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Towards an Ontological Theory of Substance Intolerance and Hypersensitivity

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Abstract

A proper ontological treatment of intolerance—including hypersensitivity—to various substances is critical to patient care and research. However, existing methods and standards for documenting these conditions have flaws that inhibit these goals, especially translational research that bridges the two activities. In response, I outline a realist approach to the ontology of substance intolerance, including hypersensitivity conditions. I defend a view of these conditions as a subtype of disease. Specifically, a substance intolerance is a disease whose pathological process(es) are realized upon exposure to a quantity of substance of a particular type, and this quantity would normally not cause the realization of the pathological process(es). To develop this theory, it was necessary to build pieces of a theory of pathological processes. Overall, however, the framework of the Ontology for General Medical Science (which uses Basic Formal Ontology as its uppermost level) was a more-than-adequate foundation on which to build the theory.

Keywords

allergy; allergic condition; hypersensitivity; ontology; drug intolerance; substance intolerance; hypersensitivity reaction; realist ontology; translational research

Introduction

A proper ontological treatment of intolerance—including allergies or hypersensitivity—to various substances such as food, drugs, vaccines, and radiocontrast media is critical to patient care and research. These conditions are common, have potentially fatal effects if not managed properly, and—because avoidance of repeat exposure to the particular substance involved remains the mainstay of management—limit therapeutic choices.

The prevalence of intolerance conditions rivals that of common diseases. The overall prevalence of hypersensitivity conditions of all types is approximately 10-15% [1]. This estimate does not include any other types of intolerance (such as that due to enhanced gastric motility caused by certain macrolide antibiotics, for example), yet it rivals the prevalence of diabetes mellitus, which one recent estimate pegs at 8% [2]. An estimate of the prevalence of drug-hypersensitivity conditions alone is 7% and 10-20% for outpatient and inpatient

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populations, respectively [3]. Food, insect, and other environmental hypersensitivities account for the remainder. In addition to drug hypersensitivity, common hypersensitivity conditions include allergic rhinitis, insect hypersensitivity, food hypersensitivity, and contact dermatitis.

The importance of these conditions is highlighted by the fact that medical records (both paper and electronic) nearly always have special sections dedicated to documentation of drug hypersensitivity. These sections of the record are typically prominent and exist at least in both the history and physical report and the initial set of orders upon admission to the hospital.

Given the emphasis placed on interoperability of data for patient care in various federal initiatives, and the criticality of data standards for conducting translational research, it is essential to have a standard, coherent ontology of these conditions. This standard should support both clinical applications, such as drug-allergy checking in the electronic medical record and research applications, such as aggregating data across sites to facilitate translational research.

In this paper, I will argue that existing methods of documenting these conditions and standards for documenting them electronically have flaws that inhibit these goals. I will then outline a systematic approach to the ontology of intolerance conditions and an implementation of it in the Substance Intolerance Ontology (SIO).

This work is related to that of Ceusters et al. of their analysis of adverse drug events for the REMINE ontology [4], in that the manifestation of substance intolerance conditions are often included in the class of so-called adverse events. However, Ceusters et al. do not address hypersensitivity conditions or intolerances in their work. They do however provide a few terms and their definitions that are useful in this work.

The Current State-of-the-art and its Flaws

The lack of a well-founded treatment of substance intolerances manifests itself in current approaches to their documentation as well as in proposed standards for documenting them electronically.

Documentation of Intolerances

Eliciting ‘allergies’ has long been a component of the standard patient interview [5]. If the patient reports having an ‘allergy’ to a particular type of substance—also known as the allergen (e.g., penicillin, peanuts), the interviewer will typically ask what ‘reaction’ the patient had to the substance (e.g., rash, anaphylaxis). A thorough interviewer will also ask about all exposures to the substance, their duration, whether a reaction occurred, and if so, the time from exposure to onset of any reaction, and the nature and duration of the reaction [6].

In the paper-based medical record, clinicians record the information so obtained in various places. For patients being admitted to an inpatient setting, clinicians record allergies in the History and Physical report and in the admission orders. Outpatient paper records vary widely, but allergies are typically recorded in a prominent place where they may be viewed easily from visit to visit (that is, the allergy information is not typically buried in progress notes which are specific to each visit).

The information recorded includes the substance to which the patient is allergic at a minimum. It may also include the reaction or reactions the patient experienced when exposed to the substance in the past and the date of (or duration since) the patient first

experienced the reaction. If the patient reports no allergies, then the clinician makes an entry of 'No known drug allergies' or 'No known allergies' (frequently abbreviated NKDA and NKA, respectively), to indicate that she asked about allergies and the patient reported none.

In the electronic world, not much is different. A key consideration is codification of the allergen to support drug-allergy checking during physician order entry. To allow entry of free-text allergens is to gather many entries that could and should have been coded originally [7]. Usually the allergy section of the electronic medical record is distinct from other sections of the EMR such as medication orders, problem list, laboratory results, diagnoses, and orders. Many EMRs also allow the user to indicate whether the 'allergy' is a hypersensitivity or intolerance. Some EMRs have the capability to prevent the entry of medication orders until an allergy history is documented (including NKDA when applicable).

