

PERVASIVE CAUSES OF DISEASE

by

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PREFACE

Why did I write this book, what are its contents, what is new, who is the intended audience, and how will readers benefit from it?

Motivation

For most of the past decade, I have been developing text mining procedures to identify potential discovery of new treatments for serious diseases. During this period, it became clear to me that discovery of new treatments for serious diseases, while both interesting and challenging, would be insufficient to reverse or eliminate disease. It became evident that eliminating the [foundational causes](#) of disease was at least as important as applying new treatments, if there were to be any hope for full or partial reversal of disease.

Toward that end, I developed a holistic medical principle that would form the bedrock of a healing protocol: **Removal of cause is a necessary, but not sufficient, condition for restorative treatment to be effective** (where 'removal' encompasses 'neutralization' in those cases where actual 'removal' is not possible). To prevent any disease, the foundational causes that underlay the disease symptoms need to be identified and removed as **comprehensively, thoroughly, and rapidly** as possible. To reverse disease (if irreversible damage has not been done and genetic predisposition is not a dominant factor), the preventive steps above need to be implemented as well. If the preventive protocols are inadequate for reversing disease progression, they need to be augmented by treatments. The first step in either disease prevention or reversal is to identify the full spectrum of potential foundational causes, or contributing factors, for the disease(s) of interest.

It also became evident to me that **much of the information required to identify and eliminate these foundational causes of disease is in the literature already**, but is not being extracted and exploited adequately. There is little financial incentive for much of the research community to focus on eliminating causes relative to instituting new treatments. Additionally, extracting these foundational causes comprehensively from the literature is a complex [text mining](#) problem. I firmly believe that the Literature-Related Discovery and Innovation ([LRDI](#)) text mining approach I had been developing for more than a decade is uniquely capable of identifying these foundational causes (and treatments) comprehensively.

About three years ago, I started a series of proof-of-principle demonstrations to show that foundational causes (and treatments, in some cases) could be identified comprehensively and efficiently for single diseases. In these demonstrations, I have been identifying an order of magnitude more foundational causes for each disease than any other published papers have reported.

However, it became clear to me that identifying foundational causes for any one disease provides a limited perspective on the potential comprehensive damage resulting from foundational causes. To produce a deeper understanding of the health degradation and restoration processes, foundational causes for **'all' diseases collectively** need to be identified.

Moreover, it also became clear to me that many foundational causes are not seeing the light of day in the published literature for myriad reasons, and those unpublished foundational causes might be as important, if not more important, than those appearing in the published literature. Thus, not only would the foundational causes for all diseases have to be addressed in any documentation of such a massive study, but the unique text mining approach that generated these foundational causes would have to be examined in detail, and the myriad reasons for foundational causes having been excluded from the published literature would have to be addressed as well.

The study identifying foundational causes for 'all' diseases was initiated in early 2014, and fully completed in 2015. Then, the issue of appropriate documentation arose. My initial thoughts were to publish a series of journal articles. One or more articles would address the voluminous foundational causes that were identified, at least one article would address the innovative text mining approach that generated these results, and at least one article would address the many reasons important foundational causes are being excluded from the biomedical literature.

Unfortunately, the separate journal publication approach would have fragmented the results, and would have greatly decremented the value of an integrated interdisciplinary presentation. Producing a book allowed a full exposition and integration of the study's results and conclusions, not constrained by journal limitations.

Contents

The overall theme of this book is preventing and reversing chronic diseases using the holistic medical principle: **removal of cause is a necessary, but not sufficient, condition for restorative treatment to be effective**. The specific focus of this book is identifying, categorizing, and analyzing the [pervasive foundational causes](#) of ~4000 diseases, allowing these *actionable* causes to then be eliminated.

These foundational causes are based on analysis of hundreds of thousands of biomedical journal articles from the premier medical literature. The foundational causes are categorized and analyzed by discipline, as well as by the underlying main sources of these causes.

There is a [substantial section](#) outlining the deficiencies and distortions of the premier biomedical literature on which this book is based. These inadequacies lead to

- 1) concealment of the full extent of the pervasive foundational causes of chronic disease;
- 2) reduced perceptions of health risk among individuals and policy-makers;
- 3) inadequate regulation and public health policy at the national and global levels.

There is also a [lengthy section](#) describing the text mining/ information technology advances that allowed the pervasive foundational causes to be extracted efficiently from the huge volumes of biomedical journal articles retrieved.

Novelty

While the individual direct foundational causes identified in this book are 'known', in the sense that they exist in the published literature, they have not been integrated anywhere near the extent they are integrated in this book. The new 'insights' in this book are:

- 1) the enormity of potential foundational causes that are possible;
- 2) the enormity of potential foundational causes that have to be eliminated for any person to prevent or reverse chronic disease (assuming irreversible damage has not been done or overwhelming genetic predisposition is not operable);
- 3) the enormity of potential combinations of foundational causes that have to be identified and researched (many of whose individual components have not yet been identified); and
- 4) the depth to which each potential foundational cause must be eliminated for prevention or reversal to occur.

Most papers addressing chronic disease take the form: here's a symptom(s); here's what my drug can do to suppress that symptom(s), and here're some of the other symptoms that can arise as a result of my drug. They're using a 22-caliber handgun for a problem that requires a howitzer!

Additionally, one chapter ([#9](#)) has been devoted to integrating the myriad approaches by which foundational causes have been prevented from appearing in the literature; these causes are therefore not amenable to identification through text mining. The potential enormity of these 'known unknowns' cannot be underestimated! I have not seen any other source that integrates the full spectrum of the types of suppressive approaches identified in [Chapter 9](#).

Audience

There are three communities to whom this book is targeted. First is the 'disease prevention and reversal' community. This encompasses the public health community, medical practitioners involved clinically with disease prevention and reversal, and individuals interested in what the present approach has to offer (they should heed the warnings in the Disclaimer). The pervasive foundational cause taxonomies in [Chapters 3](#) and [8](#) should be of particular interest to this community. Additionally, the cataracts researcher and clinician community might have interest in the identification of foundational causes for cataracts used as an [example](#) in Chapter 5.

Second is the text mining and information technology community. This would cover the full spectrum of researchers interested in extraction of useful information from any type of text, since the techniques developed in this book can be readily adapted to extracting useful information from myriad types of text. The concepts and algorithms in [Chapters 2](#) and [7](#) should be of special interest to this community.

The third community is harder to define. There is one segment of this book ([Chapter 9](#)) that addresses myriad reasons for foundational causes (deliberately or non-deliberately) either not entering the published literature, or entering the published literature in distorted form. While

professional disciplines that would have an interest in [Chapter 9](#) could be identified (such as bioethicists), it would behoove every citizen to understand how well the published literature reflects what is actually needed for improved health. If significant foundational causes are not represented accurately in the published literature, the 'red flags' should be raised.

Benefits

The interested reader will gain a deeper understanding of the main causative factors that drive chronic diseases and (to some extent) infectious diseases, and will also gain an understanding of the broad spectrum of rigorous actions required to prevent and/ or reverse these diseases. The reader will be able to see why there are no 'magic bullets' to prevent or reverse these diseases, and will be able to understand why motivation, discipline, and hard work are required to achieve, or regain, good health. Finally, the motivated reader will see that much of what is required to reverse serious disease may not be in the far future, **but may potentially be available in the here and now**, for selected individuals!

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EXECUTIVE SUMMARY

Removal of cause is a necessary, but not sufficient, condition for restorative treatment to be effective. To prevent any disease, the foundational causes that underly the disease symptoms need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse disease (if irreversible damage has not been done and strong genetic predisposition is not a dominant factor), the preventive steps above need to be implemented, and treatments to reverse progression (if necessary) need to be applied. The first step in either prevention or reversal protocols is to identify the full spectrum of potential foundational causes (or contributing factors) for the diseases of interest.

The main purpose of this book is to identify the pervasive foundational causes of disease published in the open literature. An advanced text mining/ information technology approach was developed to:

- 1) retrieve large numbers of biomedical journal records that covered all ~4000 diseases in the [Pubmed MeSH tree](#) and had a high probability of containing cause-disease linkage information; and
- 2) provide targeted queries for extracting foundational causes from MeSH and text fields in these retrieved biomedical records.

The key element of this text mining approach was to generate MeSH and text terms that would link to MeSH and text representations of foundational causes in the retrieved records, and then to separate and extract the foundational causes from their combinations with the linking terms.

Over 800 foundational and actionable causes are (conservatively) identified that impact thirty or more diseases. A [hierarchical taxonomy](#) consisting of five broad categories at the top level (Lifestyle, Iatrogenic, Biotoxic, Occupational/Environmental, Psychosocial/Socioeconomic) has been generated to categorize these pervasive foundational causes.

Lifestyle pervasive causes include: excessive fat, sugar, salt, meat, refined carbohydrates, and high-temperature cooking; malnutrition, starvation, dehydration; sedentary lifestyle, especially prolonged sitting; inadequate sleep; substance abuse (cocaine, methamphetamine, etc, excessive alcohol and smoking).

Iatrogenic pervasive causes include drug side-effects, surgical complications, radiotherapy side effects, and diagnostics side-effects.

Drugs that produce highly pervasive side-effects include antineoplastic agents, anti-infective agents, anti-inflammatory agents, cardiovascular agents, central nervous system agents, immunosuppressive agents, hematologic agents, and steroids/hormones. Drugs that produce moderately pervasive side-effects include antihypertensive agents, gastrointestinal agents, lipid regulating agents, dermatologic agents, vaccines/ vaccination, anti-bone-loss agents, antidiabetic agents, and antirheumatic agents. Drugs that produce pervasive side-effects include anti-allergic agents, anti-hypertensive agents, and antithyroid agents.

Surgeries that produce highly pervasive complications include transplantation (especially solid organ and cell), cardiovascular, orthopedic, gastrointestinal, kidney/ urologic, and brain/ neural. Surgeries that produce moderately pervasive complications include dental/ oral/ nose/ ear, gynecologic, respiratory/ thorax, and liver/ spleen. Surgeries that produce pervasive complications include ocular, breast, dermal/ tissue/ neck, thyroid, pancreas, and general procedures.

Diagnostics that produce pervasive side-effects include iodinated radio-contrast agents, invasive diagnostic procedures, diagnostic errors, and ionizing radiation.

Biotoxic foundational causes include: aflatoxin; myriad bacteria and viruses.

Occupational/Environmental foundational causes include: industrial and household chemicals and materials, especially hydrocarbons, solvents, and many other chemical compounds that emphasize chlorine, nitrogen, chromium, and carbon; agricultural chemicals, especially pesticides/ herbicides/ insecticides; materials, especially heavy metals, particulates, and nanometer-sized materials; electromagnetic radiation, especially ionizing (e.g, gamma rays, x-rays), non-ionizing (e.g., wireless communications), non-visible, and visible; sound, especially noise and ultrasound; both high and low temperature, and traumatic levels of force.

Psychosocial/ socioeconomic foundational causes emphasize psychological, especially variants of abuse (including child abuse, sexual abuse, and partner abuse) and psychological stress.

Genetic causes were not addressed in this book or included in the taxonomy. The main focus of the book is on foundational causes that are somewhat *actionable* (action could, at least in theory, be taken to attenuate, neutralize, or eliminate them). It is difficult to modify a person's genetic endowment presently, but that may not be true in the future. Genetic manipulation is in its infancy, and may some day be the treatment of choice for genetically-based diseases.

There appear to be five main sources of the 800 pervasive foundational causes: Direct Technology, Indirect Technology, Inadequate Regulation, Individual Choice, Poverty.

Direct Technology (the degree of direct impact of technology on the foundational cause) plays a strong role in Lifestyle, Iatrogenic, and Occupational/ Environmental pervasive foundational causes, and may play a role in whether exposure to bacteria and viruses results in symptoms and diseases. Modern technology impacts the growing, processing, and preparation of foods, and many of the adverse effects identified can be traced back to the use (mis-use) of technology. The Iatrogenic adverse effects are mainly due to the high-technology-based drugs, surgery, therapies, and diagnostics. The Occupational/ Environmental adverse effects result mainly from the employment of modern technology in commerce and in the workplace.

Indirect Technology reflects those adverse behaviors enabled by Direct Technology. One example is reduced labor because of modern technology, leading to the highly damaging sedentary lifestyle that exists today. Another example is large numbers of people able to live in inhospitable northern climates because of modern transportation, food logistics, clothing, and

shelter. This results in less exposure to sunlight and less Vitamin D production, contributing to diseases related in part to Vitamin D deficiency such as multiple sclerosis, schizophrenia, and chronic inflammatory bowel disease.

Inadequate Regulation is strongly coupled to the introduction of high technology in all aspects of life. Many of the problems with foods resulted from relatively unregulated chemicals, materials, and other contaminants entering the food supply during agriculture and livestock practices. Many of the Occupational/ Environmental exposures arose from relatively unregulated harmful substances entering the workplace and the environment, especially in, but not limited to, less developed countries. Many of the Iatrogenic problems could be traced to drugs and other procedures entering practice with insufficient statistically powerful front-end long-term testing in humans, and inadequate evaluation of side-effects.

Individual Choice reflects decisions by people to choose unhealthy dietary components, sedentary activities, recreational drugs, elective drugs and surgery, unhealthy occupations, unhealthy residential environments, unhealthy relationships, etc. There is the unwritten corollary assumption that these people have adequate knowledge about the consequences of their choices, and there are no other major factors that limit their choices. For many people, this assumption is false. They have very limited knowledge about the consequences of these choices, either through

- 1) accurate information not being available, or
- 2) apathy in searching out this information, or, as [Chapter 9](#) implies,
- 3) being provided incorrect information.

Poverty limits individual choices about diet, occupations, and environment, and plays a strong role in malnutrition and the diseases of deficiency resulting therefrom directly and indirectly. By limiting access to modern medicine, poverty avoids some of the causative side-effects listed in the taxonomy, but at the same time, denies many of the benefits available from modern medicine. Poverty is probably responsible for many of the communicable diseases among children in the world today, especially in third-world countries.

Many, if not most, people are exposed to at least tens of the ~800 pervasive foundational causes identified in this book, and perhaps tens more of the foundational causes that did not reach the threshold of *pervasive*. Given the potential ***synergistic*** effects of these causes acting in concert, the opportunity for contracting one or more of the diseases mentioned in this book is significant. As a result, the large number of increasing non-communicable diseases observed globally should come as no surprise. To prevent serious disease, or reduce the effects of disease once contracted, the major foundational causes applicable to each individual must be identified, and eliminated/ neutralized as ***comprehensively, thoroughly, and rapidly*** as practicable.

Finally, what is the main takeaway message from this book? The industrial revolution produced rapid technology implementation accompanied by inadequate technology regulation, licensing, and safety monitoring. In parallel, individuals made poor informed choices, as well as

uninformed choices, in their use of, and exposure to, this technology. This has led to the replacement of communicable diseases with non-communicable diseases as the leading cause of mortality and illness globally. Modern technology has become an integral part of our lifestyle, impacting the growing and processing of food, the medical diagnostics/ treatments/ surgeries, commerce, and the environment.

To minimize these adverse effects of technology on health, strong regulation, licensing, and safety testing and monitoring are required. There are both technical deficiencies and parochial organizational incentives that limit regulation and safety monitoring, and many of these deficiencies and disincentives are listed in [Chapter 9](#).

The lack of stringent safety monitoring is particularly troublesome. Databases for collecting the fundamental safety information of adverse effects are typically [passive](#), and can under-represent real-world adverse effects by an order of magnitude or more. Many clinical and field trials of potential toxic agents typically have little statistical power because of their limited size. Many times the participant samples don't represent the user population adequately. Animal experiments are not always translatable to human outcomes.

Combinations of potentially toxic stimuli are not tested, which excludes those foundational causes that only exert toxic effects in combinations, and downgrades the impacts of synergistic combinations of known toxins. Clinical and field trials for licensing especially, but also safety monitoring, are typically very limited in time horizon. There are diseases that don't appear until three-five decades after the initiating stimulus because of potential latencies, and both drug and non-drug technologies are typically introduced into practice well before the long-term safety tests have been performed.

In essence, the citizens of this planet have become the testbed in a global experiment to identify the short- and long-term impacts of technologies on our health.

Chapter 1

INTRODUCTION

1A. Overview

I have been text mining the premier technical and medical literatures for over two decades, with emphasis on potential discovery of new treatments for serious diseases in the past decade [1-12, 14-15]. Our research group identified orders of magnitude more potential discovery of new treatments than any of the other literature-based discovery practitioners [14]. However, during this decade, it became clear to me that discovery of new treatments for serious disease would be insufficient to reverse or eliminate the disease. It became evident that elimination/ neutralization of the foundational causes of disease is at least as important as applying new treatments, if there were to be any hope for full or partial reversal of disease.

Toward that end, I developed a holistic medical principle that would form the bedrock of a healing protocol: **Removal of cause is a necessary, but not sufficient, condition for restorative treatment to be effective** [12]. To prevent any disease, the foundational causes that underlie the disease symptoms need to be identified and removed as **comprehensively, thoroughly, and rapidly** as possible. To reverse disease (if irreversible damage has not been done and genetic predisposition is not a dominant factor), the preventive steps above need to be implemented, and treatments to reverse progression (if necessary) need to be applied. The first step in disease prevention or reversal is to identify the full spectrum of potential foundational causes, or contributing factors, for the disease(s) of interest.

It is also evident that much of the information required to identify and eliminate these foundational causes of disease is in the literature already, but is not being extracted and exploited adequately. There is little financial incentive for much of the research community to focus on eliminating causes relative to instituting new treatments. Additionally, extracting these foundational causes comprehensively from the literature is a complex text mining problem. To compound the problem, there are no uniform definitions of causes, resulting in foundational causes (tangible causes over which we have some control, like smoking, diet, exposure to harmful chemicals and radiations, etc) being classified along with diseases/ symptoms in general causative categories labeled as e.g. 'risk factors'.

In 2012, in order to do a proof-of-principle test of foundational cause identification, I initiated a study to identify published foundational causes for chronic kidney disease (CKD), and included identification of published CKD treatments as well in the study. I categorized the foundational causes into two definitional groups, direct and indirect. Direct foundational causes are those where the cause co-occurs with the disease in a given document, and can also be viewed as a potential *innovation*. Indirect foundational causes are those where the cause and disease occur in separate documents, and where identification of the cause for the disease can be viewed as a literature-based *discovery*. Direct and indirect treatments were defined in a similar manner.

The results were astounding [12]! There were ~800 direct foundational causes identified for CKD, and ~100 indirect foundational causes identified. There were also ~800 direct treatments identified for CKD, and ~100 indirect treatments. As was discussed in [12], these were *very conservative* numbers. Far more direct and indirect foundational causes and treatments for CKD were possible to identify. The sheer volume of results provided a more complete picture of how patients develop CKD, and a more comprehensive picture of what was required to prevent and possibly reverse CKD.

I then initiated foundational causes identification studies (for a few other chronic diseases) that are presently in different states of completion. However, in the process of performing these single disease studies, it also became clear to me that identifying foundational causes and treatments for any one disease provides a limited perspective on the potential comprehensive damage resulting from foundational causes. To produce a deeper understanding of the health degradation and restoration processes, foundational causes and treatments for all diseases collectively need to be identified.

Examining all diseases for potential causes would allow:

- 1) a comprehensive discipline hierarchical taxonomy for categorizing foundational causes to be constructed;
- 2) a comprehensive latent (underlying) variable taxonomy for categorizing the main sources of these foundational causes to be constructed;
- 3) the generation of very large amounts of potential discovery of foundational causes by extrapolating known foundational causes of diseases to closely related diseases of interest;
- 4) a better understanding of the myriad pathways through which a given foundational cause can impact myriad diseases and symptoms;
- 5) maximization of the number of important diseases potentially impacted by individual causes or causes operating synergistically, for the purpose of setting public health policy;
- 6) increased confidence (through greater statistics) that a foundational cause is really a foundational cause and not an anomaly.

I emphasize foundational causes, because once these causes have been identified, their removal would be *actionable* (from different perspectives) by public health researchers, practitioners, and policy makers. Obviously, some foundational causes would be eliminated more easily than others.

At the end of the CKD paper, I outlined in general terms how a study identifying foundational causes and treatments for myriad diseases could be executed. After the CKD study was completed, I focused on the foundational causes component of this multi-disease study. The present book describes the detailed approach taken to identify:

- 1) the foundational causes of the ~4000 diseases listed in the Pubmed MeSH tree;

- 2) the further culling of these foundational causes into *pervasive* foundational causes of disease (those that impact at least a threshold number of myriad diseases);
- 3) the disciplines into which these foundational causes can be categorized; and
- 4) the underlying latent factors that constitute the main sources of these pervasive foundational causes.

An important component of this book ([Chapter 9](#)) is a detailed discussion of why even the voluminous foundational causes that were identified may be a **highly under-reported** representation of what exists in the global community. Chapter 9 also presents some [examples](#) of negative human and economic consequences of the under-reporting of foundational causes.

1B. Structure of Book

[Chapter 2](#) presents a *summary* of the text mining methodology used to identify the individual and pervasive foundational causes, and [Chapter 7](#) presents a very *detailed* text mining methodology.

[Chapter 3](#) contains the results of the text mining and analyses, with the centerpiece being the [taxonomy](#) that categorizes the pervasive foundational causes, and [Chapter 8](#) is a detailed expansion of [Chapter 3](#). [Chapter 8](#) contains the central detailed results of this book, which is the [taxonomy of pervasive foundational causes](#) including illustrative examples (for each sub-category of foundational causes) relating cause to disease.

[Chapter 4](#) contains discussion and conclusions, with much of the focus on the [latent variables](#) that characterize the main sources of the foundational causes. [Chapter 5](#) contains suggested further research that would expand the results of the present study. It also contains an example of identifying foundational causes of a single disease, [cataracts](#), using a streamlined text mining approach.

The remaining chapters supplement and illuminate the summary material in Chapters 1-4.

[Chapter 6](#) contains the background material for the book, and a detailed definition of [foundational causes](#). [6A](#) contains the Background material for the Literature-Related Discovery and Innovation (LRDI) text mining approach that constituted the bulk of the information technology component of this study, and [6B](#) contains the Background material on studies performed to identify causes of multiple diseases. [6C](#) contains a detailed definition of *foundational cause*.

[Chapter 9](#) describes the under-reporting of adverse events by different methods and for different reasons, and conveys the critical message that ***what is not being reported in the biomedical literature may be as important as the voluminous information that is being reported***. [Section 9C](#) provides some examples of human and economic consequences resulting from under-reporting of adverse events and negative findings.

Chapter 2

SUMMARY METHODOLOGY

(see [Chapter 7](#) for detailed methodology)

2A. Data Sources

Selected records obtained with the Pubmed search engine of Medline are used as the source of all data.

2B. Study Selection

A direct foundational cause i of disease j exists when i co-occurs with j in a document and has been judged to be a cause of j . For purposes of this book, a toxic stimulus was deemed a foundational cause if

- 1) the research author stated/ implied/ inferred the toxic stimulus was a cause and
- 2) the information presented supported the research author's conclusion.

A threshold of two papers/ documents or more was used for computational purposes; there had to be at least two papers/ documents in which the foundational cause co-occurred with the disease in order for the foundational cause to be considered to have an impact. Had only one paper/ document been used as the threshold, the number of diseases impacted by a given foundational cause **would have increased by anywhere from 50% to 150%**.

To obtain pervasive foundational causes, matrices of foundational causes vs disease were generated from the extracted data, where the contents of cell i,j were the numbers of papers in which cause i co-occured with disease j . Then, for each foundational cause, an integration was performed over each matrix cell to arrive at the numbers of cells (diseases) that contained two or more entries. Pervasive causes were then arbitrarily divided into highly pervasive, moderately pervasive, and pervasive groupings. Numbers of diseases/ symptoms/ conditions impacted by each type were: highly pervasive, >100; moderately pervasive, 70-100; pervasive, 30-70.

2C. Data Extraction

Three approaches were used to identify *direct* foundational causes of disease. The first approach used [MeSH Qualifiers](#) to retrieve the records for analysis. The second used generic MeSH terms (relatively unambiguously related to foundational causes) to retrieve the records, and the third used text terms applied to the Title field to retrieve the records. The query terms in the MeSH Qualifiers and text Title field approaches served as linking terms to allow straight-forward extraction of the potential foundational causes terms.

One approach was used to identify a few sample *indirect* causes of disease, where an indirect cause i of disease j exists when i (which is not a direct foundational cause of disease j) has been identified as a direct foundational cause of disease/ symptom k , and disease/ symptom k

is closely related to disease j . A normalized diseases/ symptoms square matrix was used to quantify the closeness of any two diseases/ symptoms.

Why are these indirect foundational causes important? As I state in section [8A4](#), "indirect foundational causes of a disease may be potential direct foundational causes of the disease that have not yet been identified through research. If this is true, having a systematic approach to identifying potential direct foundational causes of disease **would open up vast areas for future biomedical research**. This book presents such a systematic approach."

Chapter 3

RESULTS

3A. Causes

A hierarchical taxonomy consisting of six broad categories at the top level (Lifestyle, Iatrogenic, Biotoxic, Occupational/Environmental, Psychosocial/Socioeconomic, and Genetics) was generated to categorize the pervasive foundational causes. The first five categories will be summarized in this section; **the Genetics causes will not be discussed further, as mentioned previously.**

Two main top-level types of results were selected for presentation and discussion. First, identifying those foundational causes that are pervasive, or quasi-universal; they impact large numbers of diseases and symptoms. Second, identifying a few sample indirect foundational causes of diseases, and showing that there may be **many thousands** of such indirect impacts potentially identifiable using the present technique.

3A1. Direct Foundational Causes

Many caveats showing why the numbers of foundational causes presented here may be vast under-representations of the numbers of operational foundational causes are presented in detail in [Chapter 9](#). Summarily, many adverse events are not reported and published in the literature [70-125], or, if they are reported and published, many are not accessed due to inadequate search algorithms. The under-reporting occurs at the patient, doctor, researcher, journal, corporate, and Federal agency levels, mainly because of myriad incentives and few disincentives for under-reporting. See [Chapter 9](#) for further examples.

Over-reporting cannot be excluded as well. As is shown in [Chapter 9](#), there are strong publication pressures especially in academia, and, depending on the nature of the foundational cause, a finding not warranted by the data could be rushed into publication.

Top-Level Taxonomy of Direct Foundational Causes of Disease

[Table 3-1](#) reflects the top-level categories of the direct foundational causes of disease taxonomy, and it is followed by a more detailed description of the contents in each of the categories listed in Table 3-1. The three columns in Table 3-1 reflect categorization by type of foundational cause (Lifestyle, Iatrogenic, Biotoxic Agents, Occupational/ Environmental Exposures, Psychosocial/ Socioeconomic, and Genetics); category assignments are not unique. The findings in the first five categories will now be summarized by sub-category; more detailed findings and categorizations, along with many illustrative examples, are shown in [Chapter 9](#).

