intellectual property offices, regulatory agencies, and the shadow medical economy) and instead of becoming "active pharmaceutical ingredients" (ANVISA 2022:168) become food supplements, phytotherapic compounds, natural products, manipulated drugs, or cosmetic treatments. As my preliminary conclusions suggest, through whichever paths of circulation, the future of such unauthorized biotechnologies depends on previous informal acceptance during their experimental stage, support outside regulatory science, and on its capacity to be reincorporated into other drug categories (Gardner et al. 2017).

These preconditions are also provided by what Margaret Sleeboom-Faulkner calls *life assemblages*. I.e, communities and/or networks whose members "share questions related to the definition of what is 'a life worth living' [and] mind-sets that assume moral change toward life as inevitable and experience the transgression of ethical boundaries as a normal result of developments in science and technology" (Sleeboom-Faulkner 2014:2). Correspondingly, I consider nonscientific collaborative activities,

conducted by and among a plurality of actors (stakeholders, market agents, patient groups, biochemical actants, and media) which "underpin the scientific ones" to be *bionetworking practices* (Sleeboom-Faulkner 2014:160). By paying attention to them, I have been able to understand the making of biomedical worlds and the rise of contemporary forms of bio-governance. The delineation of medical semiotics is crucial for this task.

Medical semiotics and semiotization

Referring mainly to the making of medicine in the interwar period, Ilana Löwy states

> Doctors who grapple with complicated, multi-layered and slippery pathological phenomena tend to tinker with the conceptual and technical resources at hand, and are more often guided by ad hoc considerations than by a drive for theoretical coherence. Indeterminacy, boundary concepts, and practices are therefore essential elements in medicine. Medicine works as a scientific approach, a socio-cultural system, a profession, and an institution *because* it is heterogenic, and because it provides multiple, and partly incommensurable, interpretative frameworks. (Löwy 2008:172, italics in original)

Inspired by this and by views of materials and signs as co-extensive (e.g. Williams 2005 [1980], Law 2019), I conceive medical semiotics throughout this article as a heuristic tool. I use it to refer to the set of instrumentalizable resources with communicative capacities that medical professionals mobilize to make sense of and to manipulate the complex realities they encounter. These instrumentalizable resources in turn co-shape their users as adherents of medico-scientific collectives maintained and/or expanded around common premises and proceedings as distinct from other collectives.

Conceptually, these medico-scientific collectives and/or networks and their common principles resemble what Ludwik Fleck called respectively "thought collectives" and "thought styles" (Fleck 1979 [1935]), which gravitate toward each other:

> If we define "thought collective" as *a community of persons mutually exchanging ideas or maintaining intellectual interaction, we will find by implication that it also provides the special "carrier" for the historical development of any field of thought, as well as for the given stock of knowledge and level of culture. This we have designated thought style*. The thought collective thus supplies the missing component (Fleck 1979 [1935]):39, italics in original)

In medicine, thought styles and thought collectives seem to evolve through material semiotics that, by acting simultaneously as their means of exchange and as what they exchange, materially and symbolically realize their worlds, while holding them together as a *whole*. In other words, medical semiotics dialectically enable the unfolding, reproduction, and actualization of thought styles (ideas) and corresponding collectives (people) by acting as the stuff out of which their respective shared world comes into being (materials and symbols).

As I see it, the potential elements that make up medical semiotics only become co-constitutive parts of them after having been taken from somewhere else and subsequently transposed into the flow of a given ongoing medical inquiry by those networked professionals engaged in tackling the latter as a legitimate medical problem. I call this process *semiotization*. In principle, these co-opted resources can comprise virtually anything ranging from organisms and their parts, remembrances and/or stories, peers, concepts, institutions, habits, funds, technologies, skills, and mood dispositions. While the ways they are (re)arranged are co-affected by outside actors, selectivity is crucial for involved adherents. Here ignorance comes into play as a key practice that helps to actualize and reinforce a thought style and collective.

As a generative part of medical semiotics, ignorance excludes virtually the same instrumentalizable resources which might make out medical semiotics (including colleagues, interactions, technologies, ideas, and words). "As a semiotic material entity in its own right," Katharina Paul and Christian Haddad explain, "ignorance should be considered a part, conceptually and methodologically, of what we discern with Foucault as the 'regime of truth' that underpin social, political and policy processes broadly understood" (Paul and Haddad 2019:303). Tabooing implies world-building ignorance (Bargatzky 2007:282) as certain topics cannot be spoken of, and questions and contradictions that

might threaten the coherence of a thought style are left unaddressed. In this sense, the medical semiotics of one thought collective come into being as much through converging forces as they do through drawing up boundaries between them and competing collectives. I.e., others (including equals) which question their principles and, therefore, their legitimacy as medical endeavors.

Fieldwork and analysis

Partially inspired by Actor-Network-Theory, I have been following VAB and other contested immunotherapies in Brazil and associated biopolitical artifacts through participant observation, autoethnography, digital methods, and archive research, since 2009. In that year, after having been diagnosed with psoriatic arthritis, I entered the world of immunosuppressants while living in North Europe and then shifted to that of immunostimulants users during fieldwork in Brazil. Following a successful therapeutic experience through immunostimulation,[1] I decided to research the ongoing disputes between these two therapeutic models, framed as such by medico-scientific interlocutors in Brazil, as a personal, anthropological, and public health issue. Since then, I have explored how unauthorized biotechnological innovations circulate throughout society, affecting different parts of it while being co-regulated by a plurality of actors who often remain invisible to established biomedicine.