What's wrong with how we document today

Despite dedicated sections of the record for 'allergies', hypersensitivity conditions appear elsewhere in the record. For example, seasonal allergies to plant substances such as pollen frequently appear in the record as diagnoses and/or problems, and not as 'allergies'. Worse, ICD-9-CM and SNOMED CT codes exist for drug hypersensitivity conditions as well and these codes may appear on the problem list. For example, ICD-9-CM has 10 codes under the 3-digit header V14 Personal history of allergy to medicinal agents. The ICD-9-CM code V14.0 represents *Personal history of allergy to penicillin*.

Similarly, laboratory testing for hypersensitivity conditions, although relatively infrequent, are also present in the record elsewhere, namely the laboratory results section. Thus, a laboratory test that indicates a hypersensitivity condition to ragweed, for example, will not be present in the 'allergies' sections of the record, nor in the problem list or diagnosis section. The results of skin testing for hypersensitivity conditions often appear only in textual progress notes or consultant reports.

In addition to this scattering of evidence for hypersensitivity conditions throughout the record, non-hypersensitivity conditions frequently appear in the 'allergies' section, such as nausea and vomiting associated with erythromycin. Lutomski et al found that only 78% of patients with a documented 'antibiotic allergy' met their criteria for a true hypersensitivity condition [8]. Although evidence for a true, type I IgE-mediated hypersensitivity reaction to radiocontrast media is increasing [9], many reactions to radiocontrast media appear to be due to other mechanisms [10]. Although the distinctions may be minimal with respect to current approaches to management, they are significant for research.

This current state of affairs poses fundamental problems for patient care and research. First, the net effect is that the 'allergies' section of the typical medical record is insufficiently sensitive and specific for identifying hypersensitivity conditions and intolerance conditions. Second, there is rarely a clear distinction among hypersensitivity conditions and intolerances. These conditions have different genetic and other biological factors involved in their pathogenesis. Third, data are recorded in proprietary formats using proprietary identifiers for drugs, other non-drug allergens (such as food and plant allergens), reactions, and so forth. Thus, health information exchange and use of clinical data in translational science are inhibited.

Limitations of Current Standardization of Intolerance Information

ICD-9-CM—As mentioned previously, ICD-9-CM has just 10 codes for hypersensitivity diseases, and none for other types of intolerance disease. It does not have any codes for

types of molecules or the pathological processes they set in motion (e.g., type I hypersensitivity reaction).

SNOMED-CT—SNOMED-CT has ‘concepts’ for the representation of hypersensitivity diseases, as well as other types of substance intolerance. For example, it has *91936005 Allergy to penicillin*. However, SNOMED CT asserts that both the allergy and the allergic reaction are types of disease. For example, both *Allergy to substance* and *Allergic reaction to substance* are descendants of *Disease* in the July, 2009 version. This confusion may arise from the fact that the current method of documenting allergic conditions is to state as evidence for their existence what reaction occurred in the past. Furthermore, SNOMED-CT asserts that the substance causes the intolerance. However, the allergic condition for example exists in the absence of substance, so these assertions of causality are incorrect.

MedDRA—(the Medical Dictionary for Regulatory Activities) Terminology. Despite being perhaps the most directly relevant artifact to the task at hand, given its role in the process of regulation of drug products, MedDRA has numerous flaws that prevent it from being taken seriously as the basis for an ontological theory of intolerance and hypersensitivity. It does not define its terms [11], it does not meet desiderata even for medical terminologies [12] let alone formal ontologies, and not only must great care be taken when using MedDRA for its intended purpose [13], even greater care must be taken to adapt it to other purposes [14]. With respect to substance intolerances, MedDRA fundamentally confuses hypersensitivity conditions with the immune reactions that occur upon exposure. For example, MedDRA states that *Contrast media allergy* and *Contrast media reaction* are entities (siblings) of the same type: Allergies to food, food additives, drugs and other chemicals. A key aspect of the present work is that it carefully distinguishes hypersensitivity conditions from hypersensitivity reactions.

The **NCI Thesaurus** has limited representation of substance intolerances and makes fundamental mistakes. For example, it states that serum sickness is a type of delayed-type (or type IV) hypersensitivity, which is incorrect. Serum sickness is a type III hypersensitivity reaction, mediated by antibodies (type IV hypersensitivity reactions are cellular-mediated immune reactions). The NCI Thesaurus has no representation of type III hypersensitivity reaction.

Standard categorization of drug reactions—Many authors divide adverse drug reactions into the categories of *unpredictable reactions* and *predictable reactions* [15]. The former include hypersensitivity reactions, whereas the latter include exaggerated physiological activity such as enhanced gastric motility due to erythromycin. These terms, however, have an epistemological basis and thus they do not represent universals. Indeed, genetics research is increasingly enabling the prediction of development of hypersensitivity to certain types of substances [16].