TABLE 3-1 Top-Level Taxonomy of Direct Pervasive Foundational Causes of Disease

CATEGORY	SUB-CATEGORY	SUB-SUB-CATEGORY
1. Lifestyle	1A. Diet	
	1B. Activity	
	1C. Substance Abuse	
	1D. Other	
2. Iatrogenic	2A. Drugs	
	2B. Radiotherapy	
	2C. Surgery/ Invasive Procedures	
	2D. Diagnostic Agents/ Procedures	
3. Biotoxic Agents	3A. Mycotoxins	
	3B. Exotoxins	
	3C. Bacteria/ Fungi/ Parasites	
	3D. Viruses	
	3E. Other	
4. Occupational/ Environmental Exposures	4A. Chemicals/ Materials	4A1. Industrial/ Household Chemicals/ Materials
		4A2. Agricultural Chemicals
		4A3. Materials
	4B. Physical/ Mechanical	4B1. Electromagnetic Radiation
		4B2. Sound
		4B3. Temperature
		4B4. Force/ Pressure/ Physical Trauma
		4B5. Other
	5.	5A. Psychological

Psychosocial/ Socioeconomic	5B. Sociological	
	5C. Economic	
6. Genetics	6A. Polymorphism/ Genotypes/ Haplotypes	
	6B. Mutations	
	6C. Linkages	
	6D. Risk Alleles	
	6E. Genotoxicity	
	6F. Familial	
	6G. Congenital	

End of Table 3-1

More Detailed Description of Table 3-1 Category Contents

1. Lifestyle

Lifestyle includes choices mainly under individual control, and is divided arbitrarily into Diet, Activity, Substance Abuse, Other.

1A. Diet

1A1. Summary of Results

Poor diet reflects the adverse effects of excesses and deficiencies of dietary components. It has been used to induce myriad diseases in test animals, and it was a critical disease factor from many epidemiological and case studies. The most highly pervasive components of this diet sub-category tend to be high-fat, high-sugar, high-salt, [high-meat](#), high-refined carbohydrates, and the high-temperature cooking that results in harmful products (e.g., advanced glycation end products, heterocyclic amines and nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides).

Many deficiencies listed in the literature may be symptoms of metabolic problems, not foundational causes in the present sense. Thus, a Vitamin A deficiency may be due to insufficient Vitamin A intake (foundational cause), or some metabolic problem that results in reduced Vitamin A levels (symptom). Deficiencies of water, fiber, protein, legumes/ pulses, minerals, melatonin, and other nutrients (sunlight, selenium in soil, germs/ hygiene hypothesis) may result in adverse effects, but the only deficiencies that reach the pervasive threshold are the more general ones of malnutrition, starvation, and dehydration.

Many food additives are accompanied by adverse effects, and these effects may be under-diagnosed and under-researched. Many of the excesses and deficiencies mentioned above are the result of substances being added to, or removed from, the fresh whole food. The large numbers of additives include phosphates/ phosphorous, glycerin, sodium glutamate, palmitate, 2,3-pentanedione, etc. None of the specific additives reach the level of *pervasive* in the present results. Depending on how one defines 'food additives', those with the widest impacts tend to include the major items listed under excesses above, such as fat, sugar, and salt. These components are typically added to foods for taste enhancement, not nutritional improvement.

1A2. Caveats on Interpreting Diet Results

See [boxed caveats](#) in Chapter 8.

1B. Activity

The main sub-categories of Activity are exercise, sedentary lifestyle, and sleep. Exercise in the right amounts at the right intensity is viewed as beneficial, but excessive exercise in time and intensity (as well as related heat stroke) could be harmful. Sedentary lifestyle (lack of exercise) is problematic, and mentioned quite often. Prolonged sitting in all its variants appears to be a **highly under-recognized factor contributing to many diseases**. Its importance will

probably increase substantially with the advent of increased computer use for work and recreation. Insufficient sleep, both in quality and duration, is a problem area as well.

1C. Substance Abuse

Substance abuse includes 'recreational' drugs of all types (cocaine, methamphetamine, etc), other substances such as laxatives, common household products not usually identified as recreational drugs (such as mothballs), and especially *excessive cigarette smoking and alcohol*. Excessive alcohol use is implicated as a contributor to myriad diseases. Results for very moderate use, especially beer and red wine, are somewhat mixed. There may be a hormetic (beneficial) effect operating at very low doses (~ one drink per day), although consensus does not exist on that point.

1D. Other

Relatively few items are placed into this category, such as tattooing and body piercing.

The individual foundational causes identified with Lifestyle are usually studied in isolation, and *synergistic* effects are typically not identified. Given the number of Lifestyle component combinations that could be synergistic, and adding in

- 1) the foundational causes from the remaining categories identified here to the potential combinations and
- 2) foundational causes that surface only when operating in synergy but which have not yet been identified here as individual foundational causes,

it is clear that only the tip of the foundational causes iceberg is being exposed in this book.

2. Iatrogenic

Iatrogenic reflects diseases, symptoms, and injuries resulting from medical treatment, and is divided into four sub-categories: Drugs; Radiotherapy; Surgeries/ Invasive Procedures; Diagnostic Agents/ Procedures. Iatrogenic is a massive category, due mainly to the large numbers of drugs and surgeries that have side-effects and complications. The main categories are presented in this section, and illustrative examples of adverse effects from the main drugs and surgeries/ treatments are presented in [Chapter 8](#). For purposes of brevity when generating the drug categories, each drug is listed in one category only in Chapter 8.

The more frequently a drug is used, or the more frequently surgery or invasive treatments are employed, the more opportunity for side-effects and complications, and the more opportunity for publications describing these side-effects and complications. This book does not provide an indication of how often such side-effects and complications would occur as a percentage of use.

2A. Drugs

The Iatrogenic drug sub-category differs (from a text mining perspective) from the two categories that follow: Biotoxic Agents and Environmental/ Occupational Exposure. For drugs

that address symptoms related to a given disease, the Iatrogenic effects range in publication frequency from rare to modest (in the disease core literature). For drugs that primarily address symptoms not related to the disease of interest, publication frequency related to Iatrogenic effects is high (in the disease core literature).

Thus, for example, an antineoplastic drug that co-occurs in a paper with a cancer sub-type would rarely be shown having an adverse impact on the cancer, and would most frequently be shown as having a side-effect causing some other disease/ symptom. An antineoplastic drug that co-occurs with a non-cancer disease would almost always be a side-effect from the drug used for treating cancer (unless its application to the non-cancer disease was being explored in the study). Thus, an antineoplastic drug/ drug category that co-occurs with Mild Cognitive Impairment (MCI) would almost always, if not always, reflect an MCI side-effect resulting from cancer treatment. Almost every paper (in the disease core literature) dealing with Biotoxic Agents and Environmental/ Occupational Exposure relates to causing one or more disease-related symptoms.

The most highly pervasive drug categories include antineoplastic agents, anti-infective agents, anti-inflammatory agents, cardiovascular agents, central nervous system agents, immunologic factors, hematologic agents, and steroids/ hormones. Moderately pervasive drug categories include antihypertensive agents, gastrointestinal agents, lipid regulating agents, dermatologic agents, vaccines/ vaccination, anti-bone-loss agents, antidiabetic agents, and antirheumatic agents. Pervasive drug categories include anti-allergic agents, anti-hypotensive agents, antithyroid agents.

There are many specific drugs identified with very high frequencies. The main message here is that drugs across the board are not benign. Individually, drugs can contribute to causing serious disease. Drug combinations (with both drugs and non-drugs) may have the potential to exacerbate the adverse effects of individual drugs through *synergistic* effects.

2B. Radiotherapy

Radiotherapy has an extremely large number of side-effects/ complications, being associated with numerous neoplastic and non-neoplastic diseases.

2C. Surgery; Invasive Procedures

The following categorization is not unique. Some procedures could be assigned to multiple categories.

The most highly pervasive surgeries include transplantation, cardiovascular, orthopedic, gastrointestinal, kidney/ urologic, and brain/ neural. Moderately pervasive surgeries include dental/ oral/ nose/ ear, gynecologic, respiratory/ thorax, and liver/ spleen. Pervasive surgeries include ocular, breast, dermal/ tissue/ neck, thyroid, pancreas, and general procedures.

Transplantation in particular covers an extremely broad category of foundational causes, and these foundational causes operate on different levels. There are foundational causes due to the transplant preparation process, the surgery, the immune suppression drugs, and foundational causes that appear to be the result of the transplant (the transplant left the person more

susceptible to disease). As in the case of drugs, these absolute numbers of complications from all surgical and invasive procedures must be considered in light of the numbers of procedures performed.

2D. Diagnostic Agents/Procedures

The main diagnostic sources are radio-contrast agents (especially iodinated agents), invasive diagnostic procedures, and diagnostic errors. Ionizing radiation for diagnostics is also causative.

3. Biotoxic Agents

Biotoxic Agents reflect mainly the biological substances to which we are exposed naturally, but sometimes accidentally, and sometimes by design. This category is divided into five sub-categories: Mycotoxins; Exotoxins; Bacteria/ Fungi/ Parasites; Viruses; Other. It was also large, due mainly to the large numbers of bacteria and viruses.

3A. Mycotoxins

Only aflatoxins reached the pervasive level.

3B. Exotoxins

For purposes of the present analysis, a substance was considered an exotoxin if it was administered externally, through experiments or otherwise. Thus, amyloid beta, an endogenous substance, could be viewed as an endotoxin when internal processes are being discussed, but also as an exotoxin when given in laboratory experiments. As a group, mycotoxins were pervasive, but no individual exotoxin could be identified as pervasive.

3C. Bacteria/ Fungi/ Parasites

3D. Viruses

Bacteria and viruses are dominant in sub-categories 3C and 3D. Bacteria are somewhat ubiquitous, so the flexibility of cause removal for this sub-category is much less than for the Lifestyle and Iatrogenic categories. Unlike the Iatrogenic drug category, where the disease causative nature of the drug depends on whether the drug is used as a treatment for a specific disease, the causative nature of the bacteria and viruses is unambiguous. Almost every Title containing a virus or bacterium describes a disease or symptom caused by the bacterium or virus.

3E. Other

The Other category consists mainly of toxic plants.

4. Occupational/ Environmental Exposures

Occupational/ Environmental Exposures are those typically man-made substances and radiations to which we are exposed in our jobs and larger environment. It is divided into

chemicals/ materials and physical/ mechanical, and the further divisions of these major categories are also shown. This category is also massive, due mainly to the large numbers of chemicals and materials. Restriction to pervasive foundational causes masks the true impact of the 'chemicals' component. At lower frequencies of occurrence in records, there are massive numbers of chemicals identified as foundational causes, and many of their impacts are quite serious. Additionally, extraction of the very lowest frequency text representations of foundational causes from the retrieved records is most difficult. Thousands of direct foundational causes may have gone unidentified, both in the 'chemicals' category and in other categories in this taxonomy as well.

4A. Chemicals/Materials

4A1. Industrial and Household Chemicals/ Materials

This particular sub-category (which includes hydrocarbons, solvents, other chemical compounds, etc) is very broad, with large numbers of these myriad chemical compounds in the literature. All the chemical types mentioned have copious adverse effects, especially compounds containing chlorine, nitrogen, chromium, and carbon.

4A2. Agricultural Chemicals

This sub-category (which includes pesticides, herbicides, insecticides, etc) impacts the larger population through the food supply, and has devastating effects on the agricultural workforce. Given the ubiquitous nature of agricultural chemicals and industrial/ household chemicals in daily life, eliminating them will be challenging.

4A3. Materials

The materials/ particulates (e.g., heavy metals, particulates, nanoparticles, etc) that constitute this category are broadly-based, and in many cases have become part of the average lifestyle.

4B. Physical/ Mechanical

The main components of this sub-category, the different forms of radiation emitted to the environment (electromagnetic [ionizing, non-ionizing, visible, non-visible], noise, ultrasound, high temperature, low temperature, high pressure, high force, physical trauma) are ubiquitous. Avoiding exposure to these emissions (e.g., electromagnetic fields/ wireless communications, vehicle exhausts, noise, metals in agriculture, etc) would require a major change in lifestyle (and probably location) for most people. The 'Other' category is an amalgam of traumatic injuries due to pets and various diseases transmitted by pets (or animals in general).

5. Psychosocial/ Socioeconomic

Psychosocial/ Socioeconomic are those foundational causes that reflect personal problems, social interactions, larger societal interactions, and economic relationships. Stress in all its variants was a major causative factor, especially psychological stress. There were large

numbers of papers focused on variants of abuse, including child abuse, sexual abuse, and partner abuse. Sociological and economic types of causes seemed to play less of a direct role.

End of More Detailed Description of Table 3-1 Category Contents

3A2. Indirect Foundational Causes

Presently, a highly time-consuming manual approach only has been used to identify [indirect foundational causes](#) of disease. Four simple examples will be shown to display the process. The diseases/ symptoms selected are Chronic Kidney Disease (CKD) and Cataracts, and the goal is to generate discovery of potential new foundational causes for these diseases.

3A2a. CKD

From the Disease-Disease square matrix normalized, a number of diseases can be identified that have a stronger than average relationship with CKD. One of these is Hypertension. From the Title text version of the causes-Diseases matrix, 1,3-dipropyl-8-sulphophenylxanthine is listed as a direct foundational cause of Hypertension. A search of Pubmed validates this statement in a number of articles. The adenosine receptors antagonist, 1,3-dipropyl-8-sulphophenylxanthine, was not listed as a direct foundational cause of any kidney disease. Therefore, 1,3-dipropyl-8-sulphophenylxanthine is a candidate indirect foundational cause (potential discovery) of CKD through the two-link path 'cause-Hypertension-CKD'.

Also, from the same matrix, Childhood Adversity is listed as a direct foundational cause of Hypertension. A search of Pubmed validates this statement in a number of articles. Childhood Adversity was not listed as a direct foundational cause of any kidney disease. Therefore, Childhood Adversity is also a candidate indirect foundational cause (potential discovery) of CKD through the two-link path 'cause-Hypertension-CKD'.

3A2b. Cataracts

From the Disease-Disease square matrix normalized, a number of diseases/ symptoms can be identified that have a stronger than average relationship with Cataracts. One of these is Diabetes. From the Title text version of the causes-Diseases matrix, 'brominated trihalomethanes' is listed as a direct foundational cause of Diabetes. A search of Pubmed validates this statement in a number of articles. 'Brominated trihalomethanes' was not listed as a direct foundational cause of Cataracts. Therefore, 'Brominated trihalomethanes' is a candidate indirect foundational cause (potential discovery) of Cataracts through the two-link path 'cause-Diabetes-Cataracts'.

From the same matrix, Splenectomy is listed as a direct foundational cause of Diabetes. A search of Pubmed validates this statement in a number of articles. The surgical procedure, Splenectomy, was not listed as a direct foundational cause of Cataracts. Therefore, Splenectomy is also a candidate indirect foundational cause (potential discovery) of Cataracts through the two-link path 'cause-Diabetes-Cataracts'.

Identification of indirect foundational causes is an area ***highly recommended*** for future research. Far more is possible with an algorithm that exploits the network properties of the causes-Diseases matrix coupled to the Disease-Disease matrix. The greater the number of indirect pathways between the potential/ indirect foundational cause of interest and the disease of interest, the greater the chances the indirect (potential direct) foundational cause will be a direct

foundational cause. The stronger the linkages between the diseases on these indirect pathways, the greater the chances the indirect (potential direct) foundational cause will be a direct foundational cause.

Chapter 4

DISCUSSION AND CONCLUSIONS

Approximately 800 direct pervasive foundational causes are identified in this book. Thousands more toxic stimuli were identified that fell below the numerical threshold selected for pervasive, but given the conservative approach used for computing impacts, many of these additional toxic stimuli may in reality be direct pervasive foundational causes as well.

These direct pervasive foundational causes are divided into six categories (Lifestyle, Iatrogenic, Biotoxic Agents, Occupational/ Environmental Exposures, Psychosocial/ Socioeconomic, Genetics) for clarity of exposition, and only the first five are examined. There appear to be a handful of [latent variables](#) constituting the major sources for the pervasive foundational causes: Direct Technology, Indirect Technology, Inadequate Regulation, Individual Choice, Poverty. Each of these five major sources (latent variables) will be discussed now.

Direct Technology (the degree of direct impact of technology on the foundational cause) plays a strong role in Lifestyle, Iatrogenic, and Occupational/ Environmental pervasive foundational causes. In addition, through its impact on the immune and other critical systems, modern technology may play a role in whether exposure to bacteria and viruses results in symptoms and diseases. Modern technology impacts the growing, processing, and preparation of foods, and many of the adverse effects identified can be traced back to the use (mis-use) of technology. The Iatrogenic adverse effects are mainly due to the technology-based drugs, surgery, and diagnostics. The Occupational/ Environmental adverse effects result mainly from the employment of modern technology in commerce and in the workplace.

Indirect Technology reflects those adverse behaviors enabled by Direct Technology. One example is reduced labor because of modern technology, leading to the highly damaging sedentary lifestyle that exists today. Another example is large numbers of people able to live in inhospitable northern climates because of modern transportation, food logistics, clothing, and shelter. This results in less exposure to sunlight and less Vitamin D production, contributing to diseases related in part to Vitamin D deficiency such as multiple sclerosis, schizophrenia, and chronic inflammatory bowel disease.

Inadequate Regulation is strongly coupled to the introduction of high technology in all aspects of life. Many of the problems with foods derive from relatively unregulated chemicals, materials, and other contaminants entering the food supply during agriculture and animal husbandry. Many of the Occupational/ Environmental exposures arise from relatively unregulated harmful substances entering the workplace and the environment, especially in less developed countries, but in more developed countries as well. Many of the Iatrogenic problems could be traced to drugs and other procedures entering practice with insufficient front-end long-term testing, and inadequate evaluation of side-effects.

Two major aspects of Inadequate Regulation revolve around insufficient safety: inadequate safety data gathering, and inadequate safety testing. Much of the adverse impact data gathering tends to be from *passive* surveillance systems, where response rates can be an order of

magnitude less than real-world incidence rates, or more. Pre-market testing, in many cases, suffers from inadequate sample sizes, unrepresentative samples, insufficient long-term testing, and insufficient combination testing to identify potential synergistic effects. Insufficient long-term testing on humans is particularly troubling, since many serious diseases may have decadal latency periods from specific toxic stimuli. Additionally, results from animal testing (which could be long-term from the perspective of many short-lived animals used in testing) do not necessarily translate to human outcomes.

Individual Choice reflects decisions by people to choose unhealthy dietary components, sedentary activities, recreational drugs, elective drugs and surgery, unhealthy occupations, unhealthy residential environments, unhealthy relationships, etc. There is the unwritten corollary assumption that people have adequate knowledge about the consequences of these choices, and there are no other major factors that limit their choices. For many people, this is a highly unrealistic assumption. They have very limited knowledge about the consequences of these choices, either through

- 1) accurate information not being available, or
- 2) apathy in searching out this information, or, as Chapter 9 implies,
- 3) being provided incorrect information.

Poverty limits individual choices about diet, occupations, and environment. Poverty plays a strong role in malnutrition and the diseases of deficiency resulting therefrom, directly and indirectly. By limiting access to modern medicine, poverty avoids some of the causative side-effects listed in the taxonomy, but at the same time, denies many of the benefits available from modern medicine. Poverty is probably responsible for many of the communicable diseases among children in the world today, especially in third-world countries.

Many, if not most, people are exposed to at least tens of the ~800 direct pervasive foundational causes identified in this book, and perhaps tens more of the foundational causes that did not reach the threshold of *pervasive*. Given the potential synergistic effects of these causes acting in concert, the opportunity for contracting one or more of the diseases mentioned in this book is significant. To prevent serious disease, or reduce the effects of disease once contracted, the major foundational causes applicable to each individual must be identified, and eliminated as comprehensively, thoroughly, and rapidly as practicable.

The health policy that derives from the above findings would contain two main components: persuasion and mandates. Persuasion would be applied to influence Lifestyle/Individual Choice, which is the 'low-hanging fruit' of foundational causes. Mandates would be applied to influence Inadequate Regulation, the next level up on the tree. Effective persuasion and mandates depend strongly on the most scientifically accurate biomedical information being placed in the biomedical literature, and then communicated to the public in a straight-forward manner.

This book has taken a large step in identifying the voluminous pervasive foundational causes that need to be eliminated. Because of the limitations mentioned previously, the results from the analyses of this book should be viewed as proof-of-principle demonstration. To enhance these results, an adequately resourced study using an in-house Medline database would need to be performed in order to allow more comprehensive queries to be used and greater amounts of source data to be accessed.

However, while the addition of more foundational causes obtainable with an expanded study would provide a more complete picture of foundational causes, the elimination of the specific and categorical causes identified here may be adequate to prevent or (alone or in concert with treatments) reduce/ halt/ reverse the progression of many major diseases. The main problem is identifying the 'mix' of foundational causes to be removed for any individual patient, and especially the degree of foundational cause removal required for halting/ reversing the progression of any disease.

For example, does a poor diet have to be improved by 50% to be effective in disease reversal? 90%? In the multiple sclerosis (MS) reversal study summarized in Chapter 9, [sub-section D](#), where Dr. Terri Wahls was able to reverse her MS, Dr. Wahls' symptom removal and especially damage reversal were not effective until her diet achieved near-'pristine' status. There is no reason to believe

- 1) that similar dietary improvement would not be required to reverse any disease (for those cases where the damage may not yet be irreversible or genetic predisposition is not overly dominant), or
- 2) that similar improvement in other types of cause removal would not be required to reverse any disease.

The degree of cause removal required for reversal (with or without the requirement for additional treatments) would probably be different among patients. The major roadblock would be individual choice. It would require high discipline and compliance on the part of the patient. For those patients who are willing (like Dr. Wahls) to do whatever it takes to reverse their disease, and who have no intrinsic limitations based on strong genetic predisposition or irreversible damage, the findings in this book offer a starting point for an effective protocol.

Chapter 5

SUGGESTED FURTHER RESEARCH

This book has identified a large number of pervasive foundational causes (within the context of a much larger number of foundational causes, most of which have not yet shown to be pervasive), and has also implied that many more pervasive and non-pervasive foundational causes await to be uncovered. To achieve the latter, three research efforts are suggested.

5A. Larger Study on Pervasive Foundational Causes of Disease

First, an adequately-resourced study using more databases, more records, more fields, and more complex queries would identify many more potential foundational causes. Most of these potential foundational causes would probably have low occurrence frequency in retrieved journal records, but would result in a more populated causes-diseases matrix. An in-house version of Medline is highly recommended, as it would circumvent the limitations of most search engines used now. Adding records indexed in the Science Citation Index journals that are not indexed in Pubmed would also prove valuable.

5B. Semi-Automated Protocol for Identifying Potential Indirect Foundational Causes of Disease

Second, a more automated and comprehensive protocol for identifying indirect foundational causes is recommended. Given the linkages among the various biological systems (neural, immune, endocrine, circulatory, etc), a foundational 'cause' that impacts any of these systems would have some ripple effect on the other systems, and therefore on other diseases. Prioritizing these indirect foundational causes would be important, as it could show which potential indirect foundational causes for a particular disease should be researched. Having a prioritized list of indirect foundational causes (potential direct foundational causes) would **open the door to vast amounts of potential biomedical research.**

5C. More Streamlined Approaches for Identifying Foundational Causes for Single Diseases - Cataracts Example

5C1. Overview

The only single disease for which the foundational causes identification technique has been used (and published) is CKD [12]. The CKD study did not incorporate the streamlining advances made in the present pervasive foundational causes study. There would be value in having more detailed foundational causes identified for other specific diseases, allowing the recommended healing approaches in the CKD study and the present pervasive foundational causes study to be tested and demonstrated for specific diseases. I recommend strongly that myriad streamlining approaches for foundational cause identification be developed and applied to myriad different diseases.

I also recommend that items additional to foundational causes be examined in parallel, including treatments, mechanisms, signalling pathways, biomarkers, etc. The present approach

can be expanded straight-forwardly to include these other items, and a full network of linkages can be readily established.

Examining individual diseases allows the full core database for a single disease to be retrieved and analyzed, because of the smaller retrievals required for a single disease compared to the massive retrievals for the present pervasive foundational causes study. In turn, the single disease study allows much lower frequency foundational causes to be identified, since there is no requirement that they be pervasive. Obviously, the single disease studies will have substantial overlap with the present pervasive foundational cause study because of the pervasive foundational causes they share in common.

I'll end this chapter with an example of a single disease foundational cause identification study, performed using the more streamlined techniques developed for the present pervasive foundational causes study. The purpose of this example is to show the level of detail possible with the single disease study compared to the broader pervasive foundational cause study. This example should be viewed as the starting point for developing new methods to streamline the analytical effort even further, and to add on other quantities of interest.

5C2. Cataracts Foundational Cause Identification Example

5C2a. Objectives

The purpose of this brief example is to identify foundational (tangible) and actionable causes of cataracts.

5C2b. Methodology

The methods used are similar to those for the larger study in this book. Selected records obtained with the PUBMED search engine of Medline were used as the source of all data. Three approaches were used to identify direct foundational causes of disease. The first approach used MeSH Qualifiers to retrieve the records for analysis. The second used generic MeSH terms (relatively unambiguously related to causes) to retrieve the records, and the third used text terms applied to the Title field to retrieve the records. The query terms in the MeSH Qualifiers and text Title field approaches served as linking terms to allow straight-forward extraction of the potential foundational causes terms. For further details on each of these approaches, see Chapter 7.

5C2c. Summary of Results

Approximately 500 direct and 25 indirect foundational and actionable causes for cataracts were identified, and categorized in the same hierarchical taxonomy as was used in the larger pervasive foundational causes study of this book.

Lifestyle foundational causes included:

excessive fat, sugar, glucose, galactose, glycemic loading, salt, protein/ meat/ milk, refined carbohydrates, calories, cholesterol, soy/ genistein, herbs/ St. John's Wort, selenium, linoleic acid, linolenic acid, water, fried snacks, and maternal caffeine;

deficient water (dehydration), fruit, vegetables, tryptophan, protein, thiamine, iron, methionine, tannic acid, magnesium, zinc, Vitamin A, inositol pentaphosphate, histidine, ascorbic acid, beta-carotene, and general malnutrition;

sedentary lifestyle, including prolonged sitting;

inadequate sleep; and

substance abuse (LSD, maternal methamphetamine, excessive alcohol and smoking).