I began meeting VAB users and health professionals, including scientists, in several Brazilian cities. Some VAB assemblages are formed at the local or intraregional level around those who provide it. Most importantly, I managed to establish and maintain close relationships with those directly responsible for the development, production, promotion, and distribution of VAB. In addition to the field access I gained due to my status as a former patient and client, I became more involved in further physical and virtual networks of immunostimulants supporters, accompanying them over the years. To address VAB in its own complexity (Hine 2007) my research became multi-sited. It explores multiple and interconnected VAB-related locations distributed in space and time, including online. My different interlocutors are not necessarily aware of each other. However, against the background of immunosuppression as standard treatment, immunostimulants' users bionetwork and are bionetworked through VAB and/or other immunostimulants as innovative biotechnologies.

Through an analysis of VAB users' narratives about their therapeutic-regulatory experiences and bionetworking practices, I re-trace associations and map key relations that have constituted VAB as a traveling biotechnology, and as an object of legal dispute. I systematize and integrate this material using constructivist Grounded Theory to identify actors and networks involved in related controversies, and to learn how they conceptualize their respective realities. While paying attention to how the shared experiences and responses of immunostimulants' users co-constitute a particular biotechnological and immunological culture, and to my observations of their bionetworking practices, I combine historical reconstitutions of the development and circulation of immunotherapies and juridical analyses of their legal-epistemological constraints.

In this article, I approach one crucial element that, in my opinion, preconditions the therapeutic and legal experiences of participants in immunostimulant life assemblages: the medical semiotics that support medico-scientists alongside associated biotechnologies. For this reason, I here use a minimal part of the empirical material co-produced through my broader research, mainly in Brazil's southeastern region, a hub of industry, biotechnology innovation, and medico-scientific institutions.

The health professionals directly involved with VAB and other immunostimulant therapies who participated in this research comprise physicians at private offices and public hospitals, medico-scientists at public universities and private laboratories and clinics, and other health professionals such as pharmacists and nurses. Most of the research participants are over 50 years old, have established careers, belong to the middle or upper-middle classes, and live with relative financial stability. Despite the many differences between research participants and the highly heterogeneous therapeutic landscape in Brazil, most of them share three characteristics: they have extensive biomedical education and experience; are critical of immunosuppression as standard approach to treat

immunopathologies; and instead use unconventional therapies, many of which are immunostimulants, to treat people diagnosed with immunopathologies.

I discuss my findings in three sections. In the first, I describe how contemporary established biomedicine conceives and deals with autoimmune diseases, mainly with rheumatoid arthritis (RA) and consider how different biomedical approaches to autoimmune diseases evolved historically and culturally. In particular, I examine the implications of the hegemonic idea that the immune system can provoke immunopathologies, and its associated medical semiotic, which co-constitutes patients as self-destructive bodies/persons whose overreactive immune response must be suppressed to control their autoimmune symptoms. With it, I highlight tensions between biomedical views of immunity as a disease-causative agent and, as we will see, immunity as a mediator between multiple entities.

In the second, I delve into VAB and apitherapy as two local unconventional therapies used to treat RA through immunostimulation contrary to globally established standard therapies. The related medical semiotic renders patients' immunity as capable of self-regulation, and as becoming dysfunctional when it is weakened. I emphasize how regulatory authorities find the idea of immunostimulation to be inconceivable and suggest that this explains why they have not legitimized this mode of treatment, despite the fact that they have been developed by biomedical actors. Finally, I summarize central aspects of these controversies in light of the struggles for therapeutic legitimacy.

Inflammation as sign of autoimmune-overreactivity

Trying to control RA through immunosuppression

In 2017, on a television program in Brazil, which now circulates on the Internet, rheumatologist Rezende stated RA "is an autoimmune disease." He went on to explain,

> This means that the organism itself is generating that inflammatory reaction. We have a defense mechanism, which is the immune system. It serves to fight bacteria [and] viruses that try to invade the body. When there is a deregulation of this immune system, it can attack the joints. So, [RA] is a disease in which *the body itself is generating an aggression*. Normally, against the joints of the hands, feet [etc.] [My emphasis]

Another rheumatologist, Santos, a member of the Brazilian Society for Rheumatology (SBR) and university professor, explained that the main cause of RA is "genetic baggage" during an online public lecture (mediated by a patients' organization and sponsored by big pharmaceutical companies in 2021) on medical innovation for RA. He communicated this as a tragedy to his patients by jokily telling them, "There is no one who wants it, there are those who can [have it]." Santos also recognized "environmental factors that also collaborate with [RA]," and cited smoking as capable of causing and worsening RA. When "an altered immune response happens," he asserted, "You start to already have the disease but you still don't have symptoms." The treatment starts "when the symptoms appear."

As Teixeira, another rheumatologist, explained during a similar webinar in 2022,[2] "joint inflammation" is "the main form of presentation" of RA as a state of "chronic inflammatory autoimmune disease," in which "we produce antibodies against components of our body." According to him,

> The main characteristic of rheumatoid arthritis, without a doubt, what should alert doctors and patients from the beginning, is that arthritis does not only cause pain, [and] inflammation, [but] it [also] causes erosion. What is erosion? They are bites on the bone that determine the irreversible loss of movement over time.

Teixeira reminded the audience that RA is a "systemic disease." I.e., "it affects the whole organism or at least several organs: the respiratory system, the lungs, the blood, the peripheral nervous system (so, the compression neuropathies), the vascular system."