A Realist Approach to the Ontology of Intolerance

In this work, I build on the realist definitions of disease, disorder, and diagnosis of Scheuermann et al [17] and the Ontology for General Medical Science (OGMS) [18]. OGMS in turn, uses Basic Formal Ontology (BFO) [19] as its upper level, and the definitions I present in this work also adhere to BFO where they do not derive from OGMS.

The current OGMS definitions of disorder, disease, pathological process, and diagnosis are:

Disorder: A causally relatively isolated combination of physical components that is (a) clinically abnormal and (b) maximal, in the sense that it is not part of some larger such combination.

Disease: A disposition (i) to undergo pathological processes that (ii) exists in an organism because of one or more disorders in that organism.

Pathological process: A bodily process that is clinically abnormal.

Diagnosis: The representation of a conclusion of an interpretive process that has as input a clinical picture of a given patient and as output an assertion (diagnostic statement) to the effect that the patient has a disease of such and such a type.

The term ‘clinically abnormal’ is primitive in OGMS (meaning it has neither a human-language text definition nor a definition in some logical formalism), but Scheuermann et al. give the following explication of it [17]:

When we say that some bodily feature of an organism is *clinically abnormal*, this signifies that it: (1) is not part of the life plan for an organism of the relevant type (unlike aging or pregnancy), (2) is causally linked to an elevated risk of either pain or other feelings of illness, or of death or dysfunction, and (3) is such that the elevated ‘risk’ exceeds a certain threshold level.

Note that this explanation of ‘clinically abnormal’ does not rely on current medical knowledge, although as with all of science, as we make new discoveries we may learn that various entities do or do not meet these criteria. If today’s understanding of ‘clinically abnormal’ were the basis of OGMS, then OGMS would be frozen in place and could never evolve to include such discoveries.

With respect to the term ‘bodily process’ used in the definition of ‘pathological process’, OGMS is incomplete in two respects. First, OGMS represents bodily process as a subtype of process (from BFO), but does not provide an Aristotelian, text definition for it. Also, OGMS has no term for a clinically-normal bodily process (which would be a sibling of pathological process). Whether the term ‘biological process’ from the Gene Ontology (GO:0008150) fulfills this need is a current topic of discussion in the development of OGMS [20].

It is also important to note that at the time of this writing, the definition of disorder was undergoing substantial review and discussion [21]. Nevertheless, the essential notion is that an alteration in the physical structure and/or makeup of an organism (i.e., disorder) disposes the organism to undergo pathological processes, and this disposition is a disease.

Initial definitions

A **substance intolerance** is a disposition to undergo a pathological process upon exposure to a quantity of molecules of a certain type, and this quantity would not normally induce such processes. Here, I use ‘normally’ as an antonym of ‘clinically abnormal[ly]’. For example, severe nausea and vomiting due to usual therapeutic doses of erythromycin is an intolerance, as is a disposition to undergo a true type I hypersensitivity reaction upon exposure to penicillin. However, toxicity due to supra therapeutic doses—such as hepatic necrosis due to ingestion of a massive quantity of acetaminophen—is not an intolerance, as the disposition for this process to occur is present in nearly every human being.

Under this definition, an intolerance of a particular type (e.g., a hypersensitivity to penicillin) is a disease. This view is consistent with the fact that clinicians document many hypersensitivity conditions such allergic rhinitis on patients’ diagnosis and problem lists. Intolerances are a special type of disease, however, because realization of the disposition requires the presence of a foreign substance at a particular location in the body. If we redefine substance intolerance in terms of disease, then a **substance intolerance** is a disease whose pathological process(es) are realized upon exposure to a quantity of substance of a

particular type, and this quantity would normally not cause the realization of the pathological process(es).

Although the substance in question must be present in the body for the realization of the disposition, it is not part of the disorder that is the physical basis of the intolerance. Otherwise, the distinction between persons allergic to penicillin and persons not allergic to penicillin, for example, would become blurred. Furthermore, if we considered the substance as part of the disorder, each hypersensitivity reaction would be a new disease particular, since the body nearly always clears the substance between exposure events. A patient with a history of three reactions to penicillin-class antibiotics would have a history of three different disease particulars, each self-limited. But in reality, there are three hypersensitivity-reaction particulars, each a realization of an underlying hypersensitivity disease and hence the foreign substance is not part of the disorder.

Thus, the intolerance disease exists in the absence of the substance. That is, persons with hypersensitivity to penicillin, for example, predictably undergo pathological processes upon exposure to penicillin, whereas persons without penicillin-hypersensitivity disease do not.

This view is slightly more counterintuitive for intolerance diseases that do not involve hypersensitivity reactions, because hypersensitivity diseases require previous exposure to the substance for the underlying disorder to develop (see below). Under these definitions, we say that an individual has an intolerance disease even if she is never exposed to the substance in question and thus never suffers any untoward effects of the disease. Indeed, no human being need ever discover a disease (disposition) for it to exist. For example, even if Jane Doe never ingests erythromycin or any other macrolide-type antibiotic or compound, she has a disease if such ingestion, had it occurred at a 'clinically normal' quantity, would have induced severe nausea and vomiting. This situation is additionally a consequence of the view of disease as a disposition. Dispositions exist even if they never are realized [22].