Iatrogenic foundational causes included:

drug side-effects, especially from antineoplastic agents, anti-infective agents, central nervous system agents, immunosuppressive agents, antihypertensive agents, lipid regulating agents, and steroids/hormones, and somewhat less from anti-inflammatory agents, cardiovascular agents, antidiabetic agents, and dermatologic agents;

surgical complications, especially ocular, transplantation, kidney, and gynecologic;

therapeutic ionizing radiation in the ocular region (radiotherapy, iodine brachytherapy, and nuclear medicine);

diagnostics centered around ionizing radiation (radiography, X-Ray Computed Tomography, and fluoroscopy).

Non-ionizing MRI was also causal, as were phenylephrine, phenazine-methosulfate, and D-xylose.

Biotoxic foundational causes included:

Exotoxins (e.g., bee sting, bovine lens membrane protein, CA⁺⁺, Calcium, phospholipid hydroperoxides, spermine, tgf-beta, xenobiotics, butterfly hair;

Bacteria/ Fungi/ Parasites (e.g., eye-fluke, parasite, and xanthurenic acid);

Viruses (e.g., hbv intrauterine, herpes simplex virus type 1, hiv-1, measles, puumala virus, rubella virus, and viral hepatitis b); and

'Other' (e.g., 3-hydroxyanthranilic acid, 3-Hydroxykynurenine, 4' -pyridyl) - 1 piperazine aryloxypropanol or aryloxypropyl derivatives, and 4-hydroxynonenal).

Occupational/ Environmental foundational causes included:

industrial/ household chemicals/ materials, especially hydrocarbons, solvents, and many other chemical compounds that emphasized carbon, nitrogen, and sulfur;

agricultural chemicals, especially pesticides/ herbicides/ insecticides;

materials, especially heavy metals and particulates;

electromagnetic radiation, especially ionizing, non-ionizing, non-visible, and visible;
sound/ noise; both high and low temperature; and traumatic levels of force.

Psychosocial/ socioeconomic foundational causes included:

low education, low socioeconomic status, nonprofessional occupation, social class, low income, and poverty.

5C2d. More Detailed Results in Taxonomy

The majority of causes shown in the boxed taxonomy below are direct causes of cataracts; they are not highlighted. Indirect causes of cataracts are highlighted by **bolding**, *italicizing*, and underlining. For example: ***brominated flame retardants***.

Appendix 5-1 contains a table of the indirect causes highlighted in the taxonomy. These indirect causes for cataracts are direct causes of diabetes, a disease closely linked to cataracts, or direct causes of aggregated/ glycated/ oxidized proteins, conditions characteristic of cataracts. The small numbers of indirect causes of cataracts shown in Appendix 1 are the tip of a much larger iceberg. Many more indirect causes could have been identified, both from more extensive examination of diabetes and aggregated/ glycated/ oxidized proteins, and from examination of other diseases and characteristic conditions closely linked to cataracts.

TAXONOMY OF FOUNDATIONAL CAUSES OF CATARACTS

1. LIFESTYLE

The Lifestyle category is sub-divided into Diet, Activity, Substance Abuse, Other

1A. Diet

Poor Diet is ubiquitous. It is used to induce cataracts in test animals, and it is a critical cataract factor from many epidemiological and case studies. Excesses of dietary components in both directions, both too much and too little, can be harmful. In particular, excesses of total fat/ vegetable oil/ non-olive oil, sugar (sucrose/ sorbitol/ fructose/ sugar alcohols/ xylose), glucose, galactose, glycemic loading, salt, protein/ meat/ milk/ liquid protein, total/ refined carbohydrates/ rice gruel, calories, cholesterol, soy/ genistein, herbs/ St. John's Wort, selenium, linoleic acid, linolenic acid, water, fried snacks, and maternal caffeine have adverse impacts on cataract development.

Many deficiencies listed in the literature are symptoms, not foundational causes in the present sense. Thus, a Vitamin A deficiency may be due to insufficient Vitamin A intake, or some metabolic problem that results in reduced Vitamin A. Deficiencies of water (dehydration), fruit, vegetables, tryptophan, protein, thiamine, iron, methionine, tannic acid, magnesium, zinc, Vitamin A, inositol pentaphosphate, histidine, ascorbic acid, beta-carotene, and general malnutrition have adverse effects on cataract development

Food/ dietary additives are another problem area. Foods are modified from their original state to enhance taste, appearance, and shelf life, among other characteristics. While some additives are harmless, many are accompanied by adverse effects. Adverse reactions to additives may be under-diagnosed and under-researched. Many of the excesses and deficiencies mentioned above are the result of substances being added to, or removed from, the fresh whole food. Additives identified include monosodium-L-glutamate and excessive vitamin/ mineral supplements, including multivitamins, Vitamin C/ ascorbic acid and Vitamin E, and Menadione. The literature is mixed on the harmful impacts of the latter two vitamins. Additionally, depending on how one defines 'food additives', those with the widest impacts tend to include the major items listed under excesses above, such as fat, sugar, and salt, which tend to be added to foods for taste enhancement.

1B. Activity

The main sub-categories of Activity are exercise, sedentary lifestyle, and sleep.

Exercise in the right amounts at the right intensity is viewed as beneficial in reducing cataract incidence, especially walking and running.

Sedentary lifestyle (lack of exercise) is problematic. Prolonged sitting appears to be an under-recognized factor contributing to cataract development. The link between prolonged sitting

and cataracts is unclear; is it from the reduced circulation characteristic of the sitting, or from the toxic radiation emanating from the (typically) TV or computer monitor screens being watched while sitting? Its importance will probably increase substantially, with the advent of increased computer use for work and recreation and the attendant prolonged sitting required.

Insufficient sleep, and its under-production of melatonin, is hypothesized to result in insufficient detoxification of carbonyls, and the resultant enhancement of cataract potential. This general area of the role of sleep in detoxification of ocular structures appears to be heavily under-researched, and there may be other physical, chemical, and biological mechanisms operable in the detoxification of ocular structures due to deep and adequate sleep.

1C. Substance Abuse

Substance abuse includes maternal methamphetamine, LSD, alcohol, and nicotine abuse, and especially **excessive alcohol and smoking**.

1D. Other

Relatively few items are placed into this category, such as excessive childbearing and excessive work hours per day.

The foundational causes identified with Lifestyle are usually studied individually, and ***synergistic*** effects are typically not identified. Given the number of Lifestyle component combinations that could be synergistic, and adding in the causes from the remaining categories to the potential combinations, it is clear that only the tip of the cataract foundational causes iceberg is being exposed in the present study.

2. Iatrogenic

The 'side-effects' from drugs and the complications from surgery and invasive treatments predominate in this category. One needs to be careful here. The more frequently a drug is used, or the more frequently surgery or invasive treatments are employed, the more opportunity for side-effects and complications, and the more opportunity for publications describing these side-effects and complications.

2A. Drugs

Appendix 5-2 lists the specific drugs identified by drug class. The main drug classes, both by numbers of drugs and numbers of records identified, include antineoplastic agents, anti-infective agents, central nervous system agents, immunosuppressive agents, antihypertensive agents, lipid regulating agents, and steroids/ hormones. The next level includes anti-inflammatory agents, cardiovascular agents, antidiabetic agents, and dermatologic agents.

The main message here is that drugs across the board are not benign. Individually, they can contribute to causing serious disease, and in the combinations that many people take, they may have the potential to exacerbate the causes of individual drugs through ***synergistic*** effects.

2B. Radiotherapy

Radiotherapy is identified as a cause under the headings of radiotherapy, iodine brachytherapy, and nuclear medicine. All these terms focus on ionizing radiation in the ocular region for therapeutic purposes.

2C. Surgery; Invasive Procedures

Appendix 5-3 lists the specific causal surgeries by class. The categorization is not unique; some procedures could be assigned to multiple categories. The main surgical classes are ocular, transplantation, kidney, and gynecologic. There are a large number of transplantation records, and the main causal components tend to be the radiation and drugs required for immunosuppression such that the organs/ cells would not be rejected. As in the case of drugs, these absolute numbers of complications from all surgical and invasive procedures must be considered in light of the numbers of procedures performed.

2D. Diagnostic Agents/ Procedures

The main diagnostic causes are centered around ionizing radiation, including radiography, X-Ray Computed Tomography, and fluoroscopy. Non-ionizing MRI is also causal, as are phenylephrine, phenazine-methosulfate, and D-xylose.

3. Biotoxic Agents

Biotoxic Agents reflect mainly the biological substances to which we are exposed naturally, but sometimes accidentally, and sometimes by design. This category is divided into sub-categories shown, and is modest in size compared to drugs.

Exotoxins include bee sting, bovine lens membrane protein, CA⁺⁺, Calcium, phospholipid hydroperoxides, spermine, tgf-beta/tgf-beta2, xenobiotics, butterfly hair, **2-Deoxy-D-ribose**, and **6-Hydroxydopamine**. For purposes of the present analysis, a substance is considered an exotoxin if it is administered externally during experiments. Thus, amyloid beta, an internal substance, could be viewed as an endotoxin when internal processes are being discussed, but also as an exotoxin when given in laboratory experiments.

Bacteria/ Fungi/ Parasites include eye-fluke, parasite, and xanthurenic acid. Viruses include hbv intrauterine, herpes simplex virus type 1, hiv-1, measles, puumala virus, rubella virus, and viral hepatitis b. 'Other' includes 3-hydroxyanthranilic acid, 3-Hydroxykynurenine, 4' -pyridyl - 1 piperazine aryloxypropanol or aryloxypropyl derivatives, and 4-hydroxynonenal.

4. Occupational/ Environmental Exposures

Occupational/ Environmental Exposures are those typically (not always) man-made substances and radiations to which we are exposed in our jobs and larger environment. It was divided into chemicals/ materials and physical/ mechanical, and the further divisions of these major categories are also shown. This category is large, due mainly to the large numbers of

chemicals, materials, and radiation types.

4A. Chemicals/ Materials

4A1. Industrial/ Household Chemicals/ Materials

This particular sub-category (which includes hydrocarbons, solvents, other chemical compounds, etc) is broad.

Hydrocarbons include polycyclic aromatic hydrocarbons, *dibenzo[a,e]fluoranthene*, 1,2-benzoanthracene, phenanthrene, naphthalene, naphthalene and dimethyl Sulfoxide, styrene, *JP-8/Jet Fuel*, *polychlorinated biphenyls (PCBs)*, and *tetrachlorodibenzo-p-dioxin*.

Solvents include *3,4-dimethyl-2,5-hexanedione* and *brominated trihalomethanes*.

Chemical Compounds include carbon monoxide, carbon tetrachloride, 1,2-naphthoquinone, boron hydride disulfide, dimethyl sulfoxide, ethylene oxide, Formaldehyde, formaldehyde-methanol, paraformaldehyde H₂O₂, nitric oxide, nitrocompounds, nitrogen oxides, nitrates, organic nitrate explosives, oxygen, sodium iodate, TNT, selenite, and sulfur dioxide.

'Other' includes paraphenylenediamine, arsenic, ionomycin, calcium ionophore, CA₂₊₊, alloxan, 4-diethylaminoethoxy-alpha-ethyl-benzhydrol/ RGH-6201, ethylnitrosourea, methylnitrosourea, N-methyl-N-nitrosourea, glutaraldehyde, hair dyes, N-butyl-N-(4-hydroxybutyl)-nitrosamine, Peroxynitrite, S-(1,2-dichlorovinyl)-L-cysteine/ (DCVC), silica, guanidinium chloride, chlorophenates, *mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)*, *mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)*, *brominated flame retardants*, and *bisphenol A, p,p'-DDE*.

4A2. Agricultural Chemicals

This sub-category (pesticides, herbicides, insecticides, etc) includes triazin-derivative, methyl isocyanate, diamide, aminotriazole, 3-aminotriazole and carbon tetrachloride, 3-aminotriazole and light, diquat, juglone, mirex, and paraquat. It impacts the larger population through the food supply, and has devastating effects on the agricultural workforce.

A3. Materials

The materials/ particulates sub-category includes heavy metals, particulates, etc

'Heavy metals' includes gold, cadmium, lead, mercury, methylmercury, palladium, plutonium, iron, and nickel.

'Particulates' includes smoke, solid fuel in unflued indoor stoves, biomass fuel smoke, biomass fuels, biomass stoves, diesel exhaust, exposure to fire and dust per day, cheap cooking fuels, indoor biofuel exposure, kerosene cookstoves, rice straw fuels, wood fuel, and urban residence.

The materials that constitute this category are broadly-based, and in many cases have become

part of the average lifestyle.

4B. Physical/ Mechanical

The main components of this sub-category, the different forms of radiation and other physical phenomena in the environment (electromagnetic [ionizing, non-ionizing, visible, non-visible], sound, high temperature, low temperature, high pressure, high force, physical trauma) are ubiquitous. Avoiding exposure to these emissions would require a change in lifestyle for most people.

4B1. Electromagnetic Radiation

Ionizing radiation includes radioactive air pollution, particle radiation, particulate radiation, chernobyl nuclear accident, cobalt radioisotopes, cobalt-60, cosmic radiation, gamma ray, heavy ions, nuclear reactors, nuclear warfare, actinide radiation, alpha particles radiation, CNS radiation, cranial radiation, helium ion radiation, high-let radiation, infrared radiation, radiation injuries, x-rays, space radiation, TBI radiation, total cranium radiation, radioactive pollutants, radioisotopes, radium, radon, uranium, RA224/RA-224/radium-224 radiation, proton radiation, protons, RU-106 radiation, PD-103 radiation, and neutron radiation.

Non-Ionizing radiation includes microwaves and mobile phone base station.

Non-Visible radiation includes uvr, uvr 300nm, uvr-b, uv, uva, uvb, sunlight, photosensitizing agents and sun exposure, puva, p-uva, uvb and l-buthionine sulfoximine, and solar radiation.

Visible radiation includes blue light, diode-laser, light, light artificial, shorter wavelengths-environmental lighting, riboflavin and exposure to daylight fluorescent lamps, photons, photo-oxidation, laser, welding.

'Other' includes electric, electrical injuries, electricity, electrocution, and lightning.

4B2. Sound includes noise.

4B3. Temperature includes burn, heat, high temperature, hot temperature, thermal, and cold.

4B4. Force/ Pressure/ Physical Trauma includes mechanical stress, ocular compression, and traumatic.

4B5. 'Other' includes altitude and latitude.

5. Psychosocial/ Socioeconomic

Psychosocial/ Socioeconomic are those causes that reflect personal problems, social interactions, larger societal interactions, and economic relationships. This category includes low education, low socioeconomic status, nonprofessional occupation, social class, low income, and poverty. The causes in this category are proxy causes for the more immediate causes such as poor diet and adverse environmental/ occupational exposures. Low income/

low education are associated with poor diet, occupations with adverse exposures, and residences in higher adverse exposure neighborhoods.

5C2e. Discussion of Taxonomy Results

Approximately 500 direct foundational causes and 25 indirect foundational causes of cataracts were identified. Given the streamlined nature of the query, there may be more direct causes (probably relatively rare) remaining to be identified, and *many more* indirect causes remaining to be identified.

5C2f. Acknowledgements

I acknowledge and appreciate the contribution of Russell W. Read, M.D., Ph.D, to the study on cataract foundational causes reported in section 5C. Professor Read responded to numerous biomedical questions during the course of the cataracts study, and his insights were very helpful. Any errors in section 5C are solely my responsibility.

5C2g. Appendices to Chapter 5

Appendix 5-1 Cataract Indirect Causes - Validated

CAUSE	LINK
2-Deoxy-D-ribose	PROTEIN AGGREGATION
6-Hydroxydopamine	PROTEIN AGGREGATION
JP-8/Jet Fuel	PROTEIN AGGREGATION
dibenzo[a,e]fluoranthene	PROTEIN AGGREGATION
3,4-dimethyl-2,5-hexanedione	PROTEIN AGGREGATION
indinavir	DIABETES
saquinavir	DIABETES
stavudine	DIABETES
didanosine	DIABETES
brominated trihalomethanes	DIABETES
mono(2-ethyl-5-hydroxyhexyl) phthalate/(MEHHP)	DIABETES
mono(2-ethyl-5-oxohexyl) phthalate/ (MEOHP)	DIABETES
pancreaticoduodenectomy	DIABETES
Clomipramine	DIABETES
polychlorinated biphenyls/PCBs	DIABETES
basiliximab	DIABETES
polyinosinic:polycytidylic acid	DIABETES
noise	DIABETES
Splenectomy	DIABETES
brominated flame retardants	DIABETES
tetrachlorodibenzo-p-dioxin/TCDD	DIABETES
bisphenol A	DIABETES
<i>p,p'</i> -DDE	DIABETES

Appendix 5-2 Drugs and Drug Classes Identified

2A1. Antineoplastic Agents

chemotherapy; antineoplastic combined chemotherapy protocols; vincristine sulfate; tamoxifen; PARP inhibitors; 3-Aminobenzamide; nitroaspirin; mitomycin C; methylglyoxal; methotrexate; buthionine sulfoximine; iodoacetic acid; Interferon-alpha; Imatinib; hydroxyurea; H-89; doxorubicin; cytostatics; Cyclophosphamide; buthionine sulfoximine; busulphan; busulfan; bleomycin; ara C; 1-beta-D-arabinofuranosyl-cytosine/ 1-beta-D-arabinofuranosylcytosine; antimetabolites; antiestrogen; Androgen deprivation therapy; 5-fluorouracil; streptozotocin;

2A2. Anti-Infective Agents

-Anti-Bacterial Agents/ Anti-Fungal Agents/ Anti-Parasite Agents

antimalarial agents; valinomycin; tetracyclines; propamidine isethionate; plumbagin; hyperbaric oxygen therapy; nigericin; Naphthoquinone; mepacrine; hygromycin B; erythromycin; disophenol; daptomycin; CJ-13,454; chloroquine; chlorhexidine; Calcimycin; 2,6-diiodo-4-nitrophenol;

-Antiviral/ Antiretroviral Agents

Ribavirin; Pegylated interferon; HAART; ganciclovir implantation; dibenzyl derivatives; Amantadine; *indinavir; saquinavir; stavudine; didanosine*

2A3. Anti-Inflammatory Agents

ibuprofen; gout medication; gamma secretase modulator; E2012; colchicine; CJ-12,918; allopurinol;

2A4. Cardiovascular Agents

ouabain; isosorbide; calmidazolium; beta-blocker; amiodarone; adrenaline;

2A5. Central Nervous System Agents

-Analgesics and Pain Relievers

xylazine; N-acetyl-p-benzoquinone imine; ketamine-xylazine; Chloral hydrate; benzodiazepams; aspirin long-term; Acetaminophen;

-Depressants/ Antidepressants and Stimulants

venlafaxine; tricyclic antidepressants; tranquilizers; selective/serotonin reuptake inhibitors; Ritalin; phenylpiperazine; phenobarbital; paroxetine; monoamine oxidase inhibitors; Methylphenidate; iprindole; fluvoxamine; amitriptyline; *Clomipramine*;

-Mood Stabilizers

antipsychotic agents; anti-epileptic drugs; anticonvulsants; ziprasidone; trifluoperazine; thioxanthenes; quetiapine; prochlorperazine; phenytoin; phenothiazines; phenothiazine derivatives; perphenazine; olanzapine; Methotrimeprazine; dilantin; Dibenzothiazepines; diazepam; Chlorpromazine; Carbamazepine; butyrophenols;

-Neurotransmitters

2A6. Immunologic Factors

-Immunosuppressive Agents/ Immunosuppression

tacrolimus; Prednisone; prednisolone; Mycophenolic Acid; Immunosuppressive Agents; Cyclosporin; Azathioprine/ Azathioprin; **basiliximab**;

-Immunostimulation Agents

Concanavalin A; **polyinosinic:polycytidylic acid**;

2A7. Hematologic Agents

-Coagulants

eltrombopag;

-Anticoagulants

Heparin;

-Other

deferoxamine; cyanate;

2A8. Steroids/ Hormones

-Steroids/Hormones

testosterone; pregnadienes; megestrol acetate; hydroxyprogesterones; hormone replacement therapy; estrogens; estradiol; dexamethasone; desoxycorticosterone; cortisone; budesonide; androstadienes; androgens; aldosterone; adrenocorticotrophic hormone/ ACTH;

-Corticosteroids/glucocorticoids

triamcinolone; Triamcinolone Acetonide; triamcinolone AND photodynamic therapy; systemic cortical steroids; solumedrol; Pregnenediones; Methylprednisolone Hemisuccinate; Methylprednisolone; Hydrocortisone; cortisol; corticosteroid; glucocorticoids; Fluorometholone; fluocortolone; Fluocinolone Acetonide; fludrocortisone acetate; dexamethasone phosphate; dermocorticosteroids; deflazacort; Decadron; Cortodoxone; Betamethasone; beclomethasone dipropionate; Beclomethasone; 17-alpha-Hydroxyprogesterone

2A9. Antihypertensive Agents

timolol; spironolactone; potassium-sparing diuretics; diuretics; Pilocarpine; PD 78787; nifedipine; indapamide; furosemide; calcium channel blockers; 3-[4-[4-(3-methylphenyl)-1-piperazinyl]butyl]-2,4-imidazolidione;

2A10. Gastrointestinal Agents

SDZ ICT 322

2A11. Lipid Regulating Agents

3-beta(2-diethylaminoethoxy) androst-5-en-17-one hydrochloride/ 3 beta-(2-diethylaminoethoxy)- androst-5-en-17-oneHCl/ U18666A; triparanol; lovastatin; simvastatin; statins;

2A12. Dermatologic Agents

Nicotinamide; methoxypsoralen/ methoxsalen/ 8-MOP; isotretinoin;

2A13. Vaccines/Vaccination

rubella vaccination;

2A14. Anti-Bone-Loss Agents

2A15. Antidiabetic Agents

oral hypoglycemic agents; NVS001; sulfamides; PPARgamma agonist; PPARdelta agonist; insulin; Ciglitazone;

2A16. Antirheumatic Agents

2A17. Anti-Allergic Agents

Epinephrine;

2A18. Anti-Hypotensive Agents

2A19. Antithyroid Agents

thyroid hormones;

2A20. Antiemetic Agents

RG 12915; 5-HT3 antagonist;

2A21. Ocular Agents

myotics; Miochol; Echothiophate iodide/ Echothiophate;

2A22. Urological/Renal Agents

Finasteride; Cysteamine;

2A23. Other

chlorphentermine; oral contraceptives;

Appendix 5-3 Surgeries And Invasive Treatments Identified

2C. Surgery; Invasive Treatments

The following categorization is not unique. Some procedures could be assigned to multiple categories.

2C1. Transplantation

transplantation; transplantation conditioning; stem cell transplantation; solid organ transplants; renal transplantation; kidney transplantation; bone marrow transplantation; corneal transplantation; pancreas transplantation;

2C2. CardioVascular

2C3. Gastrointestinal

2C4. Kidney/Urologic

Propecia; renal dialysis; hemodialysis;

2C5. Brain/Neural

mannitol;

2C6. Orthopedic

orthopedic surgery;

2C7. Dental/ Oral/ Nose/ Ear

2C8. Gynecologic

surgical menopause; hysterectomy; ovariectomy;

2C9. Respiratory/Thorax

2C10. Liver/Spleen

Splenectomy

2C11. Ocular

photodynamic therapy; photochemotherapy; trabeculectomy-air; trabeculectomy; trabeculectomy with mitomycin c; sulfur hexafluoride; vitrectomy; silicone; silicone lens; silicone oil; perfluorohexyloctane; retinal attachment surgery; keratoplasty; laser coagulation; laser corneal surgery; laser epilation; laser iridectomy; laser iridotomy; laser photoablation; laser photocoagulation; laser therapy; lasik; lens implanatation; lens implementation; penetrating keratoplasty; photorefractive keratectomy; radial keratotomy; glaucoma surgery;

2C12. Breast

2C13. Dermal/Tissue/Neck

2C14. Thyroid

thyroidectomy;

2C15. Pancreas

pancreaticoduodenectomy;

2C16. General Procedures

2C17. Other

hyperbaric oxygen therapy;

Chapter 6

BACKGROUND

6A. LRDI Background

LRDI [1-3] is a text mining approach that

- a) integrates discovery generation from disparate literatures with the wealth of knowledge contained in prior art to
- b) potentially prevent and reverse chronic and infectious diseases [4-12] and
- c) potentially solve technical problems that appear intractable [13].

The LRDI *discovery* component operates by linking two or more literature concepts that have not been linked heretofore (i.e., disjoint) in order to produce novel, interesting, plausible, and intelligible knowledge (i.e., potential discovery). The disjoint literatures can be linked by matching of common text [7] and/ or common references [9] and/ or other common features. The LRDI *innovation* component reflects the potential improvement of present practice or exploitation of dormant but promising prior discovery. The present book uses LRDI discovery and innovation components to identify direct (Innovation) and indirect (Discovery) foundational causes of large numbers of diseases and symptoms.

LRDI's main focus has been medical applications. A comprehensive review of published LRDI techniques [1,14-15] concluded that none (except for the author's; e.g. [7]) generated actual discovery; most generated innovation. Additionally, most were focused on finding treatments rather than finding and eliminating foundational causes. The author's systemic and integrative approach (in the present LRDI incarnation) gives equal weight to discovery (and innovation) of causes and treatments. The treatments cover the total system as well as specific organs and sub-systems. A review of the LRDI literature shows LRDI applications to single diseases, focused on identifying discovery in treatments. A review of the larger medical literature shows that no study, LRDI or otherwise, examines the breadth of causes, diseases, and symptoms shown in the present book.

There have been six generations of LRDI to date. The first two generations (2004-2009) tended to use combinations of biomedical terms and classes of potential solutions of interest in the queries for identifying potential discovery treatments [4-7]. These early LRDI generations also included a Latent Semantic Analysis approach to help identify discoveries for alternative methods of water purification [13]. The background, methodology, and lessons learned from these first two LRDI generations were summarized in a Special Issue of Technology Forecasting and Social Change [1-2, 8].

The first generation used combinations of query terms like ('protein oxidation' AND 'plant extracts'). The second generation used more complex combinations like (('protein aggregates' AND 'Lewy bodies') AND 'plant extracts'), and examined large numbers of combinatorials as part of the query for potential discovery [4-7]. The third generation (2010)

used more functional terms (e.g., 'inhibit viral entry'), and included adjacency operators (e.g., 'inhibit' within five words of 'viral entry') that allowed application to full text [10]. The third generation was also the first of our LRDI studies to address infectious disease (SARS), and showed the LRDI approach was equally applicable to chronic and infectious diseases. These first three LRDI generations restricted potential treatment discovery to non-drug approaches and substances.