Regarding therapeutic possibilities, Rezende explained,

> The treatment has improved a lot in terms of people being able to control this system [. . .] There are a number of remedies that we can use. And the drugs today manage to hold back the disease, prevent progression to deformities and maintain the patient's quality of life. Above all, in the early stages, the patient has a normal life. *These remedies, hence, manage to delay the evolution of the disease. We cannot heal* [i.e., let] the patient go

> without medication. But the goal of the treatment is for him to be fine [by] taking medicine. There are pills, subcutaneous injections, vein injections, different types of treatment. *All with the same objective: the control of the disease.* [My emphases]

Santos, during his 2021 lecture, described how, after receiving the diagnosis, one begins with the "Disease-Modifying Anti-Rheumatic Drugs" (DMARDS), also called "synthetics drugs." Methotrexate (MTX) and Leflunomide are the most important among them. During acute periods, Santos explained, one can additionally prescribe corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). However, their use should be discontinued as soon as possible due to the increased risk of developing cardiovascular diseases, and other side effects. Additionally, changing everyday habits like nutrition and physical activities can help. Simultaneously, Santos asserted, rheumatologists try to monitor and forecast how the disease might develop. Clinical and laboratory information such as age, quantity of joints affected, levels of rheumatoid factor, erosion, anti-cyclic citrullinated peptide, c-reactive protein, and erythrocyte sedimentation rate, and observations of whether and how patients respond to the drugs are useful for this. As Santos said,

> When you, even with treatment, still have four or more inflamed joints, when those metrics to assess activity, and also those questions we ask to see how your life is going, are not adequate from a laboratory point of view [. . .], [then] what does that entail? Erosion, destruction . . . meaning *you* are not well controlled. [My emphasis]

When patients do not respond to DMARDs, Santos affirmed, "anti-TNFs [anti-tumor necrosis factor drugs] were always the first choices." Then, he revealed, "Here begins the therapeutic part:"

> We have a lot of medications today. They're all good . . . I'm not going to say that this one is better than that one, that one is better than this one. No! It varies according to the [patient's] individuality. I'm from the time when we still had Etanercept, Infliximab, and Adalimumab. When one didn't work, I gave another. It didn't work, [then] I gave another one. I'd come back to the first one, [then] the patient would answer.

Explaining through his PowerPoint presentation the workings of anti-TNFs, which belong to the "biologics," Santos pointed to one of the extremities of the drawing of Adalimumab's molecular structure as "the part that catches TNF; [. . .] that one, from Etanercept, is the receptor that TNF binds to; and this one is the part that catches the antibody."

During his talk, Santos also introduced JAK-inhibitors as biotechnological innovations, reporting how they function, their ongoing favorable approval processes and their increasing availability through the Brazilian Unified Healthcare System (SUS), where biologics are readily available through government subsidies. Yet, just like corticosteroids, NSAIDs, DMARDs, and biologics (Buer 2014, 2015, 2017), JAK-inhibitors are also immunosuppressants. After all, as he resumed, "immunosuppression is what rheumatologists mostly do," and "it's obvious that if we had a drug that solved everyone's problem, there wouldn't be reasons for us to continue launching new drugs." Paradoxically, as Santos stated in another talk one year later, biologics and JAK-inhibitors only have a sustainable effect if patients continue to take either MTX or Leflunomide.

What Rezende, Teixeira, and Santos disseminate to patients and lay audiences in Brazil, is the contemporary global rheumatological understanding about what autoimmune diseases are, and how to identify and deal with them. Yet, according to Warwick Anderson and Ian Mackay, the idea of autoimmunity, that one's own immune system can harm oneself, was "almost unthinkable until the 1950s" (Anderson and Mackay 2014:2).

Expanding inflammation as a sign of self-harming

At the turn of the 20th century, as microorganisms were identified as potential causes of health problems, discrediting the Aristotelian theory of *spontaneous generation*, inflammation had become understood, mainly since zoologist Élie Metchnikoff, as a normal defense reaction of one's organism. Complementarily, medico-scientist Paul Ehrlich argued, as part of his *side-chain theory*, that "antibodies" (*Antikörper*) conducted this defense against invading biological agents that he called

"antigens." Ehrlich also proposed the principle of *horror autotoxicus* to refer to one's body tendency to be self-tolerant and, therefore, to not attack itself. This became hegemonic within medical sciences (Tauber and Chernyak 1991).

Nevertheless, mainly from the 1940s, experiments which demonstrated that antibodies generated by one's organism to target antigens were also targeting one's own cells accumulated (Mackay 2010: A255–A257). "Autoantibodies" and "self-antigens," i.e. the dysfunctional activities of antibodies and antigens, were mobilized as proof that autoimmunity was possible. Dethroning the horror autotoxicus premise, persistent inflammations of unknown etiology now became signs of overreactivity or hypersensitivity provoked by autoantibodies through a regulatory failure of one's immunity to distinguish between self and non-self.