Nevertheless, the view of substance intolerances as diseases, and diseases as dispositions, is consistent with current research and approaches to adverse drug events. Indeed, identification of genetic bases for dispositions to adverse drug events, to prevent the realization of intolerance diseases by preventing or reducing exposure to certain drugs in certain individuals, is an ongoing area of active and promising research [23].

Note that SNOMED CT also takes the view that intolerance and hypersensitivity are subtypes of disease. However, SNOMED CT represents the realization of hypersensitivity diseases, hypersensitivity reactions, as diseases, also. I reject this view as a disposition is a dependent continuant under BFO, and dependent continuants (diseases) are disjoint from processes (occurrences). A process is not a disposition, nor vice versa. Thus, a hypersensitivity reaction is not a disease, but the disposition to undergo a hypersensitivity reaction is.

Classification of Substance Intolerance Diseases

There are at least three possible major axes along which one might classify substance intolerance diseases. The first possible axis is the type of pathological process towards which the affected individual has a disposition. For example, one subtype of intolerance disease is based on immunologically-mediated hypersensitivity reactions, and hypersensitivity disease may then be further divided into subtypes of type I, type II, type III, and type IV based on the corresponding types of hypersensitivity reaction. The second possible axis for classifying intolerance disease is the location in the body where the process occurs. For example, one could distinguish intolerance diseases that affect the skin (contact dermatitis), the nasal mucosa (allergic rhinitis), and the eye (seasonal allergic

conjunctivitis). Finally a third possible axis is the type of substance (i.e., type of molecule) to which the organism is intolerant. For example, one could distinguish between penicillin allergy (type I hypersensitivity to all penicillin-class molecules) and sulfonamide allergy.

Note that there is interaction among the three axes. The location is usually where the substance comes first comes into contact with the body, and thus localized hypersensitivity reactions occur in proximity to the site of exposure (e.g., nasal mucosa). Plus some substances are more likely to enter the body at particular locations than others, for example, plant pollens via the air.

Pathological process

Because the type of pathological process involved is more characteristic of substance intolerance diseases than the particular type of substance, my first distinction among its subtypes is based on the pathological process. At present, however, no ontology of pathological processes exists. Thus, I created a high-level ontology of pathological processes with a view to the classification of substance-intolerance diseases. This classification of pathological processes therefore may be inadequate or gloss over distinctions necessary to an overall theory of pathological processes.

The first major distinction I make among pathological processes is between those processes that lead to injury (injuring processes) and the pathological counterparts to physiological processes (pathophysiological processes). Besides injuring processes, there are other types of pathological processes that are not pathophysiological processes, and thus these two direct subtypes of pathological process are not be exhaustive. Regardless, other subtypes of pathological process are not necessary for the remainder of the theory I present here.

I adopt for my definition of **injuring** (or injury process—I use the gerund form to distinguish the injury process from the injury continuant created by the process) the definition of **harm** developed by Ceusters et al. [4]. Thus, in this work, harm and injuring are synonyms. Because both the present work and the work of Ceusters et al. both use BFO as an upper-level ontology, the reuse of the latter in the former is straightforward. Ceusters et al. build up their definition of harm from their definitions of **structure integrity**, **structure change**, and **integrity change** (Table 1).

The alteration in structure integrity produced by an injuring (i.e., the injury) may be reversible or irreversible, depending on whether other processes are able to repair the damage or in the language of Ceusters et al., reduce the range of circumstances under which the structure becomes dysfunctional or causes dysfunction.

Various types of injuring processes include toxic injuring, anoxic injuring, and viral injuring. Note that I am not concerned here with injuring processes that result, for example, from electromagnetic radiation. However, if BFO considers electromagnetic radiation as a continuant, then what follows could readily be adapted to represent various intolerances to electromagnetic radiation, such as photosensitivity and photophobia.

With respect to exogenous substances then, I am concerned only with toxic injuring. A **toxic injuring** (or toxic injury process) is an injuring due to direct interaction of exogenous molecules (a.k.a. xenobiotics) with the anatomical structure. Note that injurings thus do not subsume infectious diseases which are, roughly, the direct interaction of microorganisms with anatomical structures, which in turn means that injuring and pathophysiological process (which I treat in detail next) are not exhaustive in covering the subtypes of pathological process. Toxic inuring may be further subdivided on the basis of whether the substance itself—**directly toxic injuring**—or a chemically-modified form of the substance that is generated

by the metabolism of the organism—**metabolite-mediated injuring**—is responsible for the injuring.

The definition of pathophysiological process requires careful analysis. First, as stated previously, OGMS does not define ‘bodily process’ nor does it contain a term ‘physiological process’, let alone provide a definition for one. The notion of process is that of change: continuants come into existence, go out of existence, gain and lose parts, gain and lose qualities and dispositions, and in the case of qualities, change values (e.g., from blue to red, from 50 kilograms to 55 kilograms). The continuants that participate in processes may effect change, undergo change, or both. For example, in the process of glycogenolysis, glycogen undergoes change by losing glucose molecules whereas glycogen phosphorylase (among other enzymes) effects the change (by removing glucose molecules from glycogen). Processes can regulate other processes only through physical changes in the participants of the regulated process. For example, glycogenolysis is regulated (in part) through structural changes to glycogen phosphorylase.