The fourth generation (2011-2012) removed the restriction to non-drug discovery only, and allowed all types of discovery to be considered for potential treatments [11]. The fourth generation also allowed concepts to be linked through citations as well as text, and was the first of our LRDI studies to show the common features of very disparate diseases [9]. The fifth generation (2012-2013) used an enhanced version of the functional approach, removed all solution class restrictions, and gave equal weight to determining causes and treatments [12]. The evolution of LRDI, and the major study results, are described in more detail in a 2012 update [3], which the interested reader is advised to examine for more specifics. The concept behind LRDI will be summarized now.

Discovery is ascertaining something previously unknown or unrecognized. More formally, "Discovery in science is the generation of novel, interesting, plausible, and intelligible knowledge about the objects of study" [16]. It can result from uncovering previously unknown information, or synthesis of publicly available knowledge whose independent segments have never been combined, and/ or invention. In turn, the discovery could derive from logical exploitation of a knowledge base, and/ or from spontaneous creativity (e.g., Edisonian discoveries from trial and error). [17]. Innovation reflects the metamorphosis from present practice to some new, hopefully "better" practice. It can

- 1) be based on existing non-implemented knowledge,
- 2) follow discovery directly, or
- 3) resuscitate dormant discovery that has languished for decades.

LRDI is a systematic approach to bridging unconnected disciplines based on text mining procedures. LRDI allows potentially radical discovery to be hypothesized using either the technical literature alone, or the literature and its authors (e.g., text analysis followed by workshops or panels). In the LRDI context, discovery is linking two or more literature concepts that have not been linked heretofore (i.e., disjoint), in order to produce novel, interesting, plausible, and intelligible knowledge. Thus, simply linking two or more disparate concepts is a necessary, but not sufficient, condition for LRDI. In particular, concepts may be disjoint because the value of their integration has not been recognized previously, or they may be disjoint because there appears to be little value in linking them formally.

There are two types of discovery approaches commonly used in LRDI: open discovery systems (ODS) and closed discovery systems (CDS). In ODS, one starts with a problem and arrives at a solution; e.g., what are new potential treatments for cancer. In CDS, one starts with a problem literature and a solution literature, or two problem literatures, and tries to understand the

intermediate mechanisms that link the two literatures. For example, what are the mechanisms through which *drug X* can *treat breast cancer*, or what are the mechanisms by which *chemical Y* can *cause uterine cancer*? The main focus of the indirect foundational causes component of the present book is on LRDI ODS, since the goal is to identify potential foundational causes of disease.

There are two main LRDI methods for extrapolating knowledge and insights from one discipline/ technology to another: literature-based discovery (LBD) and literature-assisted discovery (LAD). The LBD approach uses technical experts to access and examine the literature from 'external' disciplines to help solve problems in the 'internal' discipline. The main LBD focus is finding potential discovery from literature analysis. The LAD approach uses technical experts from 'external' disciplines in a variety of interactive and/ or independent creative modes for the same purpose. The main LAD focus is using the literature's authors to find potential discovery. Combining LBD with LAD for full LRDI exploits the strengths of each while eliminating the weaknesses.

ODS LBD first surfaced in Swanson's 1986 pioneering paper on potential treatments for Raynaud's Phenomenon (RP). The general theory behind Swanson's ODS LBD approach, applied to two separate literatures, is based upon the following considerations [18].

Assume that two disjoint literatures can be generated, the first literature *AB* having a central theme *A* and sub-themes *B*, and the second literature *BC* having a central theme(s) *B* and sub-themes *C*. Further assume that linkages can be generated through the *B* themes that connect both literatures (e.g., *AB*→*BC*). Those linkages that connect the disjoint components of the two literatures (e.g., the components of *AB* and *BC* whose intersection is zero) are candidates for discovery, since the disjoint themes *C* identified in literature *BC* could not have been obtained from reading literature *AB* alone.

One interesting 'discovery' from Swanson's initial paper was that dietary eicosapentaenoic acid (theme *A* from literature *AB*) can decrease blood viscosity (theme *B* from both literatures *AB* and *BC*) and alleviate symptoms of RP (theme *C* from literature *BC*). There was no mention of eicosapentaenoic acid in the RP literature, but the acid was linked to the disease through the blood viscosity themes in both literatures.

There have been many papers written since 1986 that could be categorized as ODS LBD, and many of them were examined critically in the author's ARIST paper [14]. ODS LBD has powerful capabilities intrinsically; given

- 1) the large number of extant disparate medical/ technical disciplines and their literatures, and
- 2) the number of possible connections among all these disciplines,

there is much opportunity for potential discovery.

Unfortunately, the focus of almost all these past ODS LBD studies has been identification of potential treatments to eliminate symptoms, with almost no effort on identifying potential foundational causes that may be contributing to these symptoms. This includes both

foundational causes operating in isolation as well as foundational causes functioning as co-promoters. The present LRDI incarnation places equal emphasis on identifying foundational causes and treatments, and views one critically important component of treatments as the removal of foundational cause(s). The present incarnation also places equal emphasis on discovery and innovation, and assigns primary importance to the integration of disparate knowledge from the core and non-core disease literatures.

Blake, in a comprehensive 2011 ARIST article on text mining, shows no advances in ODS LBD that would alter the author's ARIST conclusions [19]. Smalheiser [20] shows that the Swanson *ABC* model is only one of several different types of models that can contribute to the development of the next generation of literature-based discovery tools. He emphasizes the need to develop a series of objective literature-based 'interestingness' measures, which can customize the output of these systems for different types of scientific investigations.

In the past decade, a number of semantic relation-based approaches have been promulgated. Cohen et al [21] use semantic indexing to identify empirically sequences of relationships known as 'discovery patterns', such as "drug x INHIBITS substance y, substance y CAUSES disease z" that link pharmaceutical substances to diseases they are known to treat. These sequences are derived from semantic predications extracted from the biomedical literature, and subsequently utilized to direct the search for known treatments for a held out set of diseases. Hu et al [22] present a biomedical semantic-based association rule system that significantly reduces spurious/ useless/ biologically irrelevant connections (the *B* terms in the *ABC* approach) through semantic filtering. Miller et al [23] advance the hypothesis of "cortisol as part of a mechanistic link elucidating the observed correlation between decreased testosterone in aging men and diminished sleep quality". Hristovski et al [24] overview myriad approaches to literature-based discovery, emphasizing semantic relations, especially 'discovery patterns'. The focus of these approaches is mainly potential treatments, and they achieve neither the breadth nor the volume of innovation and discovery of the author's approach.

6B. Causes of Multiple Diseases Background

(see [Section 6C](#) for definition of foundational causes)

There have been two generic types of approaches for identifying risk factors/ foundational causes for single or multiple diseases. One is assembling large teams of people to collect/ analyze large amounts of data from which relations among foundational causes/ risk factors and diseases can be inferred. The other is to examine data from myriad databases using automated/ semi-automated information technology approaches.

The best examples of the former are the Global Burden of Disease studies that have been performed over the past two decades, their analytical spinoffs [25-30], and related studies of more limited extent [31-35]. The value of these studies has been summarized well by Lopez [26], where he states in part: "Debates about health priorities are likely to be better informed if there is a reasonable understanding among policy makers of the comparative importance of various diseases and injuries in the population, at different ages, and how this pattern of health loss is changing over time.....the results can provide a meaningful accounting of the relative importance of different conditions in causing premature death and disability.....This was the basis for undertaking the first Global Burden of Disease (GBD) Study.....one might argue that health strategies and policies would be better served by a similarly complete and comparable understanding of the causes of various diseases and injuries, particularly those that account for substantial health loss in populations.....The challenge is how to adequately capture and quantify the full disease burden from risk factor exposures in a comprehensible and readily interpretable way so that policy discussions can be reliably informed by the outcomes, and thus respond appropriately.....Risk factor quantification is a powerful and compelling tool to support calls for policy action to improve health.....there is an urgent need to quantify important risks for major disease and injury outcomes not well covered by the current set of risk factors, including risks affecting mental health outcomes, and to expand the list of risk factors being investigated, including emerging environmental factors that are likely to significantly affect population health."

Examples of the information technology approaches include training neural networks to identify risk factors for specific diseases/ conditions [36-38], machine learning-based methods to quantify risk factors for diseases/ conditions [39-40], data based clustering and rule based prediction to identify risk factors for diseases/ conditions [41-42], Bayesian networks to identify risk factors [43-47], association rules to identify risk factors [48-49], decision trees to identify risk factors [50-54], and text/ data mining approaches [55-57]. Additionally, there is a substantial literature on information technology approaches for identifying adverse events resulting from drugs and surgery [58-70], a very limited sub-set of the total foundational causes addressed in this book.

Unfortunately, all the approaches based solely on searching the medical literature are severely limited in the depth and breadth of their output by the well-documented **under-reporting of adverse events** stemming from foundational causes, only a small sample of which is referenced here [71-125]. [Chapter 9](#) addresses some of the myriad reasons for this under-reporting of adverse events and negative findings.

The information technology approaches for identifying risk factors typically address one disease, or a limited number of diseases, and some incorporate myriad sources of data to arrive at risk factors. Both the Global Burden of Disease-type large-scale studies and the information technology approaches tend to include more than foundational causes in their typical risk factors.

This book concentrates solely on foundational causes, and identifies orders of magnitude more foundational causes/ risk factors than any of the above studies, albeit to less detail. ***None of the above studies identifies indirect foundational causes.*** This book identifies a few indirect foundational causes to illustrate the methodology, and shows that the present approach for identifying potential indirect causes ***has the capability to***

1) identify thousands, perhaps many thousands, of indirect foundational causes, and

2) open up vast areas for biomedical research.

6C. Foundational Cause - Definition

The myriad causes reported in this book are termed 'foundational'. A foundational cause is a tangible stimulus or behavior that can contribute to a symptom. Thus, excesses of calcium, water, exercise, drugs, environmental exposures, etc, can contribute to a symptom(s), and severe deficiencies of calcium, water, or exercise can also contribute to a symptom(s). Abuse, poverty, educational status, etc, can contribute to symptoms as well, even though categorizations into excesses and deficiencies may be less applicable. A foundational cause is defined as pervasive if it impacts at least a threshold number of myriad diseases.

A symptom(s)/ disease(s) is the result of imbalance between the strength of the toxic stimuli and the person's innate ability to neutralize the effects of the toxic stimuli, including the genetic factors that were not included in this book. The two are not independent; the toxic stimuli can affect the capabilities of the defensive system to neutralize incoming toxic stimuli. Thus, the incoming toxic stimuli can be viewed as a 'signature' of individual toxic stimuli, with different weightings assigned to each toxic stimulus, and the defense can also be viewed as a 'signature', with different weightings assigned to the health of the body's defensive mechanisms. Whether a symptom will materialize as a result of one or more toxic stimuli depends on whether the defensive 'signature' is able to neutralize the 'signature' of the incoming toxic stimuli.

Thus, not every person who eats a high-salt diet or undergoes radiocontrast diagnosis gets CKD, but some (more than expected randomly) do. There were a number of cases in the literature where relatively few people were reported to have adverse reactions to a given toxic stimulus. Identifying the offensive-defensive 'signature' relationships that allow toxic stimuli to translate into symptoms (within the context of understanding genetic polymorphisms and the resulting variations in biological pathways) will play a significant role in explaining why some people develop a disease and others do not when exposed to the same agent. Understanding the complex web of gene-environment interactions is the central challenge of modern medicine; our identification of myriad individual toxic stimuli and defensive system deficiencies is the first step in this long journey.

For purposes of this book, we term a toxic stimulus a (foundational) cause if

- 1) the research author stated/ implied/ inferred the toxic stimulus was a cause and
- 2) the information presented supported the research author's conclusion.

We recognize, however, that this toxic stimulus was in all probability one component of a more complex offensive-defensive 'signature' imbalance that resulted in the symptom of interest.

Chapter 7

DETAILED TEXT MINING METHODOLOGY

7A. Methodology used to Retrieve Causes-Related Articles

7A1. Identification of Foundational Causes of Disease

This book focuses on identifying 'all' direct and indirect foundational causes for thousands of diseases and symptoms. It extrapolates, and significantly advances, the techniques used in our recent study on identifying foundational causes (and treatments) of a single disease, chronic kidney disease (CKD). In the CKD study, approximately 900 direct and indirect causes of CKD were identified [12].

The goal of this book is to develop a quasi-streamlined methodology for identifying the full spectrum of potential foundational causes of disease, and then relate these foundational causes to the full spectrum of diseases and symptoms. Expanding queries developed in past studies (to identify foundational causes for single-diseases (such as [12])) to all diseases and symptoms is not practical because of the sheer magnitude of query terms required.

The first step in designing and developing a specific query for retrieving records is identifying the database(s) and search engine(s) that will be used in the retrieval process, since the query format has to be tailored to the database and search engine characteristics. Medline was selected as the database to be used, since it is the main repository of records from the premier biomedical journals. Pubmed was selected as the source search engine for the Medline database rather than Thomson Medline (which was used in the CKD study [12]).

Much larger retrievals were expected for the studies in this book relative to the CKD study because of the numbers of foundational causes and diseases expected. In Pubmed, the full retrieval can be downloaded at once; in Thompson, only 500 records per download are allowed. When downloading hundreds of thousands of records (as was done in the present studies), download time becomes important. Typically, ~600,000 records occupying ~2GB storage were imported from Pubmed in slightly over an hour for the present study.

Also, Pubmed introduces records at an earlier stage of processing. For example, a search of Thomson Medline using the text term 'virus' in the Title for records published in 2014 (search performed on 19 May 2014) retrieved 3789 records, whereas a search of Pubmed on the same day with the same query retrieved 4951 records. For the above reasons, and since the proximity search capability of Thomson Medline would not be used for this book, Pubmed was used as the data source.

Three approaches were used to develop queries for identifying foundational causes for all diseases: one highly streamlined, and two far less streamlined. The highly streamlined approach used only MeSH [Qualifiers](#) to retrieve the records from Pubmed for analysis. The first of the less streamlined approaches used generic MeSH terms (relatively unambiguously related to foundational causes) to retrieve the records from Pubmed for analysis, and the second of the less streamlined approaches used text terms (applied to the Title field) to retrieve the records from

Pubmed for analysis. The results of all three approaches were integrated in the main body of the text to provide the final taxonomy for foundational causes (Chapters [3](#) and [8](#)); the details of the three approaches follow.

7A1a. MeSH Qualifiers Approach

7A1a1. MeSH format causes

An offshoot of the MeSH Qualifier concept was used for identifying foundational causes. There are 83 topical MeSH Qualifiers used for indexing and cataloging in conjunction with MeSH Heading descriptors. All 83 were examined in more or less detail for applicability to identifying foundational causes of disease. Four were selected (after extensive validation) as producing highly relevant results when used in isolation: **adverse effects, toxicity, pathogenicity, poisoning**. A few limited combinations of the remaining MeSH Qualifiers were examined, but none were deemed to have sufficient relevance. These four MeSH Qualifiers selected constituted the query, and could also be viewed as linking terms for retrieving relevant foundational causes of disease.

This simplified query (consisting of four MeSH Qualifiers) was entered into Pubmed for the time interval 2004-2014. On 10 May 2014, 592,074 records (all with Abstracts) were retrieved and downloaded, and were imported into the Vantage Point software used for the text analysis. 591,884 unique Abstracts were displayed by the software. There were 595,730 MeSH terms (with MeSH Qualifiers) listed. All MeSH terms that included at least one of the above four Qualifiers were placed in a separate group, containing a total of 116,538 MeSH terms with Qualifiers. The software integrated over the MeSH Qualifiers to yield 9,038 MeSH Headings (no Qualifiers shown). These MeSH Headings were the foundational causes for the 4,000+ diseases expressed in MeSH terminology.

It was desired to generate a causes-diseases/ symptoms matrix for display and analytic purposes. Therefore, the diseases and symptoms needed to be identified and grouped. A detailed examination of the remaining MeSH Qualifiers, and observation of MeSH Qualifier patterns in the records where foundational causes Qualifiers appeared, showed that the following MeSH Qualifiers tended to be associated with diseases and symptoms: etiology, chemically induced, complications, pathology, diagnosis, immunology, microbiology, parasitology, physiopathology, virology, epidemiology, radiation effects, metabolism, drug effects, prevention and control. All MeSH terms that included at least one of the above fifteen MeSH Qualifiers were placed in a separate group, containing a total of 353,383 MeSH terms with Qualifiers. The software integrated over the MeSH Qualifiers to yield 17,142 MeSH Headings (no Qualifiers shown).

However, this initial list went beyond diseases and symptoms, and required further filtering. The National Institutes of Health (NIH) generates a Web site entitled MeSH Tree Structures (<http://www.nlm.nih.gov/mesh/trees.html>), which lists all the MeSH Headings in the different branches of the [MeSH tree](#). The MeSH Headings listed for all diseases and symptoms were downloaded and intersected with the above initial list of 17,142 MeSH Headings. A perusal of this filtered list, compared with the unfiltered list, showed a number of items that were

not listed in the NIH MeSH tree under one of the three categories, but, nevertheless, were impacted by the items listed as 'causes'. For the most part, these additional items could be viewed as *processes and mechanisms*. Therefore, the first 5,000 items in the list of 17,142 MeSH Headings were inspected visually, and all those that could be impacted by the 'causes' were added to the filtered list. Substantial sampling was performed to validate any selections in question. The resulting list of 5,870 diseases and symptoms was inspected visually, and any terms that were not diseases or symptoms (typically biomarkers) were removed. There were 4,147 diseases in the final list.

It became clear at this point that two different matrices would be preferable for identifying

- 1) direct foundational causes and
- 2) indirect foundational causes.

For identifying and tabulating direct foundational causes, a causes-diseases/ symptoms matrix would offer the most credibility. For identifying indirect causes, a causes-diseases/ symptoms matrix linked to a diseases/ symptoms square matrix would be preferable, because foundational causes could then be linked to the disease(s) of interest through other diseases and symptoms that were **closely related** to the disease(s) of interest.

Thus, assume i is a **direct** cause of disease $j1$, and is not a direct cause of disease $j2$. Also, assume disease $j1$ is **strongly related** to disease $j2$. Then, in the terminology of this book, i is assumed to be a potential **indirect** cause of disease $j2$, with the potential of being converted to a direct cause. This latter assumption of potential conversion to direct cause would have to be validated by lab experiments and clinical trials; hence the potential of the indirect causes for **opening up these vast additional areas of biomedical research** to ascertain whether they can be shown to be direct causes!

In the MeSH Qualifiers causes-diseases-only matrix, there are 8046 foundational causes (MeSH terminology) and 4147 diseases ([MeSH Headings No Explode](#)). Foundational causes that could be viewed as quasi-universal or pervasive are those that impacted more than a threshold number of diseases.

For identifying indirect foundational causes, two matrices sharing a common axis are plotted with this data. The upper matrix is a square symmetrical matrix of diseases and symptoms (hereafter abbreviated as Diseases) on each axis. The lower matrix is a plot of foundational causes vs Diseases. The intersection of foundational cause i with Disease j is defined as a direct foundational cause of Disease j if the matrix cell contains an entry, and a *potential* indirect foundational cause if the matrix cell does not contain an entry.

To identify potential indirect foundational causes of Disease j , direct foundational causes of Diseases **strongly associated** with Disease j are identified, and hypothesized to be potential indirect foundational causes of Disease j . Thus, for example, if Hypertension is shown to be strongly related to CKD, and substance X is a direct cause of Hypertension but not a direct cause

of CKD, then substance X is hypothesized to be an indirect cause of CKD. The stronger the relationship between the two Diseases, and the more strong pathways that exist linking other Diseases (for which substance X is a direct foundational cause) to CKD, the stronger is the basis for the assumption that substance X is a potential indirect foundational cause of CKD, and is in fact a ***Discovery*** in the Swanson sense of discovery [18] (heretofore applied only to potential treatments).

What constitutes a strong relationship/ association between two Diseases that would form a credible basis for hypothesizing potential discovery of indirect causes? Two metrics were examined. One metric was co-occurrence of two Disease MeSH terms well beyond that expected randomly. Thus, if there are Nt total records in a database, then:

- 1) the probability of MeSH term A occurring in any one record would be N_a (the number of records that contain MeSH term A in the database) divided by Nt;
- 2) the probability of MeSH term B occurring in any one record would be N_b/N_t ;
- 3) the probability of MeSH terms A and B co-occurring in one record by chance would be $(N_a/N_t)*(N_b/N_t)$; and,
- 4) the co-occurrence expected by chance would be $(N_a/N_t)*(N_b/N_t)*N_t$, or $(N_a*N_b)/N_t$.

Thus, if the actual co-occurrence C_{ab} of two Disease MeSH terms A and B is substantially larger than $(N_a*N_b)/N_t$, the linkage between Diseases A and B is assumed to be strong. The higher the ratio of actual co-occurrence to expected co-occurrence, the stronger is the assumed relationship.

The other metric examined was the Inclusion Index based on the smaller of the two frequencies of occurrence, defined as $C_{ab}/\text{MIN}(N_a,N_b)$. Because of better behavior at the limits, the latter metric was selected for estimating the strength of the relationship between the two diseases A and B. The Disease-Disease matrix was normalized using the Inclusion Index. The combination of the foundational causes-Diseases matrix and the normalized Diseases-Diseases matrix formed a foundational causes-Diseases ***network***, which allowed both direct foundational causes to be identified from the foundational causes-Diseases matrix and indirect foundational causes to be identified by tracking potential foundational causes through myriad pathways in the Diseases-Diseases component of the network.

Finally, while this MeSH Qualifier linking approach was developed for, and applied to, potential foundational causes, it can be easily modified for identifying potential treatments, identifying potential biomarkers, identifying potential mechanisms, etc.

7A1a2. Chemical Registry Number Causes

Pubmed contains two fields called Registry Number and Substance Name. Registry Number contains identifiers representing the substances mentioned in the article when such identifiers are included in the MeSH record for the substance. Substance Name may contain any of three types of supplementary concept record (SCR) data:

- 1) MeSH SCR chemical and drug terms (Class 1);
- 2) protocol terms (Class 2); and
- 3) non-MeSH rare disease terms (Class 3) from the National Institutes of Health (NIH) Office of Rare Diseases.

The MeSH Database and MeSH Browser contain all of these terms.

These two fields are combined into one field in the VP software (Chemical Registry Number-CRN), and may contain foundational causes that are not shown in the Title or MeSH Heading fields. This CRN field was examined for potential causes in the MeSH Qualifiers-retrieved database only. There were no associated linking terms in the CRN field that would allow extraction of foundational causes only, so the CRN terms had to be inspected visually. These CRN terms could be causes, treatments, and biomarkers mainly. They were read to a pre-selected cutoff frequency, and additional terms were identified at lower frequencies from intersection with externally-provided lists of toxic materials. All 1,394 resulting CRN foundational causes terms were validated by visual inspection, and constituted the y-axis of the CRN foundational causes-Diseases matrix.

7A1b. Generic MeSH Headings Approach

Generic MeSH Headings related relatively unambiguously to foundational causes were identified two ways. Results from past studies were examined, especially the CKD study [12], and generic relevant MeSH Headings were extracted. Second, a few of the most unambiguous generic MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry terms) were examined for relevance. There were 145 terms from both sources judged to produce highly relevant results (shown later). These 145 terms constituted the generic MeSH Headings query for retrieving foundational causes of disease. Pubmed was also used as the source search engine for the Medline database, for the reasons presented above.

This query was entered into Pubmed for the time interval 1994-2014. On 18 October 2014, 693,450 records (most with Abstracts) were retrieved and downloaded, and were imported into the Vantage Point software. 690,486 unique Abstracts were displayed by the software. There were 516,519 MeSH terms (mainly with, but some without, Qualifiers) listed, and 24,231 Top Level MeSH Headings (Top Level MeSH Headings represent MeSH Headings that have been integrated over the MeSH Qualifiers). In the remaining steps of the generic MeSH Headings approach, potential MeSH Headings from different sources are intersected with the 24,231 Top Level MeSH Headings, and integrated to arrive at the total foundational causes from generic MeSH Headings. In addition, visual inspection of the highest frequency Top Level MeSH Headings was performed, to insure that no relevant MeSH Headings had been overlooked in the 'dot product' components of the process described above.

First, all MeSH terms that included at least one of the four Qualifiers shown in the previous MeSH Qualifiers section were placed in a separate group. This group contained a total

of 52,949 MeSH terms. The software integrated over the MeSH Qualifiers to yield 6,543 MeSH Headings (no Qualifiers shown).

Second, the 9,038 MeSH Heading causes from the MeSH Qualifiers study in the previous MeSH Qualifiers section were imported. Third, the 1,394 Chemical Registry Substances extracted in the MeSH Qualifiers study were imported. Fourth, the 13,762 raw text causes extracted from the results of the Title text retrieval study of the next section were imported.

Then, these 6,543 MeSH Headings, combined with

- 1) the 9,038 MeSH Heading causes from the MeSH Qualifiers study in the previous MeSH Qualifiers section,
- 2) the 1,394 Chemical Registry Substances extracted in the MeSH Qualifiers study, and
- 3) the 13,762 raw text causes extracted from the results of the Title text retrieval study of the next section,

were intersected with the 24,231 Top Level MeSH Headings, to yield a total of 8,982 foundational causes. These were the foundational causes for 4,000+ diseases expressed in MeSH terminology from the relatively unambiguous MeSH Headings retrieval, and they constituted the y-axis of the Generic MeSH foundational causes-Diseases matrix.

Again, while this focused MeSH Heading approach was developed for identifying potential foundational causes, it could (with some work) be adapted to identifying potential treatments, potential biomarkers, potential mechanisms, etc.

7A1c. Title Linking Phrases Approach

Because of limitations from use of MeSH terms (not all records have MeSH descriptors, not all MeSH terms are included in those records that have MeSH terms, not all MeSH descriptors used have appropriate Qualifiers attached. etc), a text-based approach for identifying causes was added. While the Abstract field would have been most informative and appropriate, computer storage and software limitations would not allow the parsed Abstract field phrases to be opened. Therefore, the record Title field was selected for analysis.

A query consisting of two components was used to retrieve the Pubmed records that had high probability of containing foundational causes. The first component consisted of terms that, when they appeared in the Title, were associated with foundational causes in the Title relatively unambiguously. These terms were validated a priori. The second component consisted of terms that, when they co-occurred in the Title with disease names, were associated with foundational causes in the Title relatively unambiguously. The full query used to retrieve records is shown later.

This query was entered into Pubmed for the time interval 1989-2014, 616,300 records (many with Abstracts) were retrieved and downloaded on 28 September 2014, and were imported into the Vantage Point software. 536,833 unique Abstracts were displayed by the

software. There were 5,452,563 Title phrases listed, which consisted of all single-word, double-word, triple-word, and quadruple-word phrases that did not start or end with stop-words.