According to Warwick Anderson and Ian Mackay,

> Soon after World War II, clinical investigators in North America and Europe *uncovered the autoimmune origins* of systemic lupus erythematosus and rheumatoid arthritis. In the 1950s, various blood disorders and chronic inflammations of thyroid, liver, gut, and kidney also would secure *an autoimmune explanation*, *displacing conjectures about infection or hereditary predisposition and diathesis* (Anderson and Mackay 2014:48). [My emphases]

In contrast to other causal explanations for persisting inflammation, which seek its origin mostly in the interaction between one's body and elements of one's environment, the autoimmune explanation, in its purist variant, situates the origin of autoimmune diseases inside one's body as the starting point of a causal nexus complex and excludes external factors. Consequently, the establishment of autoimmunity as a model of disease causation and its global spread from the Anglosphere "marks a change in contemporary assumptions about the normal human body and its pathologies, as well as a shift in theories of biological individuality and the nature of self" (Anderson and Mackay 2014:48–49).

Indeed, at least two converging historical-cultural changes regarding personhood were occurring during the same period in Western societies: in the life sciences an explanation of disease origins through non-inherited genetics emerged (Creager 2022:481); and in society the individual person became increasingly atomized (Pina-Cabral 2021:9). Apparently, the *genetic self* and the *atomistic person* evolved intertwined with the rise of autoimmunity, helping the latter to gain momentum as a promising paradigm, not to mention possible influences of longue durée conceptions of humans, e.g., as born sinners and inherently evil (Sahlins et al. 1996). Complementarily, in the 1970s, Abdel Omran's theory of the epidemiological transition, in which the main causes of mortality in modern societies had changed from infectious to chronic diseases (then labeled "civilization diseases"), seems also to have developed at the same time as, and possibly in symbiosis with, these changes (McKeown 2009).

With the semiotization of autoimmunity as a loss of capacity to distinguish between self and non-self, a further dissociation occurs: The self is split between one's remaining identifiable self and one's alienated self. Self-harming as potential unfolding of this "new nature of self" extended the military vocabulary to describe battles within people. As David Napier noted, the metaphor "that the body is waging a war with the self" to characterize immunological disorders achieved "an undeniable prevalence" among "health-care professionals and in popular literature" (Napier 1992:185–186). Alongside its psychosociological variants, this metaphor helped to spread the notion of person as capable of self-harm at a biochemical level.

Enacting the established rheumatological rationale, rheumatologists tinker with what might be useful to control the self-destructive body by turning it into an immunocompromised person. By targeting themselves, the same people who presented inflammatory symptoms as a sign of a conflict between their bodies and non-selves, now become, unintentionally, the very cause of their own suffering. In this sense, there is no contradiction when Rezende says that "you" are not well controlled, instead of referring to controlling the disease, when immunosuppressants are not working.

Following a preemptive logic, immunosuppressants palliatively harm the patients' key organs responsible for their immunity (such as the liver through MTX) beforehand to avoid it harming itself; what is anyway expected to occur sooner or later. The goal is the relief of symptoms in the short and mid-term at the cost of side effects that would generally be less severe than the consequences of autoimmunity itself.

Given their numerous side effects, a set of mutually implicated conditions seem to legitimate the use of immunosuppressants to control the self-harming activities of one's own immunity. This includes the absence of an etiological explanation for the patients' autoimmune inflammatory over-reactivity, since this would require from physicians, in principle, a different approach, such as antibiotic treatment associated with immunological enhancement. It also requires the absence of a better therapeutic option, possibly a curative one. The sense of urgency that presses patients and physicians to initiate the treatment immediately to avoid future severe deformities also plays a role. Finally, immunosuppressants are seen as opening the path to promissory innovations and therefore resonate with the ideology of progress. The fulfillment of the promise of a stabilized relief for autoimmune symptoms, i.e., of achieving "remission" (instead of cure), is understood as being conditional on patients remaining on their palliative path.

Diverging from autoimmunity's rationale

Establishing autoimmunity as model of disease causation did not take place without ignoring, according to Dietlinde Goltz (1980), that "Ehrlich did not disallow the formation of autoantibodies, only that they were prevented from acting" (cited in Tauber and Chernyak 1991:166). Corroborating Goltz, Alfred Tauber and Leon Chernyak argue that the "general community of immunologists misinterpreted *horror autotoxicus* as prohibiting autoantibodies, altogether; that observation in itself is most revealing" (Tauber and Chernyak 1991:166). Anderson and Mackay also mention immunologists who did not embrace autoimmunity as self-caused. Ernest Witebsky, e.g., noted skeptically that "The field of autoimmunization and specifically its clinical application [. . .] seems to have developed rather explosively and I have the feeling that a situation is developing which might be rather confusing and even damaging to the entire concept" (quoted in Anderson and Mackay 2014:67). As Anderson and Mackay go on to say,

> [Autoimmunity as] pathological category continued to expand pragmatically in the 1950s and 1960s, encompassing more and more previously obscure medical conditions. As Witebsky reluctantly concluded, "the term 'immunopathology,' possibly considered by some as a contradiction in itself, [. . .] certainly looms as a new and wide field of investigative endeavor." [ibid.] (Anderson and Mackay 2014:67)

Furthermore, as Anderson and Mackay also registered,

> Some immunologists continued to favor *allergy*, believing it made more sense biologically; for example, Robin Coombs at a Wellcome Trust Witness Seminar in 1995 declared: "I can't bear this use of autoimmunity, and I shall go down fighting it to the end." (Tansey et al. 1997:47 quoted in Anderson and Mackay 2014:175)

In my opinion, the cohesion of autoimmunity as an emergent thought style disputing the hegemony over existing biomedical explanatory causative models apparently benefited from this collective ignorance, which contributed to harmonize the illusions of its enthusiasts, while reducing further ambiguities and tabooing emerging contradictions that could jeopardize its rationale. Paradoxically, e.g., through the "public acknowledgment and consensus on the reality of autoimmunization as an important cause of human disease" (Mackay 2010:A257), inflammation that once was regarded as a symptom of an unknown disease was turned into its very cause with multiple implications.