In physiological processes, normal anatomical entities cause and undergo changes in such a way that their qualities stay within a certain range of values. OGMS uses the term ‘homeostasis’ to capture this notion, referring to it as ... the disposition of the ... organism ...to regulate its bodily processes in such a way as (1) to maintain bodily qualities within a certain range or profile and (2) to respond successfully to departures from this range...[17].

Injurings differ from pathophysiological processes then, in that injurings are structural changes to normal physical components of the organism from the outside that result in disorders, and pathophysiological processes then are the realization of such disorders; that is, they are the abnormal functioning of anatomical entities modified in abnormal ways.

I can now define a **pathophysiological process** as a pathological process that is the realization of those disorders that result from structural changes to normal anatomical entities (as opposed to those disorders that result from the abnormal presence of external entities). The use of ‘clinically abnormal’ in the definition of disorder ensures that, for example, the damage to a few liver cells caused by a few milligrams or less of acetaminophen is not a disorder, and thus the realization of this damage (reduced functioning of hepatocytes) does not constitute a pathophysiological process. In other words, the body corrects damage all the time without that damage and the processes that result from that damage reaching the level of risk of feelings of illness, death, or dysfunction required for clinical abnormality. Thus, one should not assume that every process resulting from exogenously-induced structural change in the body constitutes a pathophysiological process, but only those structural changes that are types of disorder.

Pathophysiological processes may be subdivided into exaggerated realizations of a biological function and suppressed realizations of a biological function. Before defining these terms, it will be useful to review the BFO definition of ‘biological function’ and how biological functions are realized as processes. Arp and Smith [24] first define ‘function’ as:

1. a realizable dependent continuant. Thus,
2. it has a bearer, which is an independent continuant, and
3. it is of a type instances of which typically have realizations; each realization is
 - a. a process in which the bearer is participant
 - b. that occurs in virtue of the bearer’s physical makeup,

- c. and this physical make-up in something which that bearer possesses because of how it came into being.

They then define 'biological function' as a function which inheres in an independent continuant that is (i) part of an organism and (ii) exists and has the physical structure it has as a result of the coordinated expression of that organism's structural genes [24].

The key notion from these definitions is that a function is realized as a process, and exists even if it is not being realized. For example, the enzyme glycogen phosphorylase has the function to cleave glucose molecules from glycogen even when unable to carry out that function due to having undergone dephosphorylation which inactivates it.

An **exaggerated realization of a biological function** (or synonymously, an exaggerated biological functioning) is a pathophysiological process involving an abnormally large number of—or abnormal location of—the participants in the realization of a biological function. The increased number of participants—or the abnormal location of participants—is the structural change mentioned in the definition of pathophysiological process. For example, excess insulin in the blood of Jane Doe (disorder) due to an insulin-producing tumor results in exaggerated insulin-receptor binding at muscle and fat cells (i.e., there is an increased number of insulin and insulin-receptor participants), which in turn increases the number of active glucose transporters in those cells (disorder), which in turn results in an exaggerated process of glucose uptake from blood into those cells (increased number of transporters participating), which in turn results in an abnormally low number of glucose molecules in the blood (Jane's hypoglycemia disorder).

A **suppressed realization of a biological function** (or synonymously, a suppressed biological functioning) is a pathophysiological process involving an abnormally small number of participants in the realization of a biological function. For example, a deficiency of insulin in the blood of John Doe (disorder) due to absence of beta cells in the pancreas (as in type 1 diabetes mellitus) results in a suppressed insulin-binding process in muscle and fat cells, which in turn reduces the number of active glucose transporters (disorder), which in turn results in a suppressed process of glucose uptake into those cells (decreased number of transporters participating), which in turn results in an abnormally high number of glucose molecules in the blood (John's hyperglycemia disorder).

Note that a suppressed process cannot be the complete cessation of functioning; otherwise since no process exists the term would not refer to anything in this case. Instead, complete cessation of functioning must instead be handled as a process of complete inhibition, which itself may either be a novel, extraphysiological process or a pathophysiological process if it is the case that an increased number of participants in a normal inhibitory process reduces the number of participants in the regulated process to zero (or near zero). One example of a process of complete inhibition of functioning is the irreversible proton-pump inhibition of certain types of benzimidazole compounds (such as omeprazole), which reduces towards zero the number of proton-pumps (in gastric parietal cells) that participate in the excretion of protons (H^+ ions) into the gastric lumen. Since this inhibition is not the realization of a biological function, it is an extraphysiological inhibition.