The foundational causes in the retrieved records were identified three ways. First, the parsed Title phrases (arranged by inverse record frequency) were examined visually down to a threshold frequency, and foundational causes terms were extracted and validated. Given the extremely large number of Title phrases, only a very small fraction could be examined visually.

Second, for lower frequency Title phrases, the strongest linking terms (e.g., -induced, -related, -associated, -exposed, caused by, induced by, exposure to, exposed to, etc) were used to extract potential foundational causes phrases. The extracted phrases were then stripped of the linking terms, combined to avoid duplication, and added to the foundational causes identified visually in the first part.

Finally, foundational causes from myriad other sources, including past studies, government-approved lists of toxic substances, MeSH-derived causes, and CRN-derived causes, were intersected with the full list of Title phrases, and added to the foundational causes identified in the first two parts.

There were 13,762 validated foundational causes that resulted from the above extraction techniques. However, many reflected similar concepts, and could be combined using the VP software phrase combining capability. After a three-step combination approach, 6,480 foundational causes resulted, and they constituted the y-axis of the Title phrase foundational causes-diseases matrix. Some were generic, but most were specific.

While the Title phrase linking terms were developed specifically for identifying causes, a similar approach could be used to develop linking terms for identifying potential treatments, potential biomarkers, or potential mechanisms. Moreover, there could be substantial benefits gained by using Abstracts for phrase generation rather than Titles, and even full-text rather than Abstracts. While use of proximity queries with the linking terms in the Title were not required, they would be required for use in Abstracts or full-text. Adding proximity capability would be a *minor* modification to the form of the query developed below. The major issue would be switching to a database search engine that had the capability of proximity searching.

7B. Queries used to Retrieve Causes-Related Articles

7B1. MeSH Qualifier Query

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/ toxicity allows records to be retrieved related to the toxicity of Cadmium. These MeSH Qualifiers may be perceived as linking terms to the MeSH Headings, allowing for 'surgical' extraction of MeSH Headings that meet desired criteria. Thus, if MeSH Qualifiers strongly related to foundational causes can be identified, they can be used to identify MeSH Headings that are potential foundational causes of disease. As shown previously, the four MeSH Qualifiers listed below were selected as the query, and are presented in Pubmed format.

Query

adverse effects [sh] OR toxicity [sh] OR pathogenicity [sh] OR poisoning [sh]

7B2. Title Text Term Query

Because many Medline records do not contain MeSH terms, and because MeSH term assignment may not always be complete, it was decided to augment the MeSH queries with a text query. Due to computer and software limitations on storage and processing time, Titles were used as the text source rather than Abstracts or full-text.

This Title query consists of two parts: standalone terms, and terms that are intersected with diseases. Most of these terms were derived by examining Titles of records that addressed foundational causes of disease, and selecting those terms that tended to appear frequently with the foundational causes. The diseases used for the second group of terms were obtained by starting with Pubmed's list of all diseases (in MeSH terminology), converting them to text form, consolidating diseases to more generic descriptors, and adding some generic terms not in MeSH (such as cancer*).

7B2a. Standalone Terms

(([ti] is the Pubmed tag for Title field)

cardiotoxic* [ti] OR genotoxic* [ti] OR hepatotoxic* [ti] OR immunotoxic* [ti] OR intoxicat* [ti] OR nephrotoxic* [ti] OR neurotoxic* [ti] OR ototoxic* [ti] OR phototoxic* [ti] OR phytotoxic* [ti] OR toxic-effect* [ti] OR toxic-potential* [ti] OR toxic-hazard* [ti] OR toxic-combin* [ti] OR toxicities [ti] OR toxicity [ti] OR toxicological-effect* [ti] OR toxicological-evaluation* [ti] OR toxicological-impact* [ti] OR toxicological-hazard* [ti] OR toxicological-assessment* [ti] OR toxin-associated [ti] OR toxin-related [ti] OR toxin-injur* [ti] OR toxin-risk* [ti] OR lethal-toxin* [ti] OR (toxin* [ti] AND (fatal* [ti] OR adverse [ti] OR morbid* [ti] OR mortality [ti] or anaphyla* [ti] OR harm [ti] OR damag* [ti] OR deteriorat* [ti] OR exacerbat* [ti] OR trigger* [ti] OR aggravat* [ti])) OR injury-associated [ti] OR risk-associated [ti] OR virus-associated [ti] OR (Ionizing [ti] AND risk* [ti]) OR (risk-of [ti] AND adverse [ti]) OR (adverse-health-effect* [ti] AND (effects-of [ti] OR effect-of [ti])) OR adverse-

effect* [ti] OR injury-following [ti] OR related-consequences [ti] OR therapy-related [ti] OR traffic-related [ti] OR health-consequences [ti] OR long-term consequences [ti] OR anaphylactic-reaction* [ti] OR cutaneous-reaction* [ti] OR hypersensitivity-reaction* [ti] OR transfusion-reaction* [ti] OR skin-reaction* [ti] OR inflammation-reaction* [ti] OR inflammatory-reaction* [ti] OR reaction-associated [ti] OR foreign-body-reaction* [ti] OR tissue-reaction* [ti] OR infusion-reaction* [ti] OR systemic-reaction* [ti] OR (allergic [ti] AND reaction-to [ti]) OR teratogenicity [ti] OR teratogenic-effect* [ti] OR advanced-glycation [ti] OR allergenicity [ti] OR bioaccumulation [ti] OR carcinogen [ti] OR Carcinogenic [ti] OR carcinogenicity [ti] OR contaminat* [ti] OR disrupting-chemical* [ti] OR ((effects [ti] OR effect [ti]) AND subchronic [ti]) OR ((effects-of [ti] OR effect-of [ti]) AND prenatal [ti]) OR envenomation [ti] OR fatalities [ti] OR high-fat [ti] OR mutagenicity [ti] OR poisons [ti] OR poisoning [ti] OR precipitated-by [ti] OR precipitated-after [ti] OR precipitated-following [ti] OR side-effect* [ti] OR teratogenesis [ti] OR deleterious-effect* [ti] OR detrimental-effect* [ti] OR late-effect* [ti] OR adverse-metabolic-effect* [ti] OR adverse-renal-effect* [ti] OR respiratory-effect* [ti] OR negative-effect* [ti] OR adverse-reaction* [ti] OR (adversity [ti] AND (early [ti] OR child* [ti] OR life* [ti] OR social [ti] OR family [ti])) OR causative-agent [ti] OR caused-by [ti] OR exposure-to [ti] OR exposed-to [ti] OR exposures [ti] OR (damage-in [ti] AND mice [ti]) OR (damage-in [ti] AND rats [ti]) OR hepatic-damage [ti] OR liver-damage [ti] OR ((increased-risk* [ti] OR complications [ti] OR mutagenic [ti] OR adverse-outcome* [ti] OR life-threatening [ti] OR lung-injury [ti] OR renal-injury [ti] OR susceptibility [ti] OR adverse [ti] OR allergic-reaction* [ti] OR anaphyla* [ti] OR cognitive-dysfunction [ti] OR cardiac-dysfunction [ti] OR (dysfunction [ti] AND in-rats [ti]) OR erectile-dysfunction [ti] OR renal-dysfunction [ti] OR mitochondrial-dysfunction [ti] OR endothelial-dysfunction [ti] OR sexual-dysfunction [ti] OR ventricular-dysfunction [ti] OR allograft-dysfunction [ti] OR thyroid-dysfunction [ti] OR graft-dysfunction [ti] OR liver-dysfunction [ti] OR diastolic-dysfunction [ti] OR vascular-dysfunction [ti] OR organ-dysfunction [ti] OR barrier-dysfunction [ti] OR myocardial-dysfunction [ti] OR systolic-dysfunction [ti] OR voiding-dysfunction [ti] OR hepatic-dysfunction [ti] OR bladder-dysfunction [ti] OR bowel-dysfunction [ti] OR urinary-dysfunction [ti] OR swallowing-dysfunction [ti] OR anorectal-dysfunction [ti] OR cardiopulmonary-dysfunction [ti] OR fatal [ti] OR fibrosis [ti] OR high-incidence [ti] OR iatrogenic [ti] OR mortality [ti] OR morbidity [ti] OR risk* [ti]) AND (after [ti] OR following [ti] OR related-to [ti] OR resulting-from [ti] OR due-to [ti]))

7B2b. Intersect with Diseases

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Abdominal-Pregnancy [ti] OR Aberrant-Crypt-Foci [ti] OR Abnormal-Karyotype [ti] OR Abnormal-Reflex [ti] OR Abnormalities [ti] OR Abnormality [ti] OR Abortion [ti] OR Abruptio-Placentae [ti] OR Abscess* [ti] OR Acalculous-Cholecystitis [ti] OR Acanthamoeba-Keratitis [ti] OR Acantholysis [ti] OR Acanthosis-Nigricans [ti] OR Acatlasia [ti] OR Accelerated-Idioventricular-Rhythm [ti] OR Accessory-Atrioventricular-Bundle [ti] OR Achlorhydria [ti] OR Achondroplasia [ti] OR Acid-Base-Imbalance* [ti] OR Acidosis [ti] OR Acne-Keloid [ti] OR Acne-Vulgaris [ti] OR Acrocephalosyndactylia [ti] OR Acrodermatitis [ti] OR Acrodynia [ti] OR Acromegaly [ti] OR Acro-Osteolysis [ti] OR Acrospiroma [ti] OR Actinomycosis [ti] OR Activated-Protein-C-Resistance [ti] OR Acute-Abdomen [ti] OR Acute-

Generalized-Exanthematous-Pustulosis [ti] OR Acute-Kidney-Injury [ti] OR Acute-Lung-Injury [ti] OR Acute-Phase-Reaction [ti] OR Adenocarcinoma* [ti] OR Adenofibroma [ti] OR Adenolymphoma [ti] OR Adenoma* [ti] OR Adenomyoma [ti] OR Adenomyosis [ti] OR Adenosarcoma [ti] OR Adiposis-Dolorosa [ti] OR Adrenal-Insufficiency [ti] OR Adrenocortical-Hyperfunction [ti] OR Adrenoleukodystrophy [ti] OR Aerophagy [ti] OR Afibrinogenemia [ti] OR African-Horse-Sickness [ti] OR Agammaglobulinemia [ti] OR Agenesis-of-Corpus-Callosum [ti] OR Ageusia [ti] OR Aggressive-Periodontitis [ti] OR Agnosia [ti] OR Agranulocytosis [ti] OR Agraphia [ti] OR AIDS-Arteritis [ti] OR AIDS-Dementia-Complex [ti] OR AIDS-Related-Complex [ti] OR Airway-Obstruction* [ti] OR Airway-Remodeling [ti] OR Akathisia [ti] OR Akinetic-Mutism [ti] OR Albinism [ti] OR Albuminuria [ti] OR Alcohol-Withdrawal-Delirium [ti] OR Alcohol-Withdrawal-Seizures [ti] OR Alcoholism [ti] OR Alexia [ti] OR Alkalosis [ti] OR Alkaptonuria [ti] OR Alopecia [ti] OR alpha-1-Antitrypsin-Deficiency [ti] OR alpha-Mannosidosis [ti] OR alpha-Thalassemia [ti] OR Alternariosis [ti] OR Altitude-Sickness [ti] OR Alveolar-Bone-Loss [ti] OR Alveolitis [ti] OR Amaurosis-Fugax [ti] OR Amblyopia [ti] OR Amebiasis [ti] OR Ameloblastoma [ti] OR Amelogenesis-Imperfecta [ti] OR Amenorrhea [ti] OR Amino-Acid-Metabolism [ti] OR Amnesia [ti] OR amyloid-Plaque [ti] OR Amyloidosis [ti] OR Anaemia [ti] OR Anaphylaxis [ti] OR Anaplasia [ti] OR Anaplasmosis [ti] OR Anastomotic-Leak [ti] OR Ancylostomiasis [ti] OR Anemia [ti] OR Anencephaly [ti] OR Anetoderma [ti] OR Aneurysm [ti] OR Angina [ti] OR Angiodysplasia [ti] OR Angioedema* [ti] OR Angiofibroma [ti] OR Angioid-Streaks [ti] OR Angiokeratoma [ti] OR Angiolipoma [ti] OR Angiomatosis [ti] OR Angiomyolipoma [ti] OR Anhedonia [ti] OR Aniridia [ti] OR Anisakiasis [ti] OR Aniseikonia [ti] OR Anisocoria [ti] OR Anisometropia [ti] OR Ankylosis [ti] OR Anodontia [ti] OR Anomia [ti] OR Anophthalmos [ti] OR Anorexia [ti] OR Anovulation [ti] OR Anoxia [ti] OR Anthracosilicosis [ti] OR Anthracosis [ti] OR Anthrax [ti] OR Antithrombin-III-Deficiency [ti] OR Anuria [ti] OR Aortic-Coarctation [ti] OR Aortic-Valve-Insufficiency [ti] OR Aortic-Valve-Prolapse [ti] OR Aortitis [ti] OR Aphakia [ti] OR Aphasia [ti] OR Aponia [ti] OR Aplasia [ti] OR Apnea [ti] OR Apoptosis [ti] OR Appendicitis [ti] OR Apraxia [ti] OR Apraxias [ti] OR Arachnoid-Cyst* [ti] OR Arachnoiditis [ti] OR Arcus-Senilis [ti] OR Argininosuccinic-Aciduria [ti] OR Argyria [ti] OR Arnold-Chiari-Malformation [ti] OR Arrhythmia* [ti] OR Arterial-Stiffness [ti] OR Arterio-Arterial-Fistula [ti] OR Arteriolosclerosis [ti] OR Arteriosclerosis [ti] OR Arteriovenous-Fistula [ti] OR Arteriovenous-Malformations [ti] OR Arteritis [ti] OR Arthralgia [ti] OR Arthritis [ti] OR Arthrogyposis [ti] OR Arthropathy [ti] OR Arthus-Reaction [ti] OR Artificial-Lens-Implant-Migration [ti] OR Asbestosis [ti] OR Ascariasis [ti] OR Ascariidiasis [ti] OR Ascites [ti] OR Ascorbic-Acid-Deficiency [ti] OR Aspergillosis [ti] OR Asphyxia [ti] OR Asthenia [ti] OR Asthenopia [ti] OR Asthenozoospermia [ti] OR Asthma [ti] OR Astigmatism [ti] OR Astrocytoma [ti] OR Ataxia [ti] OR Atherosclerosis [ti] OR atherosclerotic-plaque [ti] OR Athetosis [ti] OR Atrial-Fibrillation [ti] OR Atrial-Flutter [ti] OR Atrial-Premature-Complexes [ti] OR Atrial-Remodeling [ti] OR Atrioventricular-Block [ti] OR Atrophic-Vaginitis [ti] OR Atrophy [ti] OR Autolysis [ti] OR Autonomic-Dysreflexia [ti] OR Avian-Leukosis [ti] OR Avitaminosis [ti] OR Azoospermia [ti] OR Azotemia [ti] OR Babesiosis [ti] OR babinski-Reflex [ti] OR Bacteremia [ti] OR Bacteriuria [ti] OR Balanitis [ti] OR Balanitis-Xerotica-Obliterans [ti] OR Balantidiasis [ti] OR Barrett-Esophagus [ti] OR Bell-Palsy [ti] OR Bell's-Palsy [ti] OR Beriberi [ti] OR Berylliosis [ti] OR beta-Thalassemia [ti] OR Bile-Reflux [ti] OR Biliary-Atresia [ti] OR Biliary-Dyskinesia [ti] OR Biliary-Fistula [ti] OR Binge-

Drinking [ti] OR Biotinidase-Deficiency [ti] OR Bird-Fancier's-Lung [ti] OR Birth-Injuries [ti] OR Birth-Weight [ti] OR Bladder-Exstrophy [ti] OR Blast-Crisis [ti] OR Blastomycosis [ti] OR Blepharitis [ti] OR Blepharoptosis [ti] OR Blepharospasm [ti] OR Blindness [ti] OR Blister* [ti] OR Blood-Group-Incompatibility [ti] OR Blood-Loss [ti] OR Bluetongue [ti] OR Body-Weight [ti] OR Bone-Anteversion [ti] OR Bone-Cysts [ti] OR Bone-Demineralization [ti] OR Bone-Malalignment [ti] OR Bone-Resorption [ti] OR Bone-Retroversion [ti] OR Botulism [ti] OR Brachial-Plexus-Neuritis [ti] OR Brachydactyly [ti] OR Bradycardia [ti] OR Brain-Concussion [ti] OR Brain-Damage [ti] OR Brain-Death [ti] OR Brain-Injur* [ti] OR Brain-Ischemia [ti] OR Branchioma [ti] OR Breast-Cyst* [ti] OR Breech-Presentation [ti] OR Brenner-Tumor* [ti] OR Bronchial-Fistula [ti] OR Bronchial-Hyperreactivity [ti] OR Bronchial-Spasm [ti] OR Bronchiectasis [ti] OR Bronchiolitis [ti] OR Bronchitis [ti] OR Bronchogenic-Cyst* [ti] OR Bronchomalacia [ti] OR Bronchopneumonia [ti] OR Bronchopulmonary-Sequestration [ti] OR Brucellosis [ti] OR Bruxism [ti] OR Bulbar-Palsy [ti] OR Bulbo-Spinal-Atrophy [ti] OR Bulimia [ti] OR Bundle-Branch-Block [ti] OR Burkitt-Lymphoma [ti] OR Bursitis [ti] OR Buschke-Lowenstein-Tumor* [ti] OR Byssinosis [ti] OR Cachexia [ti] OR CADASIL [ti] OR Cafe-au-Lait-Spots [ti] OR Calcification [ti] OR Calcinosis [ti] OR Calciphylaxis [ti] OR Calculi [ti] OR Callosities [ti] OR Cancer* [ti] OR Candidemia [ti] OR Candidiasis [ti] OR Capsule-Opacification [ti] OR Carbohydrate-Metabolism [ti] OR Carbonyl-Stress [ti] OR Carboxymethyllysine [ti] OR Carcinogenesis [ti] OR Carcinoid-Tumor* [ti] OR Carcinoma* [ti] OR Carcinosarcoma* [ti] OR Cardiac-Arrest [ti] OR Cardiac-Complexes [ti] OR Cardiac-Output [ti] OR Cardiac-Tamponade [ti] OR Cardiogenic-Shock [ti] OR Cardiomegaly [ti] OR Cardiomyopath* [ti] OR cardiovascular-health [ti] OR cardiovascular-outcome* [ti] OR cardiovascular-risk [ti] OR Carney-Complex [ti] OR Carotid-Artery-Dissection [ti] OR Carotid-Artery-Injuries [ti] OR Carotid-Body-Tumor* [ti] OR Carotid-Cavernous-Sinus-Fistula [ti] OR Catalepsy [ti] OR Cataplexy [ti] OR Cataract* [ti] OR Catatonia [ti] OR Causalgia [ti] OR Cellulitis [ti] OR Central-Nervous-System-Cyst* [ti] OR Central-Nervous-System-Helminthiasis [ti] OR Central-Nervous-System-Vascular-Malformation* [ti] OR Central-Serous-Chorioretinopathy [ti] OR Cephalopelvic-Disproportion [ti] OR Cerebellar-Ataxia [ti] OR Cerebral-Amyloid-Angiopathy [ti] OR Cerebral-Palsy [ti] OR Cerebral-Phaeohyphomycosis [ti] OR Cerebral-Ventriculitis [ti] OR Cerebrospinal-Fluid-Otorrhea [ti] OR Cerebrospinal-Fluid-Rhinorrhea [ti] OR Cerebrovascular-Trauma [ti] OR Cervical-Intraepithelial-Neoplasia [ti] OR Chagas-Cardiomyopathy [ti] OR Chalazion [ti] OR Chancre [ti] OR Chancroid [ti] OR Channelopathies [ti] OR Cheilitis [ti] OR Cheyne-Stokes-Respiration [ti] OR Chickenpox [ti] OR Chills [ti] OR Chloracne [ti] OR Choanal-Atresia [ti] OR Cholangiocarcinoma [ti] OR Cholangitis [ti] OR Cholecystitis [ti] OR Cholecystolithiasis [ti] OR Choledochal-Cyst* [ti] OR Choledocholithiasis [ti] OR Cholelithiasis [ti] OR Cholera [ti] OR Cholestasis [ti] OR Cholesteatoma [ti] OR Choline-Deficiency [ti] OR Chondroblastoma [ti] OR Chondrocalcinosis [ti] OR Chondrodysplasia-Punctata [ti] OR Chondroma [ti] OR Chondromalacia-Patellae [ti] OR Chondrosarcoma [ti] OR Chordoma [ti] OR Chorea [ti] OR Chorioamnionitis [ti] OR Choriocarcinoma [ti] OR Chorioretinitis [ti] OR Choristoma [ti] OR Choroidal-Neovascularization [ti] OR Choroiditis [ti] OR Chromoblastomycosis [ti] OR Chromosomal-Instability [ti] OR Chromosome-Aberration* [ti] OR Chromosome-Breakage [ti] OR Chromosome-Fragility [ti] OR Chromosome-Inversion [ti] OR Chylothorax [ti] OR Chylous-Ascites [ti] OR Cicatrix [ti] OR Citrullinemia [ti] OR Cleft-Lip [ti] OR Cleft-Palate [ti] OR

Clonorchiasis [ti] OR Clubfoot [ti] OR Cluster-Headache* [ti] OR Coccidioidomycosis [ti] OR Coccidiosis [ti] OR Colic [ti] OR Colitis [ti] OR Collagenous-Sprue [ti] OR Colloid-Cysts [ti] OR Coloboma [ti] OR Colonic-Polyps [ti] OR Colonic-Pseudo-Obstruction [ti] OR Color-Vision-Defects [ti] OR Coma [ti] OR Common-Cold [ti] OR Common-Variable-Immunodeficiency [ti] OR Commotio-Cordis [ti] OR Complication* [ti] OR Condylomata-Acuminata [ti] OR Confusion [ti] OR Congenital-Hyperinsulinism [ti] OR Congenital-Hypothyroidism [ti] OR Conjoined-Twins [ti] OR Conjunctivitis [ti] OR Constipation [ti] OR Constriction [ti] OR Contracture [ti] OR Coproporphyrria [ti] OR Cor-Triatriatum [ti] OR Corneal-Dystrophies [ti] OR Corneal-Endothelial-Cell-Loss [ti] OR Corneal-Neovascularization [ti] OR Corneal-Opacity [ti] OR Corneal-Perforation [ti] OR Corneal-Wavefront-Aberration [ti] OR Coronary-Aneurysm* [ti] OR Coronary-Occlusion [ti] OR Coronary-Vasospasm* [ti] OR Coronary-Vessel-Anomalies [ti] OR Cough [ti] OR Cowpox [ti] OR Coxa-Valga [ti] OR Coxa-Vara [ti] OR Craniocerebral-Trauma [ti] OR Craniofacial-Dysostosis [ti] OR Craniopharyngioma [ti] OR Craniosynostoses [ti] OR Croup [ti] OR Cryoglobulinemia [ti] OR Cryptococcosis [ti] OR Cryptogenic-Organizing-Pneumonia [ti] OR Cryptorchidism [ti] OR Cryptosporidiosis [ti] OR Cutaneous-Fistula [ti] OR Cutis-Laxa [ti] OR Cyanosis [ti] OR Cyclosporiasis [ti] OR Cystadenocarcinoma [ti] OR Cystadenoma [ti] OR Cystic-Fibrosis [ti] OR Cysticercosis [ti] OR Cystinosis [ti] OR Cystinuria [ti] OR Cystitis [ti] OR Cystocele [ti] OR Cysts [ti] OR Cytochrome-c-Oxidase-Deficiency [ti] OR Cytomegalovirus-Retinitis [ti] OR Dacryocystitis [ti] OR Dandruff [ti] OR Deafness [ti] OR Decalcification [ti] OR Decerebrate-State [ti] OR Dehydration [ti] OR Delayed-Emergence-from-Anesthesia [ti] OR Delayed-Graft-Function [ti] OR Delayed-Puberty [ti] OR Delirium [ti] OR Delta-Thalassemia [ti] OR Dementia [ti] OR Dendritic-Cell-Sarcoma [ti] OR Dengue [ti] OR Dental-Calculus [ti] OR Dental-Caries [ti] OR Dental-Deposits [ti] OR Dental-Enamel-Hypoplasia [ti] OR Dental-Fissures [ti] OR Dental-Fistula [ti] OR Dental-Leakage [ti] OR Dental-Occlusion [ti] OR Dental-Plaque [ti] OR Dental-Pulp-Calcification [ti] OR Dental-Pulp-Exposure [ti] OR Dental-Pulp-Necrosis [ti] OR Dentigerous-Cyst [ti] OR Dentin-Sensitivity [ti] OR Dentinogenesis-Imperfecta [ti] OR Dentofacial-Deformities [ti] OR Depression [ti] OR Dermatitis [ti] OR Dermatofibrosarcoma [ti] OR Dermatomycoses [ti] OR Dermatomyositis [ti] OR Dermoid-Cyst [ti] OR Desmoplastic-Small-Round-Cell-Tumor* [ti] OR Dextrocardia [ti] OR Diabetes [ti] OR Diabetic [ti] OR Diaper-Rash [ti] OR Diaphragmatic-Eventration [ti] OR Diarrhea [ti] OR Diastema [ti] OR Dicrocoeliasis [ti] OR Dientamoebiasis [ti] OR Diffuse-Axonal-Injury [ti] OR Digestive-System-Fistula [ti] OR Dihydropyrimidine-Dehydrogenase-Deficiency [ti] OR Dilatation [ti] OR Diphtheria [ti] OR Diphyllbothriasis [ti] OR Diplopia [ti] OR Dirofilariasis [ti] OR Discitis [ti] OR Disease* [ti] OR [ti] OR Disorder* [ti] OR Disseminated-Intravascular-Coagulation [ti] OR Distemper [ti] OR Diurnal-Enuresis [ti] OR Diverticulitis [ti] OR Diverticulosis [ti] OR Diverticulum [ti] OR Dizziness [ti] OR Double-Outlet-Right-Ventricle [ti] OR Dracunculiasis [ti] OR Drowning [ti] OR Drug-Hypersensitivity [ti] OR Drug-Overdose [ti] OR Drug-Induced-Liver-Injury [ti] OR Dry-Socket [ti] OR Ductus-Arteriosus [ti] OR Duodenal-Obstruction* [ti] OR Duodenitis [ti] OR Duodenogastric-Reflux [ti] OR Dupuytren-Contracture [ti] OR Dwarfism [ti] OR Dysarthria [ti] OR Dysautonomia [ti] OR Dysbiosis [ti] OR Dyscalculia [ti] OR Dysentery [ti] OR Dysfunction* [ti] OR Dysgammaglobulinemia [ti] OR Dysgerminoma [ti] OR Dysgeusia [ti] OR Dyskeratosis-Congenita [ti] OR Dyskinesia* [ti] OR Dyslexia [ti] OR Dyslipid* [ti] OR Dysmenorrhea [ti] OR Dysostoses [ti] OR Dyspareunia [ti] OR Dyspepsia [ti]