Yet, concomitantly with the rise of epigenetics, one knows that everybody produces autoantibodies, which are crucial for one's health. The term autoimmunity no longer necessarily designates an immunopathology, although it is occasionally used as its synonym, and a differentiation between healthy autoimmunity and pathological autoimmunity (or autoimmune disease) was introduced.

Correspondingly, what identifies an autoimmune disease is no longer the presence of autoantibodies but rather their quantity and the outcome of their activities (Delves et al. 2017 [1971]:500). Additionally, because different causative agents seem to regain a status as *triggers*, such as infectious diseases and psychosocial factors, there seems to be an increasing tendency to refer to such immunopathologies as "immune-mediated diseases" thus repositioning immunity as mediator.

In Brazil, some medico-scientific professionals have contested the conventional treatments based on immunosuppression, and the assumptions on which they are based. Some of their therapeutic proposals appear not only as incommensurable but also as implying advancements, consciously or not, of biomedical approaches that were left outside the epistemological boundaries that protect the current rheumatological establishment. This seems to be the case with VAB and melittin-based (bee venom) technologies in Brazil, which stimulate one's immunity through nonspecific desensitization with the help of proteins as a way of recuperating homeostasis, just as French and British medico-scientists had done during the interwar period (Löwy 2005, 2008).

Inflammation as a sign of immune-impairment

Trying to heal RA through immunostimulation (with the help of Brucella)

In the beginning of the 1980s, Veiga, a then recently retired Brazilian specialist in treating people with brucellosis, an anthropozoonosis caused by a bacteria genus called Brucella, decided out of boredom, as he told me, to do "a literature review." This included revisiting the results of an experiment on antibody production in rheumatic patients when inoculated with Brucella (Meiselas et al. 1961). After having realized that Brucella's antigenic power could be useful to treat RA, Veiga adapted the medicament Brulise to treat people with immunopathologies.

Brulise, a lysate of Brucella used as vaccinotherapy (i.e. a "curative vaccine" instead of a preventive one), was developed by Veiga in the 1940s, while he was working with his renowned homonymous uncle in the National Plague Service at the Institute Oswaldo Cruz, and registered in the 1950s. However, because most physicians were not trained in diagnosing brucellosis, and the name "Brulise" did not help selling it, officers from the Brazilian National Medicine and Pharmacy Inspection Service (SNFMF) suggested to Veiga to re-label Brulise as "Anti-Brucellic Vaccine," the common denomination for other vaccines against brucellosis. During the succeeding decades, he used VAB both at his private office and at the Brucellosis Clinic at the General Policlinic of Rio de Janeiro, where he worked as a department director.

Shortly before Veiga adapted VAB to treat immunopathologies, immunotherapy was presented in Brazil by Ricardo Veronesi, a renowned infectologist, as the "the therapy of the century" (Veronesi 1976). Capable of treating different illnesses, from cancer and arthritis to infectious diseases, he described three eventually combinable immunotherapeutic strategies: immunosuppression, and specific and nonspecific immunostimulation. As Veronesi programmatically wrote of immunostimulation,

> Regardless of the origin of the immunological "defect," genetic or acquired, transitory or permanent, this individual will be declared at "high risk" and thus a candidate for corrective [nonspecific immunostimulation] therapy (active or passive), lasting as long as the tests indicate the persistence of the "immune defect." Concomitantly, possible prophylactic measures will be taken to move away the probable etiological agents of immunosuppression (psychic *stress*, malnutrition, anemia, toxic drugs, pregnancy, etc.). (Veronesi 1976:199, italics in original)

By echoing interwar period biomedical professionals who advocated for a colloidal approach, Veronesi holistically elaborates immunosuppression as part of "a complex chemico-physico-morphological state" (Fleck 1979 [1935]:63) that is "responsible for the changed mode of reaction" (ibid.). In this sense, immunological deficiency stands between multiple agents and/or stressful situations that might induce it and immunological "defects" that it can co-generate. Noteworthy, instead of denying

infection as a model of disease causation, Veronesi integrates it alongside other potential triggers into a broader and more complex net of exchanges.

Veiga's adaption of VAB followed this approach. His treatment consists in injecting Brucella endoprotein as a nonspecific stimulatory agent in RA patients during two phases. The first, conducted intradermically, enables the gradual immunological desensitization through weekly applications of increasing dosages. The second, applied subcutaneously, consolidates one's immunological response by keeping the same higher dosage for circa one year. The whole therapy takes, on average, between two and three years, which is the estimated time needed for one's damaged immunity to recover.

Soon, VAB began gaining different professional adepts, from psychologists to rheumatologists. In the mid-1980s, physiologist Fernandes heard about VAB when some of his patients began exhibiting unexpected improvements, which they attributed to Veiga's VAB. The two doctors became collaborators, conducting a clinical test with 377 participants, whose positive results they presented at a medical conference in 1991. Following that, Fernandes prepared a randomized clinical trial (RCT) but it did not take place. While Veiga attributed it to high costs and to rheumatologists' resistance, Fernandes told me that money was not the problem but lack of interest instead. Indeed, VAB represented the antithesis of spreading immunosuppressants against which VAB users stand.