An **exaggerated immune reaction** is an exaggerated realization of a function of the immune system in response to exposure to a particular type of molecule. Exaggerated immune reactions may be further subdivided into antibody-mediated hypersensitivity reactions, immune-cell mediated hypersensitivity reactions, and anaphylactoid reactions. An **antibody-mediated hypersensitivity reaction** is an exaggerated immune reaction due to specific binding of antibody and the type of molecule involved (i.e., antigen). I discuss the definitions of antibody, antigen, and specific binding below. The first three types of

hypersensitivity reaction (types I, II, and III) are all subtypes of antibody-mediated injuring. A **cell-mediated hypersensitivity reaction** is an exaggerated immune reaction due to binding of antigen by receptors on T lymphocytes. The term ‘cell-mediated hypersensitivity reaction’ is synonymous with ‘type IV hypersensitivity reaction’. An **anaphylactoid reaction** is an exaggerated immune reaction due to stimulation of histamine release from mast cells either through non-specific antigen binding of the Fc component of IgE (immunoglobulin type E) [10].

Pathophysiological Processes and the Gene Ontology

The biological process taxonomy of the Gene Ontology has representations of tens of thousands of normal physiological processes and biological functions. One could combine these terms with **pathophysiological process**, **exaggerated realization of a biological function**, or **suppressed realization of a biological function** to represent pathophysiological processes. Note that as yet, the only relation formally approved in the Relation Ontology for connecting occurs in this manner is the *preceded_by* relation [25], which is too weak to capture fully the notion of increased or reduced participation (or abnormal change in location of participation) in the realization of a biological function..

This combination of terms could occur either in a pre-coordinated fashion in a pathophysiological-process ontology, in a post-coordinated fashion, or in some mixture of the two. The combinatorial explosion of the first approach is undesirable; the preferred approach of the Open Biomedical Ontologies (OBO) Foundry is to pre-coordinate as little as possible [26], and to compose terms post-hoc using methodologies like that of Mungall et al [27].

Another potential issue with respect to hypersensitivity and the Gene Ontology is that hypersensitivity reactions of all types are pathological processes (hence the word hypersensitivity), but the Gene Ontology—despite an objective of representing only normal processes—has representations of them. For example, GO:0001802 is the identifier for type III hypersensitivity in the biological process taxonomy. Thus, one might argue that these terms ought to be moved out of the Gene Ontology into whatever ontology of pathological processes the OBO Foundry ultimately adopts. The intention of this work is not to advocate one way or the other, but merely to point out the potential difficulty.

Definitions and Considerations Specific to Hypersensitivity Disease

The term **antigen** does not refer to any particular type of molecule, but rather the role a molecule plays in binding to immunoglobulin molecules. **Antibody** is generally synonymous with **immunoglobulin**, and refers to molecules produced by immune cells that have the function of binding foreign molecules of a specific type. **Allergen** is a type of antigen role played by a molecule or portion of molecules of a given type in either inducing a hypersensitivity disease where none previously exists or in inducing a hypersensitivity reaction where a hypersensitivity disease does exist. The literature does not seem to distinguish the two, but one could easily create sub-roles of allergen: **sensitization allergen** and **reaction-induction allergen**. These sub-roles might be of value when the molecules that have the role of sensitization allergen are of a different type than the molecules that have the role of reaction-induction allergen (for example, the patient may have been sensitized upon exposure to amoxicillin, but reacted to another penicillin-type molecule such as piperacillin or even to a cephalosporin-type molecule such as cefazolin).

The antibody binds only with particular parts of the allergen molecule. An **epitope** or **antigenic determinant** is therefore the role played by a part of a molecule of binding with

an antibody. The analogous role of the binding part of the antibody molecule is the **antigen-binding region**.

Location of Pathological Process

The location or tissues in which the pathological process occurs is also a common axis of classification of substance intolerances. For example, hypersensitivity diseases include allergic rhinitis (nose), allergic conjunctivitis (eye), contact dermatitis (skin), allergic vasculitis (a type III hypersensitivity reaction occurring in blood vessels), and so on. The key notion is that the pathological process is localized to a particular part of the body. For hypersensitivity reactions, this location is frequently the location where the exogenous substance enters the body. In the case of allergic rhinitis, for example, airborne allergens come into contact with the nasal mucosa and induce mast-cell responses there.

Conversely, some hypersensitivity reactions are systemic, such as that involved in anaphylaxis. In both the case of allergic rhinitis and anaphylaxis, a type I hypersensitivity reaction is involved, but the extent of the reaction differs. The route of exposure involved may increase the severity of the reaction, but anaphylaxis is not limited to intravenous exposure to allergen and occurs with oral ingestion and cutaneous injection (e.g., *Hymenoptera* stings), for example.

With respect to other types of intolerances, these too may be localized vs. systemic. For example, a well-known toxicity of amiodarone, to which some individuals are more susceptible than others, is pulmonary toxicity.

One might ask what constitutes an exposure and what types of exposure are necessary to initiate a pathological process. For example, in the case of type I hypersensitivity reactions the molecules of the portion of substance must enter the body deeply enough to bind with immunoglobulin E molecules on the surface of mast cells. Other substance intolerances might require greater or lesser penetration of the substance into the body to trigger pathological processes. Also, note that not every instance of exposure (to a certain quantity of substance at a particular location in the body) need initiate a pathological process. There is a disposition to undergo pathological processes upon exposure, meaning that there is an elevated risk—but not certainty—of the pathological process occurring upon exposure.