OR Dysphonia [ti] OR Dysplasia [ti] OR Dyspnea [ti] OR Dyssomnias [ti] OR Dystocia [ti] OR Dystonia [ti] OR Dysuria [ti] OR Ear-Deformities [ti] OR Earache [ti] OR Ebstein-Anomaly [ti] OR Ecchymosis [ti] OR Eccrine-Porocarcinoma [ti] OR Echinococcosis [ti] OR Echinostomiasis [ti] OR Eclampsia [ti] OR Ecthyma [ti] OR Ectoparasitic-Infestations [ti] OR Ectopia-Cordis [ti] OR Ectopia-Lentis [ti] OR ectopic-Pregnancy [ti] OR Ectromelia [ti] OR Ectropion [ti] OR Eczema [ti] OR Edema* [ti] OR edentulous-Mouth [ti] OR Egg-Hypersensitivity [ti] OR Ehrlichiosis [ti] OR Eisenmenger-Complex [ti] OR Elephantiasis [ti] OR Elliptocytosis [ti] OR Emaciation [ti] OR Embolism* [ti] OR Embryo-Loss [ti] OR Emergencies [ti] OR Emphysema [ti] OR Emphysematous-Cholecystitis [ti] OR Empyema [ti] OR Encephalitis [ti] OR Encephalitozoonosis [ti] OR Encephalocele [ti] OR Encephalomalacia [ti] OR Encephalomyelitis [ti] OR Encephalopathy [ti] OR Enchondromatosis [ti] OR Endarteritis [ti] OR Endocardial-Cushion-Defects [ti] OR Endocardial-Fibroelastosis [ti] OR Endocarditis [ti] OR Endodermal-Sinus-Tumor* [ti] OR Endoleak [ti] OR Endolymphatic-Hydrops [ti] OR Endometrial-Stromal-Tumors* [ti] OR Endometriosis [ti] OR Endometritis [ti] OR Endophthalmitis [ti] OR Endotoxemia [ti] OR Enophthalmos [ti] OR Entamoebiasis [ti] OR Enteritis [ti] OR Enterobiasis [ti] OR Enterocolitis [ti] OR Enterotoxemia [ti] OR Entropion [ti] OR Enuresis [ti] OR Enzootic-Bovine-Leukosis [ti] OR Eosinophilia [ti] OR Eosinophilic-Granuloma [ti] OR Ependymoma [ti] OR Epidermal-Cyst* [ti] OR Epidermodysplasia-Verruciformis [ti] OR Epidermolysis-Bullosa [ti] OR Epididymitis [ti] OR Epiglottitis [ti] OR Epilepsia-Partialis-Continua [ti] OR Epilepsies [ti] OR Epilepsy [ti] OR Epiphyses [ti] OR Epiretinal-Membrane [ti] OR Epispadias [ti] OR Epistaxis [ti] OR Equinus-Deformity [ti] OR Erectile-Dysfunction [ti] OR Ergotism [ti] OR Eructation [ti] OR Eruption* [ti] OR Erysipelas [ti] OR Erysipeloid [ti] OR Erythema* [ti] OR Erythroblastosis [ti] OR Erythrokeratoderma-Variabilis [ti] OR Erythromelalgia [ti] OR Erythroplasia [ti] OR Esophageal-Achalasia [ti] OR Esophageal-and-Gastric-Varices [ti] OR Esophageal-Atresia [ti] OR Esophageal-Cyst* [ti] OR Esophageal-Fistula [ti] OR Esophageal-Perforation* [ti] OR Esophageal-Spasm* [ti] OR Esophagitis [ti] OR Esotropia [ti] OR Essential-Tremor* [ti] OR Esthesioneuroblastoma [ti] OR Ethmoid-Sinusitis [ti] OR Exanthema [ti] OR Exocrine-Pancreatic-Insufficiency [ti] OR Exophthalmos [ti] OR Exostoses [ti] OR Exotropia [ti] OR Exsanguination [ti] OR Eye-Injuries [ti] OR Facial-Asymmetry [ti] OR Facial-Dermatoses [ti] OR Facial-Hemiatrophy [ti] OR Facial-Neuralgia [ti] OR Facial-Paralysis [ti] OR Factor-V-Deficiency [ti] OR Factor-VII-Deficiency [ti] OR Factor-X-Deficiency [ti] OR Factor-XI-Deficiency [ti] OR Factor-XII-Deficiency [ti] OR Factor-XIII-Deficiency [ti] OR Failure-to-Thrive [ti] OR Familial-Hypophosphatemic-Rickets [ti] OR Fanconi-Anemia [ti] OR Farmer's-Lung [ti] OR Fasciculation [ti] OR Fasciitis [ti] OR Fascioliasis [ti] OR Fascioloidiasis [ti] OR Fatigue [ti] OR Fatty-Liver [ti] OR Favism [ti] OR Febrile-Neutropenia [ti] OR Fecal-Impaction [ti] OR Fecal-Incontinence [ti] OR Feline-Panleukopenia [ti] OR Feminization [ti] OR Femoracetabular-Impingement [ti] OR Fetal-Death* [ti] OR Fetal-Distress [ti] OR Fetal-Growth-Retardation [ti] OR Fetal-Hypoxia [ti] OR Fetal-Macrosomia [ti] OR Fetal-Membranes [ti] OR Fetal-Resorption [ti] OR Fetal-Weight [ti] OR Fetofetal-Transfusion [ti] OR Fetomaternal-Transfusion [ti] OR Fever [ti] OR Fibroadenoma* [ti] OR Fibroma* [ti] OR Fibromatosis [ti] OR Fibromyalgia [ti] OR Fibrosarcoma [ti] OR Fibrosis [ti] OR Fibrous-Tumor* [ti] OR Filariasis [ti] OR Fissure-in-Ano [ti] OR Fissured-Tongue [ti] OR Fistula [ti] OR Flatfoot [ti] OR Flatulence [ti] OR Flea-Infestation* [ti] OR Fluorosis [ti] OR Flushing [ti] OR Focal-Dermal-Hypoplasia [ti] OR Folic-Acid-Deficiency [ti] OR Follicular-Cyst* [ti] OR Folliculitis [ti] OR

Food-Hypersensitivity [ti] OR Foot-Deformities [ti] OR Foot-Dermatoses [ti] OR Foramen-Ovale [ti] OR Foreign-Body-Reaction* [ti] OR Fournier-Gangrene [ti] OR Fowlpox [ti] OR Freemartinism [ti] OR Friedreich-Ataxia [ti] OR Frontal-Sinusitis [ti] OR Frontotemporal-Dementia [ti] OR Frontotemporal-Lobar-Degeneration [ti] OR Fructose-Intolerance [ti] OR Fructose-1,6-Diphosphatase-Deficiency [ti] OR Fuchs'-Endothelial-Dystrophy [ti] OR Fucosidosis [ti] OR Fungemia [ti] OR Funnel-Chest [ti] OR Furcation-Defects [ti] OR Furunculosis [ti] OR Fusariosis)

OR

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Gagging [ti] OR Gait-Apraxia [ti] OR Gait-Ataxia [ti] OR Galactorrhea [ti] OR Galactosemia* [ti] OR Gallstone* [ti] OR Ganglioglioma [ti] OR Ganglion-Cyst* [ti] OR Ganglioneuroblastoma [ti] OR Ganglioneuroma* [ti] OR Gangliosidosis [ti] OR Gangrene [ti] OR Gastric-Antral-Vascular-Ectasia [ti] OR Gastric-Dilatation [ti] OR Gastric-Fistula [ti] OR Gastric-Outlet-Obstruction* [ti] OR Gastrinoma [ti] OR Gastritis [ti] OR Gastroenteritis [ti] OR Gastroesophageal-Reflux [ti] OR Gastrointestinal-Stromal-Tumor* [ti] OR Gastroparesis [ti] OR Gastroschisis [ti] OR Genomic-Instability [ti] OR Genu-Valgum [ti] OR Genu-Varum [ti] OR Geographic-Atrophy [ti] OR Geotrichosis [ti] OR Germinoma [ti] OR Giant-Cell-Arteritis [ti] OR Giant-Cell-Tumor-of-Bone [ti] OR Giant-Cell-Tumor* [ti] OR Giardiasis [ti] OR Gigantism [ti] OR Gingival-Hypertrophy [ti] OR Gingival-Overgrowth [ti] OR Gingival-Pocket* [ti] OR Gingival-Recession [ti] OR Gingivitis [ti] OR Glanders [ti] OR Glaucoma [ti] OR Glioblastoma [ti] OR Glioma [ti] OR Gliosarcoma [ti] OR Gliosis [ti] OR Glomerulonephritis [ti] OR Glomerulosclerosis [ti] OR Glomus-Jugulare-Tumor* [ti] OR Glomus-Tumor* [ti] OR Glomus-Tympanicum-Tumor* [ti] OR Glossalgia [ti] OR Glossitis [ti] OR Glucagonoma [ti] OR Glucose-Intolerance [ti] OR Glucosephosphate-Dehydrogenase-Deficiency [ti] OR Glycat* [ti] OR Glycemia [ti] OR Glycosuria [ti] OR Glycosylat* [ti] OR Glycooxidation [ti] OR Gnathostomiasis [ti] OR Goiter [ti] OR Gonadal-Dysgenesis [ti] OR Gonorrhoea [ti] OR Gout [ti] OR Graft-Occlusion* [ti] OR Granular-Cell-Tumor* [ti] OR Granuloma* [ti] OR Granulomatosis [ti] OR Granulomatous-Mastitis [ti] OR Granulosa-Cell-Tumor* [ti] OR Graves-Ophthalmopathy [ti] OR Gynatresia [ti] OR Gynecomastia [ti] OR Gyrate-Atrophy [ti] OR Haematuria [ti] OR Haemonchiasis [ti] OR Hairy-Tongue [ti] OR Halitosis [ti] OR Hallucination* [ti] OR Hallux-Rigidus [ti] OR Hallux-Valgus [ti] OR Hallux-Varus [ti] OR Hamartoma [ti] OR Hand-Deformities [ti] OR Hand-Dermatoses [ti] OR Haploinsufficiency [ti] OR Hazard* [ti] OR Head-Injur* [ti] OR Headache* [ti] OR Hearing-Loss [ti] OR Heart-Aneurysm* [ti] OR Heart-Arrest [ti] OR Heart-Block* [ti] OR Heart-Defect* [ti] OR Heart-Failure [ti] OR Heart-Murmur* [ti] OR Heart-Septal-Defect* [ti] OR Heartburn [ti] OR Heel-Spur* [ti] OR Helminthiasis [ti] OR Hemangioblastoma [ti] OR Hemangioendothelioma [ti] OR Hemangioma* [ti] OR Hemangiopericytoma [ti] OR Hemangiosarcoma [ti] OR Hemarthrosis [ti] OR Hematemesis [ti] OR Hematocele [ti] OR Hematocolpos [ti] OR Hematoma* [ti] OR Hematometra [ti] OR Hematuria [ti] OR Hemianopsia [ti] OR Hemifacial-Spasm* [ti] OR Hemiplegia [ti] OR Hemobilia [ti] OR Hemochromatosis [ti] OR Hemoglobinopathies [ti] OR Hemoglobinuria [ti] OR Hemolysis [ti] OR Hemoperitoneum [ti] OR Hemophilia [ti] OR Hemopneumothorax [ti] OR Hemoptysis [ti] OR Hemorrhag* [ti] OR Hemorrhoids [ti] OR

Hemosiderosis [ti] OR Hemospermia [ti] OR Hemothorax [ti] OR Hepatic-Encephalopathy [ti] OR Hepatic-Insufficiency [ti] OR Hepatitis [ti] OR Hepatoblastoma [ti] OR Hepatolenticular-Degeneration [ti] OR Hepatomegaly [ti] OR Hereditary-Angioedema [ti] OR Hernia* [ti] OR Heroin-Dependence [ti] OR Herpangina [ti] OR Herpes-Genitalis [ti] OR Herpes-Labialis [ti] OR Herpes-Simplex [ti] OR Herpes-Zoster [ti] OR Heterotopic-Pregnancy [ti] OR Hiccup* [ti] OR Hidradenitis [ti] OR Hidrocystoma [ti] OR Hip-Contracture [ti] OR Hip-Dislocation* [ti] OR Hirsutism [ti] OR Histiocytic-Necrotizing-Lymphadenitis [ti] OR Histiocytic-Sarcoma [ti] OR Histiocytoma [ti] OR Histiocytosis [ti] OR Histoplasmosis [ti] OR HIV-Enteropathy [ti] OR HIV-Seropositivity [ti] OR HIV/AIDS [ti] OR Hoarseness [ti] OR Holoprosencephaly [ti] OR Homocystinuria [ti] OR Hot-Flashes [ti] OR Hutchinson's-Melanotic-Freckle [ti] OR Hyalohyphomycosis [ti] OR Hydatidiform-Mole [ti] OR Hydranencephaly [ti] OR Hydroa-Vacciniforme [ti] OR Hydrocephalus [ti] OR Hydronephrosis [ti] OR Hydrophthalmos [ti] OR Hydropneumothorax [ti] OR Hydrops-Fetalis [ti] OR Hydrothorax [ti] OR Hymenolepiasis [ti] OR Hyperacusis [ti] OR Hyperaldosteronism [ti] OR Hyperalgesia [ti] OR Hyperammonemia [ti] OR Hyperamylasemia [ti] OR Hyperandrogenism [ti] OR Hyperargininemia [ti] OR Hyperbilirubinemia [ti] OR Hypercalcemi* [ti] OR Hypercalciuria [ti] OR Hypercapnia [ti] OR Hypercellularity [ti] OR Hypercementosis [ti] OR Hypercholesterol* [ti] OR Hypercoagul* [ti] OR Hyperemesis-Gravidarum [ti] OR Hyperemi* [ti] OR Hyperesthesia [ti] OR Hypergammaglobulinemia [ti] OR Hyperglyc* [ti] OR Hyperhidrosis [ti] OR Hyperhomocystein* [ti] OR Hyperinsulin* [ti] OR Hyperkal* [ti] OR Hyperkeratosis [ti] OR Hyperkinesi* [ti] OR Hyperleptinemia* [ti] OR Hyperlipid* [ti] OR Hyperlipoproteinemia* [ti] OR Hyperlysinemias [ti] OR Hypermagnese* [ti] OR Hypernatremia [ti] OR Hyperopia [ti] OR Hyperostosis [ti] OR Hyperoxaluria [ti] OR Hyperoxia [ti] OR Hyperparathyroid* [ti] OR Hyperphagia [ti] OR Hyperphosphat* [ti] OR Hyperpigmentation [ti] OR Hyperpituitarism [ti] OR Hyperplasia [ti] OR Hyperprolactinemia [ti] OR Hypersecretion [ti] OR Hypersensitivity [ti] OR Hypersomnolence [ti] OR Hypersplenism [ti] OR Hypertelorism [ti] OR Hypertension [ti] OR Hypertensive-Encephalopathy [ti] OR Hypertensive-Retinopathy [ti] OR Hyperthyroidism [ti] OR Hyperthyroxinemia [ti] OR Hypertrichosis [ti] OR Hypertriglycerid* [ti] OR Hypertrophy [ti] OR Hyperuric* [ti] OR Hyperventilation [ti] OR Hypervitaminosis [ti] OR Hypovolemia [ti] OR Hypesthesia [ti] OR HypHEMA [ti] OR Hypoalbuminemia [ti] OR Hypoaldosteronism [ti] OR Hypoalphalipoproteinemia* [ti] OR Hypobetalipoproteinemia* [ti] OR Hypocalcemi* [ti] OR Hypocapnia [ti] OR Hypodermiomyiasis [ti] OR Hypoglyc* [ti] OR Hypogonadism [ti] OR Hypohidrosis [ti] OR Hypokalemi* [ti] OR Hypokinesi* [ti] OR Hypolipid* [ti] OR Hypolipoproteinemias [ti] OR Hypomagnese* [ti] OR Hypomethylation [ti] OR Hyponatremi* [ti] OR Hypoparathyroidism [ti] OR Hypoperfusion [ti] OR Hypophosphat* [ti] OR Hypopigmentation [ti] OR Hypopituitarism [ti] OR Hypoplasia [ti] OR Hypoprothrombinemia* [ti] OR Hypospadias [ti] OR Hypotension [ti] OR Hypothermia [ti] OR Hypothyroid* [ti] OR Hypotrichosis [ti] OR Hypoventilation [ti] OR Hypovolemia [ti] OR Hypoxemia [ti] OR Hypoxia [ti] OR Ichthyosis [ti] OR IgA-Deficiency [ti] OR IgG-Deficiency [ti] OR Ileitis [ti] OR Ileus [ti] OR Iliac-Aneurysm [ti] OR Illness [ti] OR Illusions [ti] OR Immersion-Foot [ti] OR Immunoblastic-Lymphadenopathy [ti] OR Impacted-Tooth [ti] OR Imperforate-Anus [ti] OR Impetigo [ti] OR Implant-Capsular-Contracture [ti] OR Impotence [ti] OR Incontinentia-Pigmenti [ti] OR Inert-Gas-Narcosis [ti] OR Infarction* [ti] OR Infect* [ti] OR Infertility [ti] OR Inflammation [ti] OR Inflammatory [ti] OR Influenza [ti] OR Ingrown-Nails

[ti] OR Inhalant-Abuse* [ti] OR (Injury-in [ti] AND Mice [ti]) OR (injury-in [ti] AND rats [ti]) OR Insect-Bite* [ti] OR Insect-Sting* [ti] OR Insomnia* [ti] OR Insulin-Coma [ti] OR Insulin-Resistance [ti] OR Insulinoma [ti] OR Intellectual-Disability [ti] OR Intermittent-Claudication [ti] OR Interstitial-Pneumonias [ti] OR Intertrigo [ti] OR Intervertebral-Disc-Degeneration [ti] OR Intervertebral-Disc-Displacement [ti] OR Intestinal-Atresia [ti] OR Intestinal-Fistula* [ti] OR Intestinal-Obstruction* [ti] OR Intestinal-Perforation* [ti] OR Intestinal-Polyposis [ti] OR Intestinal-Polyps [ti] OR Intestinal-Pseudo-Obstruction [ti] OR Intestinal-Volvulus [ti] OR Intracranial-Arteriosclerosis [ti] OR Intracranial-Arteriovenous-Malformations [ti] OR Intracranial-Embolism* [ti] OR Intracranial-Hypotension [ti] OR Intraoperative-Awareness [ti] OR Intraoperative-Complications [ti] OR Intussusception [ti] OR Iridocyclitis [ti] OR Iritis [ti] OR Iron-Overload [ti] OR Ischemia [ti] OR Ischemic-Attack [ti] OR Ischemic-Contracture [ti] OR Isolated-Noncompaction-of-the-Ventricular-Myocardium [ti] OR Isosporiasis [ti] OR Jaundice [ti] OR Jaw-Cyst* [ti] OR Joint-Deformities [ti] OR Joint-Instability [ti] OR Joint-Loose-Bodies [ti] OR Keloid [ti] OR Keratitis [ti] OR Keratoacanthoma [ti] OR Keratoconjunctivitis [ti] OR Keratoconus [ti] OR Keratoderma [ti] OR Keratosis [ti] OR Kernicterus [ti] OR Ketosis [ti] OR Kidney-Calculi [ti] OR Kidney-Failure [ti] OR Klatskin's-Tumor [ti] OR Krukenberg-Tumor [ti] OR Kuru [ti] OR Kwashiorkor [ti] OR Kyphosis [ti] OR Labyrinthitis [ti] OR Lacrimal-Duct-Obstruction* [ti] OR Lactose-Intolerance [ti] OR Larva-Migrans [ti] OR Laryngismus [ti] OR Laryngitis [ti] OR Laryngomalacia [ti] OR Laryngopharyngeal-Reflux [ti] OR Laryngostenosis [ti] OR Latex-Hypersensitivity [ti] OR Lathyrism [ti] OR Leber-Congenital-Amaurosis [ti] OR Lecithin-Acyltransferase-Deficiency [ti] OR Leg-Dermatoses [ti] OR Leg-Length-Inequality [ti] OR Legionellosis [ti] OR Leiomyoma [ti] OR Leiomyomatosis [ti] OR Leiomyosarcoma [ti] OR Leishmania* [ti] OR Lens-Subluxation [ti] OR Lentigo [ti] OR Leprosy [ti] OR Leptospirosis [ti] OR Lethargy [ti] OR Leukemia [ti] OR Leukemic-Infiltration [ti] OR Leukemoid-Reaction [ti] OR Leukoaraiosis [ti] OR Leukocytosis [ti] OR Leukodystrophy [ti] OR Leukoedema [ti] OR Leukoencephalitis [ti] OR Leukoencephalopath* [ti] OR Leukokeratosis [ti] OR Leukomalacia [ti] OR Leukopenia [ti] OR Leukoplakia [ti] OR Leukorrhea [ti] OR Leukostasis [ti] OR Leydig-Cell-Tumor [ti] OR Lice-Infestation* [ti] OR Lichen-Nitidus [ti] OR Lichen-Planus [ti] OR Lichen-Sclerosus-et-Atrophicus [ti] OR Limb-Deformit* [ti] OR Linear-IgA-Bullous-Dermatosis [ti] OR Lingual-Thyroid [ti] OR Linitis-Plastica [ti] OR Lipid-Metabolism [ti] OR Lipidoses [ti] OR Lipid-Peroxid* [ti] OR Lipodystrophy [ti] OR Lipoma [ti] OR Lipomatosis [ti] OR Lipoperoxidation [ti] OR Liposarcoma [ti] OR Lipoxidation [ti] OR Lissencephalies [ti] OR Lissencephaly [ti] OR Listeriosis [ti] OR Lithiasis [ti] OR Livedo-Reticularis [ti] OR Liver-Cirrhosis [ti] OR Liver-Failure [ti] OR Liver-Injury [ti] OR Loiasis [ti] OR Lordosis [ti] OR Low-Tension-Glaucoma [ti] OR Lower-Extremity-Deformit* [ti] OR Lower-Urinary-Tract-Symptom* [ti] OR Ludwig's-Angina [ti] OR Lung-Injury [ti] OR Lupus-Erythematosus [ti] OR Lupus-Nephritis [ti] OR Lupus-Vulgaris [ti] OR Lyme-Neuroborreliosis [ti] OR Lymphadenitis [ti] OR Lymphangiectasis [ti] OR Lymphangioliomyomatosis [ti] OR Lymphangioma [ti] OR Lymphangiomyoma [ti] OR Lymphangiosarcoma [ti] OR Lymphangitis [ti] OR Lymphatic-Metastas* [ti] OR Lymphedema [ti] OR Lymphocele [ti] OR Lymphocytic-Choriomeningitis [ti] OR Lymphocytosis [ti] OR Lymphogranuloma-Venereum [ti] OR Lymphohistiocytosis [ti] OR Lymphoma [ti] OR Lymphomatoid-Granulomatosis [ti] OR Lymphomatoid-Papulosis [ti] OR Lymphopenia)

OR

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Macroalbuminuria [ti] OR Macrocephaly [ti] OR Macroglossia [ti] OR Macular-Degeneration [ti] OR Magnesium-Deficiency [ti] OR Malacoplakia [ti] OR Malaria [ti] OR Malformations-of-Cortical-Development [ti] OR Malformed-Nails [ti] OR Malignant-Catarrh [ti] OR Malignant-Hyperthermia [ti] OR Malnutrition [ti] OR Malocclusion [ti] OR Mandibulofacial-Dysostosis [ti] OR Mansonelliasis [ti] OR Marijuana-Abuse [ti] OR Mast-Cell-Sarcoma [ti] OR Mastitis [ti] OR Mastocytoma [ti] OR Mastocytosis [ti] OR Mastodynia [ti] OR Mastoiditis [ti] OR Maternal-Death [ti] OR Maxillary-Sinusitis [ti] OR Measles [ti] OR Meckel-Diverticulum [ti] OR Mediastinal-Cyst [ti] OR Mediastinal-Emphysema [ti] OR Mediastinitis [ti] OR Medullary-Sponge-Kidney [ti] OR Medulloblastoma [ti] OR Megacolon [ti] OR Melanoma* [ti] OR Melanosis [ti] OR Melena [ti] OR Melioidosis [ti] OR Meningeal-Carcinomatosis [ti] OR Meningioma* [ti] OR Meningism [ti] OR Meningitis [ti] OR Meningocele [ti] OR Meningoencephalitis [ti] OR Meningomyelocele [ti] OR Menopause [ti] OR Menorrhagia [ti] OR Menstruation-Disturbances [ti] OR Mental-Fatigue [ti] OR Mental-Retardation [ti] OR Mesenchymoma [ti] OR Mesenteric-Cyst* [ti] OR Mesenteric-Lymphadenitis [ti] OR Mesenteric-Vascular-Occlusion [ti] OR Mesial-Movement-of-Teeth [ti] OR Mesothelioma [ti] OR Metabolic-Acidosis [ti] OR Metabolic-Syndrome [ti] OR Metabolism [ti] OR Metal-Metabolism [ti] OR Metaplasia [ti] OR Metatarsalgia [ti] OR Methemoglobinemia [ti] OR Metrorrhagia [ti] OR Mevalonate-Kinase-Deficiency [ti] OR Microalbuminuria [ti] OR Microcephaly [ti] OR Micrognathism [ti] OR Microinflammation [ti] OR Micronuclei [ti] OR Microphthalmos [ti] OR Microsatellite-Instability [ti] OR Microscopic-Polyangiitis [ti] OR Microsporidiosis [ti] OR Microstomia [ti] OR Microvascular-Angina [ti] OR Migraine* [ti] OR Miliaria [ti] OR Milk-Hypersensitivity [ti] OR Milk-Sickness [ti] OR Mink-Viral-Enteritis [ti] OR Miosis [ti] OR Mite-Infestation* [ti] OR Mitochondrial-Encephalomyopath* [ti] OR Mitochondrial-Myopath* [ti] OR Mitral-Valve-Insufficiency [ti] OR Mitral-Valve-Prolapse [ti] OR Mixed-Tumor* [ti] OR Molluscum-Contagiosum [ti] OR Monieziasis [ti] OR Monilethrix [ti] OR Monkeypox [ti] OR Monoclonal-Gammopathy [ti] OR Mononeuropath* [ti] OR Morning-Sickness [ti] OR Morphine-Dependence [ti] OR Motion-Sickness [ti] OR Mouth-Breathing [ti] OR Mucinoses [ti] OR Mucinoses [ti] OR Mucocoele [ti] OR Mucopolysaccharidoses [ti] OR Mucopolysaccharidoses [ti] OR Mucopolysaccharidosis [ti] OR Mucormycosis [ti] OR Mucositis [ti] OR Multicystic-Dysplastic-Kidney [ti] OR Multiple-Acyl-Coenzyme-A-Dehydrogenase-Deficiency [ti] OR Multiple-Carboxylase-Deficiency [ti] OR Multiple-Chemical-Sensitivity [ti] OR Multiple-Myeloma [ti] OR Multiple-Organ-Failure* [ti] OR Multiple-Pulmonary-Nodules [ti] OR Multiple-System-Atrophy [ti] OR Mumps [ti] OR Muscle-Cramp* [ti] OR Muscle-Hypertonia [ti] OR Muscle-Hypotonia [ti] OR Muscle-Rigidity [ti] OR Muscle-Spasticity [ti] OR Muscle-Weakness [ti] OR Muscular-Atrophy [ti] OR Muscular-Dystroph* [ti] OR Mutism [ti] OR Myalgia [ti] OR Myasthenia-Gravis [ti] OR Mycetoma [ti] OR Mycoses [ti] OR Mycosis-Fungoides [ti] OR Mycotoxicosis [ti] OR Mydriasis [ti] OR Myelinolysis [ti] OR Myelitis [ti] OR Myelolipoma [ti] OR Myiasis [ti] OR Myocardial-Bridging [ti] OR Myocardial-Ischemia [ti] OR Myocardial-Reperfusion-Injury [ti] OR Myocardial-Stunning [ti] OR Myocarditis [ti] OR Myoclonic-Cerebellar-Dyssynergia [ti] OR Myoclonic-Epileps* [ti] OR Myoclonus [ti] OR Myoepithelioma [ti] OR Myoglobinuria [ti] OR