When I met Fernandes, in 2021, expressing perplexity, he asked me: "So, the person attacks itself, right?," referring to autoimmunity as a model of disease causation, just to add shortly after, "Does it make any sense at all?" After having acquired extensive education and experience at biomedical institutions (such as public universities and *Santa Casas*), and private medical offices, he refuses to adopt immunosuppressants to treat immunopathologies. Through his search for other treatments, Fernandes became an adept of Linus Pauling and a representative of "biomolecular medicine" (or "orthomolecular" medicine). One of the focuses of biomolecular adepts is to seek to restore the homeostasis of sickened bodies through nutritional supplements. However, some nonaligned physicians consider it to be institutionalized quackery. Approximately 10 years ago, orthomolecular medicine was accused of charlatanism and publicly exposed through TV reportages in Brazil. Moreover, there are internal fissures among its adherents.

Apparently, criticism toward the use of immunosuppressants to treat autoimmune diseases was common among Brazilian old school medico-scientific professionals. Jacques Houli, a patron of Brazilian rheumatology, who in the 1960s conducted therapeutic experiments with cartilage extract and bone marrow to treat RA, argued that

> The use of these drugs [also referring to MTX as an antiblastic agent] is still under evaluation. In general, the serious side effects make the therapeutic medicine an exception. The danger of "dying of cure" makes us not recommend it, unless experimentally and carefully in the current stage of knowledge. (Houli 1973:490)

Veronesi emphasized that one should correctly and opportunely pay attention to the disease's "immunological moment" to avoid "unforgivable mistakes, such as immunosuppression when, in reality, what the patient needs is immunostimulation" (Veronesi 1976:199).

Just as some professionals were skeptical of the use of immunosuppressants to treat what they see as immune-deficiency, the new generation of rheumatologists tended to regard immunostimulation to treat what they see as immunological overreactivity as unthinkable and, nowadays, most do not even utter this possibility. To briefly illustrate VAB users' diverging approaches to inflammation and some related legal-epistemological frictions, I now recount the therapeutic-regulatory experiences of another of Veiga's medical collaborators. Additionally, I conduct a comparative digression by focusing on a similar case involving apitherapy as nonspecific immunostimulant treatment.

"Working with the immune system"

When we met at his office, in October 2021, right after the second COVID-19 wave subsided, Almeida was still exhausted from working on the pandemic frontlines. During decades, since he moved back from Rio de Janeiro, where he conducted his medical residence, he accumulated experience of treating people with autoimmune diseases, including as director of an HIV/AIDS-department. Like Fernandes,

he became an enthusiast and practitioner of chelation therapy, a contested diagnostic practice and major symbol associated with biomolecular medicine.

In Almeida's view, one "can't separate neuro, immune, endocrine, and digestive." Hence, according to him, nutrition plays an important role in autoimmune reactions: "The most important thing is this brain-intestinal connection, because any inflammation, any dysbiosis, any change in the digestive system affects the brain." He claimed that conventional medicine only treats the visible part of the iceberg, while for him "the most important lies below the water, [i.e.,] the cause." For him, "Diseases are, in reality, chronic inflammation. And there you have an arsenal of pathologies. Getting to Alzheimer's, Parkinson's, osteoarthritis, etc. [. . .] All linked to the immune system." That reminded me Veiga, who used to say that, through VAB, "The pain is gone because the inflammation is gone."

Like Veiga, Almeida learned that strengthening one's immunity is crucial to keeping healthy. As he explains, it is not him who is treating the patient's disease. Rather, he stimulates the patient's organism that, in turn, heals itself. Among other reasons, "because the immune system through its aging loses traction, diminishes the production of T lymphocytes." This aligns with Veronesi's and Veiga's rationales regarding immunostimulating approaches to treat immunopathologies. According to Veronesi,

> In an apparent paradox, immunostimulation of the T sector has offered favorable results in the treatment of diseases considered to be autoimmune, such as RA [. . .]. The explanation for such results is given by the inhibitory action of T lymphocytes on B lymphocytes responsible for the formation of autoantibodies. Stimulation of T lymphocytes would accentuate inhibition on B-lymphocytes. (Veronesi 1976:199–200)

Consonantly, Veiga explained that VAB helps the organism's immunological self-regulation by stimulating its self-production of macrophages (hence, increasing one's white blood cells; see Löwy 2005:685–688). Recently, medical scholarship has revealed the *untold* role of macrophages in the activation of T lymphocytes (Guerriero 2019). But not everyone would agree with it.

Following Almeida's continuous use of VAB, troubles arose. After a colleague in his town filed a complaint at the medical board that regulates their profession, "I went through a [disciplinary] process," he said. When he went to the audience at the Regional Medical Council, in which 23 members participated, he showed recorded materials from his patients, including both laypeople and experts, who provided testimonies that corroborated his arguments. As he described it, while speaking in his own defense, he asked during the audience:

> "Is there a rheumatologist here?"
> There were four who were in the first row. They raised their hands. [Then] I said,
> "I'm going to put you just one question: Would you please define rheumatoid arthritis?"
> [. . .] Then one of them turned, [and began to answer]
> "An autoimmune disease. . .," and I said [interrupting the rheumatologist]
> "You can stop there. Ok, my answer is here: I'm working *with* the immune system. But I'm not using steroids. [. . .] I'm trying to avoid using aggressive drugs with terrible side effects."
> [My emphasis]