Type of Substance

Clinically, the type of substance that induces pathological processes has been the most important aspect of intolerance diseases to record, because avoidance of repeat exposures is the mainstay of treatment. Fortunately, it is also the easiest aspect to determine and remember. It is usually difficult to determine with certainty which type of process occurred (except perhaps in the case of anaphylaxis but even then the underlying reaction is not always a type I hypersensitivity reaction), which clinicians often infer indirectly from the clinical manifestations of the reaction (i.e., rash, anaphylaxis, etc).

In addition, intolerance to one type of molecule also often means that an organism will not tolerate structurally related types of molecules. Thus, a patient who experienced a reaction to amoxicillin should not be given any penicillin-class antibiotic (such as piperacillin), as the risk of a life-threatening hypersensitivity reaction is high. Nearly all macrolide antibiotics enhance gastric motility to some degree, and thus a patient with severe nausea and vomiting due to erythromycin has an increased risk of the same due to clarithromycin, for example.

Note that in these cases there is one instance of substance intolerance disease. The individual is intolerant to several types of molecule that share a particular sub-structure, where that substructure is responsible for initiating the pathological process that occurs. In the case of

hypersensitivity reactions, this shared sub-structure that binds to immunoglobulin is the epitope (defined above). With respect to the most common form of penicillin-class antibiotic hypersensitivity, the shared beta-lactam ring structure (specifically, one of its key metabolites) is the epitope. The penicillin-allergic patient may be allergic as well to other classes of antibiotic that also have a beta-lactam ring, for example cephalosporins and carbapenems [15].

It is common to classify intolerances, especially hypersensitivity diseases, by broad headings such as food vs. drug vs. vs. plant vs. insect allergy. In the case of the first two headings, the designation of food and drug refer to a role that the portion of substance has. A peanut allergy, for example, is a hypersensitivity disease in response to particular proteins (or epitopes of these proteins) contained within the peanut. Peanuts themselves have the role of food (or at least numerous instances of peanut do). In the cases of plant allergy and insect allergy, the hypersensitivity is to some protein (or various epitopes of it) that is part of the plant or insect, not the entire plant or insect itself. In the case of insects, it is often the venom of an insect that is the allergen, and hence clinicians sometimes use the term venom allergy.

In this work, I make **food**, **drug**, and **venom** a subtype of the term **role of portion of substance**, which I represent as a child of the BFO term role. These terms ultimately belong in OGMS or another ontology because their definitions have broader implications and uses beyond that required for modeling substance intolerance diseases. I therefore do not attempt to define them or more specifically classify them in this work. Finally, as a consequence of these facts, the terms **food hypersensitivity**, **drug hypersensitivity**, **plant hypersensitivity**, **insect hypersensitivity**, and **venom hypersensitivity** all represent defined classes and not universals, so definitions of these terms are not essential to the core theory I introduce here, despite their common usage in patient care and public health.

The Substance Intolerance Ontology

I implemented the theory as a representational artifact using the above definitions in the OBO format using OBO-Edit v2.0. The primary reason for the choice is that OGMS is maintained in OBO. Interconverters between OBO format and the Web Ontology Language (OWL) are available. The curators of OGMS use these converters to release an OWL version of OGMS.

The top-level of the hierarchy underneath substance intolerance disease reflects the pathological processes involved, per the theory as described above (Figure 1). I include the human-readable, Aristotelian definitions from the theory with each term in the ontology. Below substance intolerance, each type of disease has a definition of the form: a substance intolerance disease whose realization is a <pathological process> process. If the type of substance is mentioned, then the template expands to: a substance intolerance disease whose realization is a <pathological process> process upon exposure to <substance>.

I also included in SIO the pathological processes I define here (Figure 2). At present, no relation exists in the Relation Ontology that connects a disposition with the process that realizes it. Thus, I inserted a placeholder relation to connect them until the Relation Ontology has an appropriate relation to use instead.

Discussion

Using the framework of Basic Formal Ontology and the Ontology for General Medical Science, I have developed an ontological theory of substance intolerance that views these conditions as diseases. I implemented it in a representational artifact, the Substance Intolerance Ontology (SIO). Specifically, I defended the view that a substance intolerance

disease is a disposition to undergo pathological processes upon exposure to a quantity of a substance, and this quantity would not normally cause such a reaction. The theory makes a careful distinction between a disposition to undergo particular processes, and the processes themselves. Pre-existing terminological artifacts such as SNOMED CT and MedDRA frequently blur this important distinction. I also reviewed and incorporated the three major axes on which these diseases are typically classified: the pathological process to which the organism is disposed, the location within the organism where the pathological process occurs, and the substance that induces the pathological process.