Myokymia [ti] OR Myoma [ti] OR Myopath* [ti] OR Myopia [ti] OR Myositis [ti] OR Myotonia [ti] OR Myotonic-Dystrophy [ti] OR Myringosclerosis [ti] OR Myxedema [ti] OR Myxoma [ti] OR Myxomatosis [ti] OR Myxosarcoma [ti] OR Narcolepsy [ti] OR Nasal-Obstruction* [ti] OR Nasal-Polyp* [ti] OR Nasal-Septal-Perforation [ti] OR Nasopharyngitis [ti] OR Nausea [ti] OR Necatoriasis [ti] OR Necrobiosis-Lipoidica [ti] OR Necrobiotic-Xanthogranuloma [ti] OR Necrolytic-Migratory-Erythema [ti] OR Necrosis [ti] OR Neointima [ti] OR Neoplasia [ti] OR Neoplasm* [ti] OR Neoplastic-Cell* [ti] OR Neovascularization [ti] OR Nephritis [ti] OR Nephrocalcinosis [ti] OR Nephrogenic-Fibrosing-Dermopathy [ti] OR Nephrolithiasis [ti] OR Nephroma [ti] OR Nephropath* [ti] OR Nephrosclerosis [ti] OR Nephrosis [ti] OR Nerve-Degeneration [ti] OR Nerve-Injur* [ti] OR Nervous-System-Malformation* [ti] OR Nesidioblastosis [ti] OR Neural-Tube-Defect* [ti] OR Neuralgia [ti] OR Neurilemmoma [ti] OR Neuritis [ti] OR Neuroacanthocytosis [ti] OR Neuroaspergillosis [ti] OR Neuroaxonal-Dystroph* [ti] OR Neuroblastoma [ti] OR Neurocysticercosis [ti] OR Neurocytoma [ti] OR Neuroectodermal-Tumor* [ti] OR Neuroendocrine-Tumor* [ti] OR Neurofibroma [ti] OR Neurofibromatos* [ti] OR Neurofibrosarcoma [ti] OR Neurogenic-Bowel [ti] OR Neurogenic-Inflammation [ti] OR Neurogenic-Urinary-Bladder [ti] OR Neuroma [ti] OR Neuromyelitis-Optica [ti] OR Neuronal-Ceroid-Lipofuscinoses [ti] OR Neuropath* [ti] OR Neuroschistosomiasis [ti] OR Neurosyphilis [ti] OR Neurothekeoma [ti] OR Neutropenia [ti] OR Nevus [ti] OR Night-Blindness [ti] OR Night-Terror* [ti] OR Nocturia [ti] OR Nocturnal-Enuresis [ti] OR Nocturnal-Paroxysmal-Dystonia [ti] OR Noma [ti] OR Nondisjunction [ti] OR Nonodontogenic-Cysts [ti] OR Nonvital-Tooth [ti] OR No-Reflow-Phenomenon [ti] OR Nose-Deformities [ti] OR Nut-Hypersensitivity [ti] OR Nystagmus [ti] OR Obesity [ti] OR Obstetric-Labor-Complications [ti] OR Ochronosis [ti] OR Ocular-Hypotension [ti] OR Odontogenic-Cyst* [ti] OR Odontogenic-Tumor* [ti] OR Odontoma [ti] OR Oedema [ti] OR Oligodendroglioma [ti] OR Oligohydramnios [ti] OR Oligomenorrhea [ti] OR Oligospermia [ti] OR Oliguria [ti] OR Olivopontocerebellar-Atrophies [ti] OR Onchocerciasis [ti] OR Onycholysis [ti] OR Onychomycosis [ti] OR Oophoritis [ti] OR Open-Bite [ti] OR Ophthalmia [ti] OR Ophthalmoplegia [ti] OR Opisthorchiasis [ti] OR Optic-Atrophy [ti] OR Optic-Disk-Drusen [ti] OR Optic-Nerve-Glioma [ti] OR Optic-Neuritis [ti] OR Oral-Fistula* [ti] OR Orbital-Cellulitis [ti] OR Orbital-Myositis [ti] OR Orbital-Pseudotumor* [ti] OR Orchitis [ti] OR Oroantral-Fistula* [ti] OR Orthostatic-Intolerance [ti] OR Ossification [ti] OR Osteitis [ti] OR Osteoarthritis [ti] OR Osteoarthropath* [ti] OR Osteoblastoma [ti] OR Osteochondritis [ti] OR Osteochondrodysplasias [ti] OR Osteochondroma [ti] OR Osteochondrosis [ti] OR Osteodystrophy [ti] OR Osteogenesis-Imperfecta [ti] OR Osteolysis [ti] OR Osteoma [ti] OR Osteomalacia [ti] OR Osteomyelitis [ti] OR Osteonecrosis [ti] OR Osteopenia [ti] OR Osteopetrosis [ti] OR Osteophyte [ti] OR Osteoporosis [ti] OR Osteosarcoma [ti] OR Osteosclerosis [ti] OR Ostertagiasis [ti] OR Otitis [ti] OR Otomycosis [ti] OR Otosclerosis [ti] OR Ovarian-Cyst* [ti] OR Overactive-Urinary-Bladder [ti] OR Overbite [ti] OR Overnutrition [ti] OR Overweight [ti] OR Oxidative-Stress [ti] OR Oxyuriasis [ti] OR Pachyonychia-Congenita [ti] OR Pain [ti] OR Pallor [ti] OR Pancreatic-Cyst* [ti] OR Pancreatic-Fistula* [ti] OR Pancreatic-Insufficiency [ti] OR Pancreatic-Pseudocyst [ti] OR Pancreatitis [ti] OR Pancytopenia [ti] OR Panniculitis [ti] OR Panuveitis [ti] OR Papilledema [ti] OR Papilloma [ti] OR Paracoccidioidomycosis [ti] OR Paraganglioma [ti] OR Paragonimiasis [ti] OR Parakeratosis [ti] OR Paralysis [ti] OR Paraneoplastic [ti] OR Paraparesis [ti] OR Paraphimosis

[ti] OR Paraplegia [ti] OR Paraproteinemias [ti] OR Parapsoriasis [ti] OR Parasitemia [ti] OR Parasomnias [ti] OR Parasystole [ti] OR Paratuberculosis [ti] OR Paresis [ti] OR Paresthesia [ti] OR Paronychia [ti] OR Parotitis [ti] OR Paroxysmal-Hemicrania [ti] OR Pars-Planitis [ti] OR Pasteurellosis [ti] OR Peanut-Hypersensitivity [ti] OR Pediatric-Obesity [ti] OR Pelger-Huet-Anomaly [ti] OR Peliosis-Hepatis [ti] OR Pellagra [ti] OR Pelvic-Organ-Prolapse [ti] OR Pemphigoid [ti] OR Pemphigus [ti] OR Penile-Induration [ti] OR Periapical-Granuloma* [ti] OR Periarthritis [ti] OR Pericardial-Effusion [ti] OR Pericarditis [ti] OR Pericoronitis [ti] OR Peri-Implantitis [ti] OR Perinephritis [ti] OR Periodontal-Atrophy [ti] OR Periodontal-Attachment-Loss [ti] OR Periodontal-Cyst* [ti] OR Periodontal-Pocket [ti] OR Periodontitis [ti] OR Periostitis [ti] OR Peritonitis [ti] OR Periventricular-Nodular-Heterotopia [ti] OR Persistent-Hyperplastic-Primary-Vitreous [ti] OR Persistent-Vegetative-State [ti] OR Peste-des-Petits-Ruminants [ti] OR Phaeohyphomycosis [ti] OR Phantom-Limb [ti] OR Pharyngitis [ti] OR Phencyclidine-Abuse* [ti] OR Phenylketonuria* [ti] OR Pheochromocytoma [ti] OR Phimosi s [ti] OR Phlebitis [ti] OR Photophobia [ti] OR Phyllodes-Tumor [ti] OR Piebaldism [ti] OR Piedra [ti] OR Pilomatrixoma [ti] OR Pilonidal-Sinus [ti] OR Pinealoma [ti] OR Pinguecula [ti] OR Pituitary-ACTH-Hypersecretion [ti] OR Pituitary-Apoplexy [ti] OR Pityriasis [ti] OR Placenta [ti] OR Placental-Insufficiency [ti] OR Plagiocephaly [ti] OR Plague [ti] OR Plasma-Cell-Granuloma* [ti] OR Plasmacytoma [ti] OR Platelet-Storage-Pool-Deficiency [ti] OR Platybasia [ti] OR Pleural-Effusion [ti] OR Pleurisy [ti] OR Pleurodynia [ti] OR Pleuropneumonia [ti] OR Pneumatosis-Cystoides-Intestinalis [ti] OR Pneumocephalus [ti] OR Pneumoconiosis [ti] OR Pneumonia [ti] OR Pneumopericardium [ti] OR Pneumoperitoneum [ti] OR Pneumorrhachis [ti] OR Pneumothorax [ti] OR Poliomyelitis [ti] OR Polyarteritis-Nodosa [ti] OR Polychondritis [ti] OR Polycystic-Kidney [ti] OR Polycythemia [ti] OR Polydactyly [ti] OR Polydipsia [ti] OR Polyendocrinopathies [ti] OR Polyhydramnios [ti] OR Polymyalgia-Rheumatica [ti] OR Polymyositis [ti] OR Polyneuropathies [ti] OR Polyps [ti] OR Polyradiculopathy [ti] OR Polyuria [ti] OR Popliteal-Cyst* [ti] OR Porokeratosis [ti] OR Poroma [ti] OR Porphyria* [ti] OR Port-Wine-Stain [ti] OR Positive-Pressure-Respiration [ti] OR Posterior-Tibial-Tendon-Dysfunction [ti] OR Post-Exercise-Hypotension [ti] OR Postoperative-Complications [ti] OR Postoperative-Nausea [ti] OR postoperative-vomiting [ti] OR Postpartum-Thyroiditis [ti] OR Potassium-Deficiency [ti] OR Pouchitis [ti] OR Precancerous [ti] OR Precocious-Puberty [ti] OR Prediabetic-State [ti] OR Pre-Eclampsia [ti] OR Pre-Excitation [ti] OR Pregnancy-Complications [ti] OR Pregnancy-in-Diabetics [ti] OR Prehypertension [ti] OR Preleukemia [ti] OR Premature-Aging [ti] OR Premature-Birth [ti] OR Premature-Ejaculation [ti] OR Premature-Obstetric-Labor [ti] OR Prenatal-Injur* [ti] OR Presbycusis [ti] OR Presbyopia [ti] OR Priapism [ti] OR Primary-Dysautonomias [ti] OR Primary-Graft-Dysfunction* [ti] OR Primary-Myelofibrosis [ti] OR Primary-Ovarian-Insufficiency [ti] OR Proctitis [ti] OR Proctocolitis [ti] OR Progeria [ti] OR Prognathism [ti] OR Prolactinoma [ti] OR Prolonged-Pregnancy [ti] OR Propionic-Acidemia [ti] OR Prosopagnosia [ti] OR Prostatism [ti] OR Prostatitis [ti] OR Prosthesis-Failure* [ti] OR Protein-C-Deficiency [ti] OR Protein-Deficiency [ti] OR Protein-S-Deficiency [ti] OR Protein-Energy-Malnutrition [ti] OR Protein-Losing-Enteropathies [ti] OR Proteinuria [ti] OR Proteostasis-Deficiencies [ti] OR Protoporphyrinemia [ti] OR Prurigo [ti] OR Pruritus [ti] OR Pseudobulbar-Palsy [ti] OR Pseudohypoaldosteronism [ti] OR Pseudohypoparathyroidism [ti] OR Pseudolymphoma [ti] OR Pseudomyxoma-Peritonei [ti] OR Pseudophakia [ti] OR Pseudorabies [ti] OR Pseudotumor-Cerebri [ti] OR Pseudoxanthoma-

Elasticum [ti] OR Psittacosis [ti] OR Psoriasis [ti] OR Psychomotor-Agitation [ti] OR Psychoses [ti] OR Pterygium [ti] OR Pubic-Symphysis-Diastasis [ti] OR Pudendal-Neuralgia [ti] OR Pulmonary-Alveolar-Proteinosis [ti] OR Pulmonary-Aspergillosis [ti] OR Pulmonary-Atelectasis [ti] OR Pulmonary-Atresia [ti] OR Pulmonary-Blastoma [ti] OR Pulmonary-Embolism [ti] OR Pulmonary-Emphysema [ti] OR Pulmonary-Eosinophilia [ti] OR Pulmonary-Nodule* [ti] OR Pulmonary-Sclerosing-Hemangioma [ti] OR Pulmonary-Valve-Insufficiency [ti] OR Pulpitis [ti] OR Pure-Autonomic-Failure [ti] OR Purine-Pyrimidine-Metabolism [ti] OR Purpura [ti] OR Pyelitis [ti] OR Pyelonephritis [ti] OR Pyoderma [ti] OR Pyometra [ti] OR Pyomyositis [ti] OR Pyonephrosis [ti] OR Pythiosis [ti] OR Pyuria [ti] OR Quadriplegia [ti] OR Rabies [ti] OR Radiation-Pneumonitis [ti] OR Radicular-Cyst* [ti] OR Radiculopathy [ti] OR Ranula [ti] OR Reactive-Oxygen-Species [ti] OR Rectal-Fistula [ti] OR Rectal-Prolapse [ti] OR Rectocele [ti] OR Rectovaginal-Fistula [ti] OR Recurrence [ti] OR Red-Cell-Aplasia [ti] OR Reflex-Sympathetic-Dystrophy [ti] OR Refractive-Errors [ti] OR Renal-Aminoacidurias [ti] OR Renal-Artery-Obstruction [ti] OR Renal-Colic [ti] OR Renal-Injury [ti] OR Renal-Insufficiency [ti] OR Renal-Osteodystrophy [ti] OR Renal-Tubular-Transport [ti] OR Reperfusion-Injury [ti] OR Respiratory-Aspiration [ti] OR Respiratory-Hypersensitivity [ti] OR Respiratory-Insufficiency [ti] OR Respiratory-Paralysis [ti] OR Respiratory-Sounds [ti] OR Respiratory-Tract-Fistula [ti] OR Restenosis [ti] OR Reticulocytosis [ti] OR Retinal-Artery-Occlusion [ti] OR Retinal-Degeneration [ti] OR Retinal-Detachment [ti] OR Retinal-Drusen [ti] OR Retinal-Neovascularization [ti] OR Retinal-Perforations [ti] OR Retinal-Telangiectasis [ti] OR Retinal-Vein-Occlusion [ti] OR Retinitis [ti] OR Retinoblastoma [ti] OR Retinopathy [ti] OR Retinoschisis [ti] OR Retrognathia [ti] OR Retrograde-Degeneration [ti] OR Retropneumoperitoneum [ti] OR Rh-Isoimmunization [ti] OR Rhabdoid-Tumor* [ti] OR Rhabdomyolysis [ti] OR Rhabdomyoma [ti] OR Rhabdomyosarcoma [ti] OR Rheumatic-Nodule* [ti] OR Rheumatoid-Nodule* [ti] OR Rhinitis [ti] OR Rhinophyma [ti] OR Rhinoscleroma [ti] OR Rhinosporidiosis [ti] OR Riboflavin-Deficiency [ti] OR Rickets [ti] OR Rigor-Mortis [ti] OR Rinderpest [ti] OR Root-Caries [ti] OR Root-Resorption [ti] OR Rosacea [ti] OR Rubella [ti] OR Rupture)

OR

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Sacroiliitis [ti] OR Salivary-Duct-Calculi [ti] OR Salivary-Gland-Calculi [ti] OR Salivary-Gland-Fistula [ti] OR Salpingitis [ti] OR Sarcocystosis [ti] OR Sarcoidosis [ti] OR Sarcoma [ti] OR Sarcopenia [ti] OR Scabies [ti] OR Scalp-Dermatoses [ti] OR Schistosomiasis [ti] OR Sciatica [ti] OR Scleredema-Adultorum [ti] OR Sclerema-Neonatorum [ti] OR Scleritis [ti] OR Scleroderma [ti] OR Scleromyxedema [ti] OR Sclerosis [ti] OR Scoliosis [ti] OR Scorpion-Sting* [ti] OR Scotoma [ti] OR Scrapie [ti] OR Scrub-Typhus [ti] OR Scurvy [ti] OR Seizures [ti] OR Seminoma [ti] OR Sepsis [ti] OR Septic-Shock [ti] OR Seroma [ti] OR Serositis [ti] OR Sertoli-Cell-Tumor* [ti] OR Sertoli-Leydig-Cell-Tumor [ti] OR Serum-Sickness [ti] OR Severe-Combined-Immunodeficiency [ti] OR Severe-Dengue [ti] OR Sex-Chromosome-Aberrations [ti] OR Sex-Cord-Gonadal-Stromal-Tumor* [ti] OR Sexual-Dysfunction [ti] OR Shwartzman-Phenomenon [ti] OR Sialadenitis [ti] OR Sialometaplasia [ti] OR Sialorrhoea [ti] OR Sick-Cell-Trait [ti] OR Siderosis [ti] OR Silicosis [ti] OR Silicotuberculosis [ti] OR Single-

Umbilical-Artery [ti] OR Sinoatrial-Block [ti] OR Sinus-Arrest [ti] OR Sinus-Pericranii [ti] OR Sinusitis [ti] OR Situs-Inversus [ti] OR Skull-Fracture* [ti] OR Sleep-Apnea [ti] OR Sleep-Bruxism [ti] OR Sleep-Deprivation [ti] OR Sleep-Paralysis [ti] OR Slipped-Capital-Femoral-Epiphyses [ti] OR Smallpox [ti] OR Smooth-Muscle-Tumor* [ti] OR Snake-Bite* [ti] OR Sneezing [ti] OR Snoring [ti] OR Somatostatinoma [ti] OR Somnambulism [ti] OR Space-Motion-Sickness [ti] OR Sparganosis [ti] OR Spasm [ti] OR Spasms [ti] OR Spastic-Paraplegia [ti] OR Spermatic-Cord-Torsion [ti] OR Spermatocele [ti] OR Sphenoid-Sinusitis [ti] OR Spherocytosis [ti] OR Sphincter-of-Oddi-Dysfunction [ti] OR Sphingolipidoses [ti] OR Spider-Bite* [ti] OR Spina-Bifida [ti] OR Spinal-Cord-Compression [ti] OR Spinal-Cord-Injur* [ti] OR Spinal-Cord-Ischemia [ti] OR Spinal-Curvature* [ti] OR Spinal-Dysraphism [ti] OR Spinal-Muscular-Atrophies-of-Childhood [ti] OR Spinal-Osteophytosis [ti] OR Spinocerebellar-Ataxias [ti] OR Spinocerebellar-Degeneration* [ti] OR Splenomegaly [ti] OR Splenosis [ti] OR Spondylarthritis [ti] OR Spondylarthropathies [ti] OR Spondylitis [ti] OR Spondylolisthesis [ti] OR Spondylolysis [ti] OR Spondylosis [ti] OR Sporotrichosis [ti] OR Sprue [ti] OR Starvation [ti] OR Status-Asthmaticus [ti] OR Status-Epilepticus [ti] OR Steatitis [ti] OR Steatorrhea [ti] OR Stenosis [ti] OR Steroid-Metabolism [ti] OR Stings [ti] OR Stomach-Volvulus [ti] OR Stomatitis [ti] OR Strabismus [ti] OR Striae-Distensae [ti] OR Striatonigral-Degeneration [ti] OR Stricture* [ti] OR Stroke [ti] OR Strongyloidiasis [ti] OR Stupor [ti] OR Stuttering [ti] OR Subacute-Combined-Degeneration [ti] OR Subacute-Sclerosing-Panencephalitis [ti] OR Subcutaneous-Emphysema [ti] OR Subdural-Effusion [ti] OR Substance-Abuse* [ti] OR Sudden-Death [ti] OR Sudden-Infant-Death* [ti] OR Sulfhemoglobinemia [ti] OR Sunburn [ti] OR Supernumerary-Tooth [ti] OR Suppuration [ti] OR Supranuclear-Palsy [ti] OR Surgical-Shock [ti] OR Surgical-Wound-Dehiscence [ti] OR Sweating [ti] OR Swine-Erysipelas [ti] OR Syncope [ti] OR Syndactyly [ti] OR Syndrome* [ti] OR Synkinesis [ti] OR Synostosis [ti] OR Synovial-Cyst* [ti] OR Synovitis [ti] OR Syphilis [ti] OR Syringoma [ti] OR Syringomyelia [ti] OR Systolic-Murmurs [ti] OR Tabes-Dorsalis [ti] OR Tachycardia [ti] OR Tachypnea [ti] OR Taeniasis [ti] OR Takayasu-Arteritis [ti] OR Takotsubo-Cardiomyopathy [ti] OR Tarlov-Cysts [ti] OR Tauopathies [ti] OR Tauopathy [ti] OR TDP-43-Proteinopathies [ti] OR Telangiectasia [ti] OR Telangiectasis [ti] OR Tendinopath* [ti] OR Tendon-Entrapment [ti] OR Tennis-Elbow [ti] OR Tenosynovitis [ti] OR Teratocarcinoma* [ti] OR Teratogenesis [ti] OR Teratoma [ti] OR Testicular-Hydrocele* [ti] OR Tetanus [ti] OR Tetany [ti] OR Tetralogy-of-Fallot [ti] OR Thalassemia [ti] OR Thecoma [ti] OR Theileriasis [ti] OR Thiamine-Deficiency [ti] OR Thinness [ti] OR Thrombasthenia [ti] OR Thromboangiitis-Obliterans [ti] OR Thrombocythemia [ti] OR Thrombocytopenia [ti] OR Thrombocytosis [ti] OR Thromboembolism [ti] OR Thrombophilia [ti] OR Thrombophlebitis [ti] OR Thrombosis [ti] OR Thrombotic-Microangiopathies [ti] OR Thymoma [ti] OR Thyroglossal-Cyst* [ti] OR Thyroid-Crisis [ti] OR Thyroid-Dysgenesis [ti] OR Thyroid-Nodule* [ti] OR Thyroiditis [ti] OR Thyrotoxicosis [ti] OR Tick-Bite* [ti] OR Tick-Infestation* [ti] OR Tick-Paralysis [ti] OR Tick-Toxicoses [ti] OR Tics [ti] OR Tinea [ti] OR Tinnitus [ti] OR Tissue-Adhesions [ti] OR T-Lymphocytopenia [ti] OR Tonic-Pupil [ti] OR Tonsillitis [ti] OR Tooth-Abrasion [ti] OR Tooth-Ankylosis [ti] OR Tooth-Attrition [ti] OR Tooth-Avulsion [ti] OR Tooth-Demineralization [ti] OR Tooth-Discoloration* [ti] OR Tooth-Erosion [ti] OR Tooth-Fracture* [ti] OR Tooth-Injur* [ti] OR Tooth-Loss [ti] OR Tooth-Migration [ti] OR Tooth-Mobility [ti] OR Tooth-Resorption [ti] OR Tooth-Wear [ti] OR Toothache* [ti] OR Torsades-de-Pointes [ti] OR Torticollis [ti] OR Toxascariasis [ti] OR