The audience did not take much longer. After Almeida,

> The rheumatologists said this was totally outside normal standards. Then, suddenly, one [of the members] from the back row said, "Gentlemen, excuse me. My vote for the kid there is yes. I'm going home, he's trying something different, I can see that he has good intentions. . ." Right after him, three or four already started [to do the same]. [. . .] That [went on until] we ended up [with the] rheumatologists, [and] I obtained the victory [with] 19. [votes]

According to Almeida's story, the four votes against his use of VAB were from the rheumatologists, while all other medical colleagues found his explanation reasonable, or at least were convinced that VAB was worth trying. One of the rheumatologists asked Almeida, "What are you actually doing?" Almeida replied, "Do you want me to teach?" and offered Veiga's contact. Despite his explanation, Almeida stated, the rheumatologists "didn't believe it." While Almeida attributed the epistemological boundary of those rheumatologists to an unwillingness to know something new, he pointed out that for him, "The important thing is that I *lived* the result" [my emphasis], and "The patients [and I], we

were able to stop taking corticoid [and] methotrexate, [...] from analgesic and steroidal and non-steroidal anti-inflammatory to hydroxychloroquine."

Yet, the tensions between immunosuppression and immunostimulation as competing therapeutic models grew surreptitiously along the decade culminating, in 2005, with ANVISA's prohibition of VAB.

Besides the official enunciation for the prohibition (i.e. that VAB was unregistered), there were other arguments mobilized to support the judicial accusations against Veiga's use of VAB, all of which suggest practices of charlatanism. First, that he was giving veterinary drugs to humans. This apparently occurred because most medical professionals were not acquainted with brucellosis' spread among humans and continued to see it only as a zoonosis. Second, he was promoting VAB publicly on the Internet. Indeed, Veiga advertised VAB online while critically comparing its effect with those of conventional immunosuppressants such as MTX, whose use he openly regarded as unethical. Further arguments include an informal accusation that he would cheat his patients by giving corticoids to them instead of an innovative curative drug. Additionally, other physicians reprehended him for using a "vaccine" to stimulate the immunity of people diagnosed with autoimmune diseases, which should be rather treated through immunosuppression.

The physicians who were using VAB explicitly at that time ceased before the possibility of being rebuked and/or legally threatened by their own colleagues. However, after the prohibition, Veiga and Fernandes republished the results of their clinical study, conducted in 1989 and originally published in 1996. This publication, alongside several online reports from VAB users (through Orkut, Facebook, blogs etc.), and the bionetworking activities of further actors such as physicians and patients' relatives, provided the medico-legal support and the informal therapeutic legitimacy that VAB needed to survive almost 10 years as a prohibited drug, until taking the path of manipulated drugs.

Immunoproteomics and regulation of melittin

Microbiologist Lúcia worked for over 30 years at a renowned public scientific institution and became a specialist in bee products such as honey and propolis. At some point, she developed psoriatic arthritis. Yet, because she is a naturalist and had witnessed how the liver and kidneys of her arthritic sister became compromised through the corticoids and anti-inflammatory drugs that she took for decades, she refused conventional medicaments. Following an unexpected positive experience that she had with bee poison therapy during a crisis in Japan, Lúcia decided to improve this treatment biotechnologically so that one would not need to experience unpleasant stings.

She then designed a research project with a research team that included an immunologist of the same institution and a professor from a federal university. Later, a specialist in inflammation and chronic pain provided the experimental model in animals. Their grant proposal was successful and the team began by setting up "an experimental apiary to collect poison where there were 10 beehives with a poison collector." As Lúcia explained, "Our idea was to start from the beginning [with the purest possible poison] so that we could replicate it later in case we need a large amount."

Following the poison's extraction and its transportation to the laboratory, "we entered a phase in which we fractionated this poison." The team used a simple column of silica gel and, after a series of chromatographic analyses to evaluate the remaining fraction's composition, they sought to separate phospholipase (an enzyme that provokes allergy and comprises approximately 80% of the poison) from other substances present in bee's poison, mainly from melittin since this "is the peptide that has action in autoimmune diseases."

> In fact, [the interruption of the body's natural production of] corticoid is what will induce you to have autoimmune diseases. [...] This is a very simple way of explaining it. But the melittin, it comes exactly there. It induces the body to produce catecholamines. [...] After using [melittin] for a while, you have these [self-produced] corticosteroids stabilized.

Later, during our conversation, Lúcia would also add a psychological aspect in the causative dynamics of immunopathology.

> If the person [. . .] is anxious, there's a tendency to have an autoimmune crisis. So this is also something that no one can control. [. . .] It has to do with the psychology that will induce you not to produce these catecholamines and you will have an autoimmune crisis.

After having obtained the isolated fractions with help of a chemistry professor and a new grant, the team initiated a study with animals, beginning with mice. After measuring melittin's analgesic properties, Lúcia told me that it "has an activity for pain equal to that of morphine." To complement their study, they induced arthritis in the animals' paw and "did those measurements of the paw, volume and such." Strikingly, "we saw the anti-inflammatory effect and the reduction of this for arthritis in mice." Additionally, they tested it in horses.

As part of their preparation for the next step, the trial with humans, the team developed two products containing melittin as its main active principle: an ointment for topical use, to be used for psoriasis and similar conditions; and a sublingual drop, which would facilitate the tests being easy to administrate. To fulfill one of the requirements for their RCT, Lúcia engaged a rheumatologist who "saw the results" of the experiments that they had done and "agreed to accompany the patients." Nevertheless, from this point on, things changed.