Note that a consequence of the OGMS definition of a disease as a disposition means that organisms have a disease even if they never suffer any feelings of illness, dysfunction, or death due to the disease. With respect to substance intolerance, a person has a disease even if he or she is never exposed to the substance and even if the likelihood of exposure is minimal. For example, if I am more sensitive than the human race as a whole to some novel compound in outer space, I have a disease. The risk of feelings of illness, dysfunction, and death that is part of the notion of clinical abnormality *is not the same risk* as that of being exposed to the substance. The risk of exposure to a penicillin-class antibiotic might be quite high, for example, in a patient admitted to the hospital with community-acquired pneumonia, and yet the risk of undergoing a pathological process as a result may approach zero in the absence of any hypersensitivity condition or other intolerance. Conversely, the risk of undergoing a pathological process might be quite high given exposure, but the risk of exposure quite small. Indeed, reducing the risk of subsequent exposures in the setting of hypersensitivity conditions is, as I have already pointed out, the mainstay of management.

This work identified several unfulfilled dependencies at a level of general ontological theory. First, this work suggests that the absence of a robust ontological theory of pathological processes could impede the development of the ontology of disease in general. In this work, it was additionally necessary to develop enough of such a theory as to accommodate intolerance disease. This work can inform efforts to address the need, but is almost certainly inadequate in and of itself to fulfill the need. In addition to the need for an ontology of pathological processes, this work identified gaps that might be filled by the Ontology for General Medical Science. Specifically, non-disease specific definitions of food, drug (medication), antibiotic, and venom are needed at a minimum. Finally, a relation that connects types of disease to types of pathological process is needed in the Relation Ontology.

Finally, I motivated the need for SIO by discussing the limitations of current approaches to representing instances and types of substance intolerances. One key limitation that this theory addresses is confusing and conflating the reactions to exposure (occurrent) with the disposition to undergo those reactions (dependent continuant). I have also highlighted the fact that the most common form of documentation of any particular intolerance disease in a particular patient is documenting details of past reactions. However, evidence for intolerance diseases often exists elsewhere in the record in other forms such as in problem lists, laboratory data, the results of skin testing (for hypersensitivity conditions), and so on. Unification of all the evidence in medical records for intolerance diseases is at present not possible because existing methods do not properly link these diseases with their evidence and often equate diseases with one form of evidence (typically reactions). By clarifying the essential nature of intolerances and their manifestations, and linking them together in an overall coherent theory, the SIO should enable the development electronic medical records and informatics systems in support of clinical and translational research that can return a list of all intolerance disease particulars in a given patient or population, regardless of what evidence exists for them.

Limitations

This work has several limitations. First, the theory does not yet address the clinical manifestations of various pathological processes. For example, hypersensitivity reactions variably cause hives, rash, urticaria, fever, etc. Addressing this limitation requires further development of a theory of signs and symptoms and their relationships to pathological processes. OGMS is in the very early stages of addressing this need, which clearly has much broader applicability than the theory of substance intolerance I defend here. Second, this work was limited by an absence of an ontological theory of pathological processes, as discussed. As such a theory evolves, it could substantially change the hierarchical organization of substance intolerance diseases I created. Nevertheless, so long as the relationships between intolerance diseases and pathological processes are present, a classifier could automatically reorganize the intolerance disease hierarchy as the pathological process hierarchy undergoes revision. Finally, at present, the SIO does not meet the OBO Foundry criterion of having a community of users. This paper is intended to serve as the foundation for the formation of such a community.

Future work

Filling out the SIO will require composition of terms from SIO, from the Chemical Entities of Biological Interest (ChEBI) ontology to denote the type of substance, from a pathological process ontology to denote the pathological process, from a symptom ontology to denote clinical manifestations, and from the Foundational Model of Anatomy ontology to denote anatomical locations. This composition might be facilitated from the creation of templates. For example, developers of the Ontology of Biomedical Investigations have created a template for easily generating new terms to denote laboratory observations [28]. Also, to operationalize a realist approach to the recording of data about substance intolerance diseases in patients or subjects of research will almost certainly require integration with a system such as the Referent Tracking system of Ceusters et al [29]. Development of a set of referent tracking templates that could be used for documenting substance intolerance diseases, the reactions that have occurred, their clinical manifestations, and the substances involved would likely facilitate the integration.

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Figure 1.
The hierarchy from BFO down to substance intolerance disease and its subtypes.



Figure 2.
The pathological process hierarchy.

Table 1

Definition of injuring (harm) as taken from Ceusters et al. [4]

Term	Parent	Definition
Structure integrity	Quality*	[An] aspect of an anatomical structure [the] deviation from which would bring it about that the anatomical structure...either (1) itself becomes[s] dysfunctional or (2) cause[s] dysfunction in another anatomical structure.
Structure change	Process*	[A process of] change in an anatomical structure of a person.
Integrity change	Structure change	[A structure change that brings] about a change in the range of circumstances under which the anatomical structure would become dysfunctional or cause dysfunction in another structure.
Injuring (harm, per Ceusters et al.)	Integrity change	[An] integrity change bringing about an <i>expansion</i> in the range of circumstances of the sort typically occurring in the life of [the organism] under which the anatomical structure would become dysfunctional or cause dysfunction in another structure. [emphasis added]

* Term is defined in Basic Formal Ontology