As she told me, "that's where our bottleneck was. [. . .] It was very expensive because, [. . .] I needed almost one and a half million [Brazilian Reais] to do these tests." Apparently, because the Board members had negative expectations from the beginning, they added anticipatory measures to attenuate the worst consequences of the trial by requiring an exceptionally higher number of potential hospitalizations, which increased the cost of the trial. Although she and her team managed to obtain the funds for the clinical phase, they did not obtain authorization from the Medical Ethics Board to implement it.

As I asked Lúcia about the reason why ethical approval had been denied, she replied,

> They didn't. [. . .] All our negatives were because we were working with poison. So, it was no use explaining that we had fractionated it, we had removed the allergenic portion from it, [. . .] we had studies done on animals [. . .]: "You're working with poison. This is not medicine." So, it was no use saying, "Look, I am working with a fraction of a poison." Just like Captopril, which is a medicine for high blood pressure made from rattlesnake venom [. . .]. It is only synthetic today, but its principle was made from this [*Bothrops jararaca*] poison.

Nevertheless, she recognized some reasons underlying the Board's negative decision. First, immunostimulating melittin-based pharmaceuticals would become strong commercial competitors of conventional ones based on immunosuppression for symptomatic therapy. Additionally, using "natural" material that is also a "poison" to immunostimulate people with immunopathologies is taboo for most physicians.

Years later, without expectations of obtaining a permit to conduct the planned RCT of her melittin-based products with people, she and her team decided to take another path: "I did a clinical trial with people who wanted [to use melittin] without government authorization. I didn't do anything with [the results]. The data are here. We did it because people asked." As she explained to me, the therapy began to appear in newspapers. At her own institution, "there were several employees with arthritis, and we said [to them]: 'Look, you are going to use it and come back here [to report your experience].'" As Lúcia positioned herself as "one of the patients" she reported to me about her own experience of participating in the informal trial, which she considered to be similar to most participants' experiences. When she initiated the treatment, she had a strong psoriasis crisis. Then, she conducted a treatment with a fraction of melittin for one year. Through the treatment, she "never had psoriasis again" and "never had arthritis again." Nevertheless, as she "went to do fieldwork with bees," she "got a sting" and ended up in the hospital. "So, what happened?" she asked:

> I think I induced a long-term allergy to bee venom. That was the studies that we had to do: knowing the side effects, knowing how much it contains, seeing the dosage... That wasn't done because we couldn't get authorization to proceed with this study.

In other words, the further studies that are necessary to verify the right doses and improve the treatment to make it safe for humans were blocked despite the positive results of standard experiments that Lúcia and her team had previously realized.

Conclusion: Medical semiotics and therapeutic legitimacy

Throughout this article, I used parts of my research materials to delineate two medical semiotics, which flourish simultaneously as outcomes and as generative of contrary medico-scientific realities in two complementary ways.

First, each of them holds together a distinct thought style and a corresponding thought collective around inflammation. One of them comprises rheumatologists who see inflammatory processes as signs of self-caused immune-overreactivity that should be controlled through immunosuppressants. The other comprises medico-scientists from other fields (like physiology, microbiology, and infectology) who might see the same inflammatory processes, in contrast, as signs of an impaired immunity that should be rather rehabilitated through immunostimulants.

Second, these medical semiotics evolve relationally toward each other, dialectically, through mutual invalidation, defining themselves and acting as opposites. E.g., medico-scientific actors who are embedded in and seek to expand one of these medical semiotics tend to see themselves as representatives of genuine medicine while they might consider colleagues whose medical semiotics question theirs, to be "charlatans" or "pharmaceutical dealers," who had sold themselves to big pharma.

Considering associated controversies, I suggest that disputes around the establishment of potential causes of immunopathologies might imply distinct semiotizations, relate to changing notions of personhood, and split biomedicine into mutually contesting streams. When medical semiotics' carriers extend their struggles for therapeutic legitimacy to legal arenas, they tend to impregnate sectors of regulatory science with those semioticized resources of which they are made and which they co-shape, such as specific terminology, theoretical premises, empirical experiments, papers, clinical studies, diagnosing strategies etc. With it, medical semiotics apparently also propagate and actualize co-existent cosmologies and understandings of human selfhood that co-constitute biomedicine. While reproducing and actualizing the biocultural environments through which they grow, medical semiotics' carriers might not give up pretensions of universal validity. Hence, developments in biomedicine are sometimes conflictive, do neither necessarily follow linear logics nor build on cumulative knowledge.

Yet, the power relations between the medical semiotics associated with immunosuppression and immunostimulation models that drive biomedicine are highly asymmetrical. When proponents of immunostimulants attempt to go throughout the legally predefined path they thrust at previous epistemological boundaries that established biomedicine maintains as to vaccine itself against disruptive medical innovations.

Notes

1. Apart from some seborrheic eczema, I have been living medication-free, asymptomatically, without sequels and restrictions for several years, whilst practicing sports regularly.
2. During his presentation, Teixeira acknowledged several conflicts of interest through his associations with big pharma companies.

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I translated all materials cited in this article, which were written or spoken originally in Portuguese, into English.

The Ethics Board of the Faculty of Social Sciences at the Goethe University Frankfurt approved the research from which this article is an output. I anonymized all persons that I cite here by giving them fictive names, including from publicly available materials, with exception of historical ones and/or the dead. Additionally, I herewith state that I am not a medical expert and I can neither confirm nor refute the efficacy of the therapies mentioned in this article.

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