Toxemia [ti] OR Toxic-Shock [ti] OR Toxocariasis [ti] OR Toxoplasmosis [ti] OR Tracheitis [ti] OR Tracheobronchomalacia [ti] OR Tracheobronchomegaly [ti] OR Tracheoesophageal-Fistula [ti] OR Tracheomalacia [ti] OR Trachoma [ti] OR Transient-Tachypnea [ti] OR Translocation [ti] OR Transposition-of-Great-Vessels [ti] OR Trauma [ti] OR Traumatic-Shock [ti] OR Tremor* [ti] OR Trichiasis [ti] OR Trichinellosis [ti] OR Trichomonas-Vaginitis [ti] OR Trichosporonosis [ti] OR Trichostrongyloidiasis [ti] OR Trichostrongylosis [ti] OR Trichuriasis [ti] OR Tricuspid-Atresia [ti] OR Tricuspid-Valve-Insufficiency [ti] OR Trigeminal-Autonomic-Cephalalgias [ti] OR Trigeminal-Neuralgia [ti] OR Triloggy-of-Fallot [ti] OR Trismus [ti] OR Trisomy [ti] OR Trombiculiasis [ti] OR Trophoblastic-Tumor* [ti] OR Trypanosomiasis [ti] OR Tubal-Pregnancy [ti] OR Tuberculoma [ti] OR Tuberculosis [ti] OR Tularemia [ti] OR Tungiasis [ti] OR Tympanic-Membrane-Perforation [ti] OR Typhlitis [ti] OR Typhus [ti] OR Tyrosinemias [ti] OR Ulcer* [ti] OR Unconsciousness [ti] OR Uniparental-Disomy [ti] OR Upper-Extremity-Deformities [ti] OR Urachal-Cyst* [ti] OR Uraemia [ti] OR Uremia [ti] OR Ureteral-Calculi [ti] OR Ureteral-Obstruction* [ti] OR Ureterocele [ti] OR Ureterolithiasis [ti] OR Urethral-Obstruction* [ti] OR Urethritis [ti] OR Urinary-Bladder-Calculi [ti] OR Urinary-Bladder-Fistula* [ti] OR Urinary-Bladder-Neck-Obstruction* [ti] OR Urinary-Calculi [ti] OR Urinary-Fistula [ti] OR Urinary-Incontinence [ti] OR Urinary-Retention [ti] OR Urinoma [ti] OR Urolithiasis [ti] OR Urticaria [ti] OR Urticaria-Pigmentosa [ti] OR Uterine-Cervical-Erosion [ti] OR Uterine-Cervical-Incompetence [ti] OR Uterine-Cervicitis [ti] OR Uterine-Inertia [ti] OR Uterine-Inversion [ti] OR Uterine-Perforation* [ti] OR Uterine-Prolapse [ti] OR Uterine-Retroversion [ti] OR Uveitis [ti] OR Vaccinia [ti] OR Vaginal-Discharge* [ti] OR Vaginal-Fistula* [ti] OR Vaginismus [ti] OR Vaginitis [ti] OR Vaginosis [ti] OR Varicocele [ti] OR Varicose-Veins [ti] OR Vasa-Previa [ti] OR Vascular-Calcification [ti] OR Vascular-Fistula [ti] OR Vascular-Malformations [ti] OR Vascular-Resistance [ti] OR Vascular-Stiffness [ti] OR Vascular-System-Injur* [ti] OR Vasculitis [ti] OR Vasoconstriction [ti] OR Vasoplegia [ti] OR Vasospasm [ti] OR Vein-of-Galen-Malformations [ti] OR Velopharyngeal-Insufficiency [ti] OR Venous-Insufficiency [ti] OR Venous-Thromboembolism* [ti] OR Ventilator-Induced-Lung-Injury [ti] OR Ventricular-Dysfunction* [ti] OR Ventricular-Fibrillation* [ti] OR Ventricular-Outflow-Obstruction* [ti] OR Ventricular-Premature-Complexes [ti] OR Ventricular-Remodeling [ti] OR Vertebral-Artery-Dissection [ti] OR Vertebrobasilar-Insufficiency [ti] OR Vertigo [ti] OR Vesico-Ureteral-Reflux [ti] OR Vesicovaginal-Fistula* [ti] OR Vesicular-Stomatitis [ti] OR Vestibular-Neuronitis [ti] OR VIRAL-Cell-Transformation [ti] OR Viremia [ti] OR Virilism [ti] OR Visceral-Prolapse [ti] OR Visna [ti] OR Vitamin-A-Deficiency [ti] OR Vitamin-B-12-Deficiency [ti] OR Vitamin-B-6-Deficiency [ti] OR Vitamin-B-Deficiency [ti] OR Vitamin-D-Deficiency [ti] OR Vitamin-E-Deficiency [ti] OR Vitamin-K-Deficiency [ti] OR Vitiligo [ti] OR Vitreoretinopathy [ti] OR Vitreous-Detachment [ti] OR Vocal-Cord-Dysfunction [ti] OR Vocal-Cord-Paralysis [ti] OR Vomiting [ti] OR Vulvar-Lichen-Sclerosus [ti] OR Vulvar-Vestibulitis [ti] OR Vulvitis [ti] OR Vulvodynia [ti] OR Vulvovaginitis [ti] OR Waldenstrom-Macroglobulinemia [ti] OR Wallerian-Degeneration [ti] OR Wandering-Spleen [ti] OR Warts [ti] OR Water-Electrolyte-Imbalance [ti] OR Wegener-Granulomatosis [ti] OR Wernicke-Encephalopathy [ti] OR Wet-Macular-Degeneration [ti] OR Wheat-Hypersensitivity [ti] OR Whooping-Cough [ti] OR Wilms-Tumor [ti] OR Xanthogranuloma* [ti] OR Xanthomatosis [ti] OR Xeroderma-Pigmentosum [ti] OR Xerophthalmia [ti] OR Xerostomia [ti] OR Yang-

Deficiency [ti] OR Yaws [ti] OR Yin-Deficiency [ti] OR Zenker-Diverticulum [ti] OR Zoonoses [ti] OR Zoster-Sine-Herpette [ti] OR Zygomycosis [ti])

7B3. Linking Terms Used to Extract Causes from Titles

There were millions of Title phrases that had to be evaluated for potential causes. Only the highest frequency phrases could be inspected visually. To access the lower frequency terms, a number of linking terms were identified.

The linking terms were obtained through visually inspecting many records containing foundational causes in the Titles, and identifying those terms that appeared frequently with the foundational causes. These linking terms include: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; workers [at end]; -exposed [at end]; -related; -associated; -infected; abuse*; toxicity. The inclusion of the term 'workers' was to identify industries that were noticeable contributors to disease. The phrases that included the linking terms eventually had to be separated from the linking terms to identify the specific foundational causes and include them in the software matrices. Other linking terms were virus* and generic bacterial headings, but these did not have to be separated from the phrases.

7B4. Linking Terms Used to Extract Diseases from Titles

In order to identify disease terms in the Titles that occurred at low frequency, linking terms had to be identified. The linking terms were obtained through visually inspecting many records containing diseases in the Titles, and identifying those that appeared frequently with the diseases. These linking terms included: disease; syndrome; infection; cancer; *toxicity; *opathy. Since specific diseases did not always appear in record Titles when the foundational causes appeared, terms that implied damage or adverse effects were used, such as *toxicity. So, for example, with a phrase like 'cadmium toxicity', 'cadmium' would be extracted as a foundational cause, and 'toxicity' would be listed as a proxy 'disease'.

7B5. Generic MeSH Terms Strongly Related to Potential Causes

A number of records with MeSH term assignments either had no MeSH Qualifiers listed or insufficient MeSH Qualifiers. In addition, while the MeSH Qualifiers used for the all-Qualifier query captured a large number of foundational causes, they were incomplete.

To generate these generic MeSH terms strongly related to potential foundational causes, results from past studies were examined, especially the CKD study [12], and generic relevant MeSH Headings were extracted. Also, a few of the most unambiguous generic MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry terms) were examined for relevance. Finally, the high and mid-frequency MeSH terms in the MeSH tree were inspected visually, and those that appeared to be generic and foundational cause-focused were selected as a query.

The MeSH Headings that resulted after the records were retrieved consisted of foundational causes, and other. Because there were no linking terms that could be used to extract only the foundational causes MeSH Headings, the output had to be inspected visually, and those terms that appeared to be foundational causes had to be extracted manually and validated. Mainly, the high frequency output terms were the only ones evaluated from visual inspection.

Additionally, a dot product approach was used to identify foundational causes with lower frequency of occurrence in the MeSH Heading field of the generic MeSH term-derived database. Four external inputs were intersected with the MeSH Headings that resulted after the records were retrieved, and any unique MeSH Headings that were found were added to the list of those identified from visual inspection. The four external inputs were:

- 1) foundational causes identified from MeSH Qualifiers in the MeSH Qualifier-derived database;
- 2) foundational causes identified from MeSH Qualifiers in the generic MeSH term-derived database;
- 3) CRN terms from the MeSH Qualifier-derived database; and,
- 4) text terms from the Title text term-derived database.

The following query was used to retrieve the records from Pubmed, where the first group of terms in parentheses consists of all diseases and symptoms from the MeSH tree expressed in the highest MeSH tree terminology, and the second group of terms in parentheses represents the MeSH terms strongly related to foundational causes:

([MH] is the Pubmed tag for MeSH Heading; [MH:NOEXP] is the Pubmed tag for MeSH Heading No Explode)

(Bacterial Infections and Mycoses [MH] OR Cardiovascular Diseases [MH] OR Chemically-Induced Disorders [MH] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities [MH] OR Digestive System Diseases [MH] OR Disorders of Environmental Origin [MH] OR Endocrine System Diseases [MH] OR Eye Diseases [MH] OR Female Urogenital Diseases and Pregnancy Complications [MH] OR Hemic and Lymphatic Diseases [MH] OR Immune System Diseases [MH] OR Male Urogenital Diseases [MH] OR Musculoskeletal Diseases [MH] OR Neoplasms [MH] OR Nervous System Diseases [MH] OR Nutritional and Metabolic Diseases [MH] OR Occupational Diseases [MH] OR Otorhinolaryngologic Diseases [MH] OR Parasitic Diseases [MH] OR Pathological Conditions, Signs and Symptoms [MH] OR Respiratory Tract Diseases [MH] OR Skin and Connective Tissue Diseases [MH] OR Stomatognathic Diseases [MH] OR Virus Diseases [MH])

AND

("Drug-Related Side Effects AND Adverse Reactions" [MH:NOEXP] OR Abnormalities, Drug Induced [MH:NOEXP] OR Abnormalities, Radiation-Induced [MH:NOEXP] OR Agricultural Workers Diseases [MH:NOEXP] OR Aids Related Opportunistic Infections [MH:NOEXP] OR Air Pollutants [MH:NOEXP] OR Air Pollutants, Occupational [MH:NOEXP])

OR Air Pollutants, Radioactive [MH:NOEXP] OR Air Pollution [MH:NOEXP] OR Air Pollution, Indoor [MH:NOEXP] OR Air Pollution, Radioactive [MH:NOEXP] OR Alcohol Drinking [MH:NOEXP] OR Alcohol Related Disorders [MH:NOEXP] OR Alcoholic Beverages [MH:NOEXP] OR Alcoholic Intoxication [MH:NOEXP] OR Alcoholism [MH:NOEXP] OR Amphetamine Related Disorders [MH:NOEXP] OR Amphetamines [MH:NOEXP] OR Arsenic Poisoning [MH:NOEXP] OR Asthma, Aspirin-Induced [MH:NOEXP] OR Asthma, Exercise-Induced [MH:NOEXP] OR Asthma, Occupational [MH:NOEXP] OR Behavior, Addictive [MH:NOEXP] OR Bullying [MH:NOEXP] OR Cadmium Poisoning [MH:NOEXP] OR Carbon Monoxide Poisoning [MH:NOEXP] OR Carbon Tetrachloride Poisoning [MH:NOEXP] OR Carcinogenicity Tests [MH:NOEXP] OR Carcinogens [MH:NOEXP] OR Carcinogens, Environmental [MH:NOEXP] OR Causality [MH:NOEXP] OR Cardiomegaly, Exercise-Induced [MH:NOEXP] OR Chemical Warfare Agents [MH:NOEXP] OR Chemically-Induced Disorders [MH:NOEXP] OR Child Abuse [MH:NOEXP] OR Child Abuse, Sexual [MH:NOEXP] OR Cholesterol, Dietary [MH:NOEXP] OR Ciguatera Poisoning [MH:NOEXP] OR Cocaine Related Disorders [MH:NOEXP] OR Cytomegalovirus Infections [MH:NOEXP] OR Dermatitis, Occupational [MH:NOEXP] OR Diet, Atherogenic [MH:NOEXP] OR Diet, High Fat [MH:NOEXP] OR Dietary Carbohydrates [MH:NOEXP] OR Dietary Fats [MH:NOEXP] OR Dietary Fats, Unsaturated [MH:NOEXP] OR Dietary Fiber [MH:NOEXP] OR Dietary Sucrose [MH:NOEXP] OR Domestic Violence [MH:NOEXP] OR Drug Contamination [MH:NOEXP] OR Drug Eruptions [MH:NOEXP] OR Drug Hypersensitivity [MH:NOEXP] OR Drug Overdose [MH:NOEXP] OR Drug-Induced Liver Injury [MH:NOEXP] OR Dyskinesia, Drug Induced [MH:NOEXP] OR Eating Disorders [MH:NOEXP] OR Environmental Exposure [MH:NOEXP] OR Environmental Illness [MH:NOEXP] OR Environmental Pollutants [MH:NOEXP] OR Environmental Pollution [MH:NOEXP] OR Environmental Pollution [MH:NOEXP] OR Escherichia Coli Infections [MH:NOEXP] OR Fast Foods [MH:NOEXP] OR Fluoride Poisoning [MH:NOEXP] OR Food Additives [MH:NOEXP] OR Food Contamination [MH:NOEXP] OR Food Hypersensitivity [MH:NOEXP] OR Foodborne Diseases [MH:NOEXP] OR Gas Poisoning [MH:NOEXP] OR Hazardous Substances [MH:NOEXP] OR Hazardous Waste [MH:NOEXP] OR Hearing Loss, Noise Induced [MH:NOEXP] OR Heavy Metal Poisoning, Nervous System [MH:NOEXP] OR Hepatitis A, Chronic [MH:NOEXP] OR Hepatitis B, Chronic [MH:NOEXP] OR Hepatitis C, Chronic [MH:NOEXP] OR Heroin Dependence [MH:NOEXP] OR Herpesviridae Infections [MH:NOEXP] OR Htlv I Infections [MH:NOEXP] OR Hypersensitivity [MH:NOEXP] OR Hypersensitivity, Delayed [MH:NOEXP] OR Hypersensitivity, Immediate [MH:NOEXP] OR Iatrogenic Disease [MH:NOEXP] OR Inhalation Exposure [MH:NOEXP] OR Iron Overload [MH:NOEXP] OR Lead Poisoning [MH:NOEXP] OR Lead Poisoning, Nervous System [MH:NOEXP] OR Lead Poisoning, Nervous System, Adult [MH:NOEXP] OR Lead Poisoning, Nervous System, Childhood [MH:NOEXP] OR Leukemia, Radiation Induced [MH:NOEXP] OR Manganese Poisoning [MH:NOEXP] OR Marijuana Abuse [MH:NOEXP] OR Maternal Exposure [MH:NOEXP] OR Mercury Poisoning [MH:NOEXP] OR Mercury Poisoning, Nervous System [MH:NOEXP] OR Morphine Dependence [MH:NOEXP] OR Mptp Poisoning [MH:NOEXP] OR Mushroom Poisoning [MH:NOEXP] OR Mutagenicity Tests [MH:NOEXP] OR Mutagens [MH:NOEXP] OR Neoplasms, Radiation Induced [MH:NOEXP] OR Neurotoxicity Syndromes [MH:NOEXP] OR Occupational Diseases [MH:NOEXP] OR Occupational Exposure [MH:NOEXP] OR Opioid

Related Disorders [MH:NOEXP] OR Opportunistic Infections [MH:NOEXP] OR Organophosphate Poisoning [MH:NOEXP] OR Paternal Exposure [MH:NOEXP] OR Plant Poisoning [MH:NOEXP] OR Pneumonia, Ventilator-Associated [MH:NOEXP] OR Poisoning [MH:NOEXP] OR Poisons [MH:NOEXP] OR Prenatal Exposure Delayed Effects [MH:NOEXP] OR Psychoses, Substance Induced [MH:NOEXP] OR Radiation Effects [MH:NOEXP] OR Radiation Injuries [MH:NOEXP] OR Radioactive Hazard Release [MH:NOEXP] OR Radioactive Pollutants [MH:NOEXP] OR Respiratory Hypersensitivity [MH:NOEXP] OR Salmonella Food Poisoning [MH:NOEXP] OR Sedentary Lifestyle [MH:NOEXP] OR Shellfish Poisoning [MH:NOEXP] OR Sleep Deprivation [MH:NOEXP] OR Sleep Disorders [MH:NOEXP] OR Sodium Chloride, Dietary [MH:NOEXP] OR Sodium, Dietary [MH:NOEXP] OR Soil Pollutants [MH:NOEXP] OR Soil Pollutants, Radioactive [MH:NOEXP] OR Spouse Abuse [MH:NOEXP] OR Staphylococcal Food Poisoning [MH:NOEXP] OR Staphylococcal Infections [MH:NOEXP] OR Streptococcal Infections [MH:NOEXP] OR Substance Abuse, Intravenous [MH:NOEXP] OR Substance Withdrawal Syndrome [MH:NOEXP] OR Substance-Related Disorders [MH:NOEXP] OR Teratogens [MH:NOEXP] OR Tobacco Smoke Pollution [MH:NOEXP] OR Tobacco Use Disorder [MH:NOEXP] OR Toxicity Tests, Chronic [MH:NOEXP] OR Virus Diseases [MH:NOEXP] OR Vitamin D Deficiency [MH:NOEXP] OR Water Pollutants [MH:NOEXP] OR Water Pollutants, Chemical [MH:NOEXP] OR Water Pollutants, Radioactive [MH:NOEXP] OR Water Pollution [MH:NOEXP] OR Water Pollution, Chemical [MH:NOEXP])

7C. Quick Reference Listing of Query Terms in 7B

7C1. MeSH Qualifier Query Terms

adverse effects
toxicity
pathogenicity
poisoning

7C2. Title Text Term Query

(included **after 7C5 below** due to size)

7C3. Linking Terms Used to Extract Causes from Titles

-induced
caused by
induced by
-contaminated
exposure to
exposure(s) [at end of phrase]
exposed to
poisoning [at end]
workers [at end]
-exposed [at end]
-related
-associated
-infected
*abuse**
toxicity
*virus**
generic bacterial headings(these did not have to be separated from the phrases)

(these did not have to be separated from the phrases)

7C4. Linking Terms Used to Extract Diseases from Titles

disease
syndrome
infection
cancer
**toxicity*
**opacity*

7C5. Generic MeSH Terms Strongly Related to Potential Causes

7C5a. MeSH Heading Terms

Bacterial Infections and Mycoses
Cardiovascular Diseases
Chemically-Induced Disorders
Congenital, Hereditary, and Neonatal Diseases and Abnormalities
Digestive System Diseases
Disorders of Environmental Origin
Endocrine System Diseases
Eye Diseases
Female Urogenital Diseases and Pregnancy Complications
Hemic and Lymphatic Diseases
Immune System Diseases
Male Urogenital Diseases
Musculoskeletal Diseases
Neoplasms
Nervous System Diseases
Nutritional and Metabolic Diseases
Occupational Diseases
Otorhinolaryngologic Diseases
Parasitic Diseases
Pathological Conditions, Signs and Symptoms
Respiratory Tract Diseases
Skin and Connective Tissue Diseases
Stomatognathic Diseases
Virus Diseases

7C5b. MeSH Heading No Explode Terms

"Drug-Related Side Effects AND Adverse Reactions"
Abnormalities, Drug Induced
Abnormalities, Radiation-Induced
Agricultural Workers Diseases
Aids Related Opportunistic Infections
Air Pollutants
Air Pollutants, Occupational
Air Pollutants, Radioactive
Air Pollution
Air Pollution, Indoor
Air Pollution, Radioactive
Alcohol Drinking
Alcohol Related Disorders
Alcoholic Beverages
Alcoholic Intoxication
Alcoholism
Amphetamine Related Disorders
Amphetamines
Arsenic Poisoning
Asthma, Aspirin-Induced
Asthma, Exercise-Induced
Asthma, Occupational
Behavior, Addictive
Bullying
Cadmium Poisoning
Carbon Monoxide Poisoning
Carbon Tetrachloride Poisoning
Carcinogenicity Tests
Carcinogens
Carcinogens, Environmental
Causality
Cardiomegaly, Exercise-Induced
Chemical Warfare Agents
Chemically-Induced Disorders
Child Abuse
Child Abuse, Sexual
Cholesterol, Dietary
Ciguatera Poisoning
Cocaine Related Disorders
Cytomegalovirus Infections
Dermatitis, Occupational
Diet, Atherogenic
Diet, High Fat
Dietary Carbohydrates
Dietary Fats
Dietary Fats, Unsaturated
Dietary Fiber
Dietary Sucrose
Domestic Violence
Drug Contamination
Drug Eruptions
Drug Hypersensitivity
Drug Overdose
Drug-Induced Liver Injury
Dyskinesia, Drug Induced
Eating Disorders
Environmental Exposure
Environmental Illness
Environmental Pollutants
Environmental Pollution
Environmental Pollution
Escherichia Coli Infections
Fast Foods
Fluoride Poisoning
Food Additives
Food Contamination
Food Hypersensitivity
Foodborne Diseases
Gas Poisoning
Hazardous Substances
Hazardous Waste
Hearing Loss, Noise Induced
Heavy Metal Poisoning, Nervous System
Hepatitis A, Chronic
Hepatitis B, Chronic
Hepatitis C, Chronic
Heroin Dependence
Herpesviridae Infections
Htlv I Infections
Hypersensitivity
Hypersensitivity, Delayed
Hypersensitivity, Immediate
Iatrogenic Disease
Inhalation Exposure
Iron Overload
Lead Poisoning
Lead Poisoning, Nervous System
Lead Poisoning, Nervous System, Adult
Lead Poisoning, Nervous System, Childhood
Leukemia, Radiation Induced
Manganese Poisoning
Marijuana Abuse
Maternal Exposure
Mercury Poisoning
Mercury Poisoning, Nervous System
Morphine Dependence
Mptp Poisoning
Mushroom Poisoning
Mutagenicity Tests
Mutagens

Neoplasms, Radiation Induced
Neurotoxicity Syndromes
Occupational Diseases
Occupational Exposure
Opioid Related Disorders
Opportunistic Infections
Organophosphate Poisoning
Paternal Exposure
Plant Poisoning
Pneumonia, Ventilator-Associated
Poisoning
Poisons
Prenatal Exposure Delayed Effects
Psychoses, Substance Induced
Radiation Effects
Radiation Injuries
Radioactive Hazard Release
Radioactive Pollutants
Respiratory Hypersensitivity
Salmonella Food Poisoning
Sedentary Lifestyle
Shellfish Poisoning
Sleep Deprivation
Sleep Disorders
Sodium Chloride, Dietary
Sodium, Dietary
Soil Pollutants
Soil Pollutants, Radioactive
Spouse Abuse
Staphylococcal Food Poisoning
Staphylococcal Infections
Streptococcal Infections
Substance Abuse, Intravenous
Substance Withdrawal Syndrome
Substance-Related Disorders
Teratogens
Tobacco Smoke Pollution
Tobacco Use Disorder
Toxicity Tests, Chronic
Virus Diseases
Vitamin D Deficiency
Water Pollutants
Water Pollutants, Chemical
Water Pollutants, Radioactive
Water Pollution
Water Pollution, Chemical

7C2. Title Text Term Query
(details expanded)

7C2a. Standalone Terms

<i>cardiotoxic*</i>	<i>therapy-related</i>
<i>genotoxic*</i>	<i>traffic-related</i>
<i>hepatotoxic*</i>	<i>health-consequences</i>
<i>immunotoxic*</i>	<i>long-term consequences</i>
<i>intoxicat*</i>	<i>anaphylactic-reaction*</i>
<i>nephrotoxic*</i>	<i>cutaneous-reaction*</i>
<i>neurotoxic*</i>	<i>hypersensitivity-reaction*</i>
<i>ototoxic*</i>	<i>transfusion-reaction*</i>
<i>phototoxic*</i>	<i>skin-reaction*</i>
<i>phytotoxic*</i>	<i>inflammation-reaction*</i>
<i>toxic-effect*</i>	<i>inflammatory-reaction*</i>
<i>toxic-potential*</i>	<i>reaction-associated</i>
<i>toxic-hazard*</i>	<i>foreign-body-reaction*</i>
<i>toxic-combin*</i>	<i>tissue-reaction*</i>
<i>toxicities</i>	<i>infusion-reaction*</i>
<i>toxicity</i>	<i>systemic-reaction*</i>
<i>toxicological-effect*</i>	<i>(allergic AND reaction-to)</i>
<i>toxicological-evaluation*</i>	<i>teratogenicity</i>
<i>toxicological-impact*</i>	<i>teratogenic-effect*</i>
<i>toxicological-hazard*</i>	<i>advanced-glycation</i>
<i>toxicological-assessment*</i>	<i>allergenicity</i>
<i>toxin-associated</i>	<i>bioaccumulation</i>
<i>toxin-related</i>	<i>carcinogen</i>
<i>toxin-injur*</i>	<i>Carcinogenic</i>
<i>toxin-risk*</i>	<i>carcinogenicity</i>
<i>lethal-toxin*</i>	<i>contaminat*</i>
<i>(toxin* AND fatal*)</i>	<i>disrupting-chemical*</i>
<i>(toxin* AND adverse)</i>	<i>(effect AND subchronic)</i>
<i>(toxin* AND morbid*)</i>	<i>(effects AND subchronic)</i>
<i>(toxin* AND mortality)</i>	<i>(effect-of AND prenatal)</i>
<i>(toxin* AND anaphyla)</i>	<i>(effects-of AND prenatal)</i>
<i>(toxin* AND harm)</i>	<i>envenomation</i>
<i>(toxin* AND damag*)</i>	<i>fatalities</i>
<i>(toxin* AND deteriorat*)</i>	<i>high-fat</i>
<i>(toxin* AND exacerbat*)</i>	<i>mutagenicity</i>
<i>(toxin* AND trigger*)</i>	<i>poisons</i>
<i>(toxin* AND aggravat*)</i>	<i>poisoning</i>
<i>injury-associated</i>	<i>precipitated-by</i>
<i>risk-associated</i>	<i>precipitated-after</i>
<i>virus-associated</i>	<i>precipitated-following</i>
<i>(Ionizing AND risk*)</i>	<i>side-effect*</i>
<i>(risk-of AND adverse)</i>	<i>teratogenesis</i>
<i>(adverse-health-effect* AND effects-of)</i>	<i>deleterious-effect*</i>
<i>(adverse-health-effect* AND effect-of)</i>	<i>detrimental-effect*</i>
<i>adverse-effect*</i>	<i>late-effect*</i>
<i>injury-following</i>	<i>adverse-metabolic-effect*</i>
<i>related-consequences</i>	<i>adverse-renal-effect*</i>

*respiratory-effect**
*negative-effect**
*adverse-reaction**
(adversity AND early)
(adversity AND child)*
(adversity AND life)*
(adversity AND social)
(adversity AND family)
causative-agent
caused-by
exposure-to
exposed-to
exposures
(damage-in AND mice)
(damage-in AND rats)
hepatic-damage
liver-damage
(increased-risk AND after)*
(increased-risk AND following)*
(increased-risk AND related-to)*
(increased-risk AND resulting-from)*
(increased-risk AND due-to)*
(complications AND after)
(complications AND following)
(complications AND related-to)
(complications AND resulting-from)
(complications AND due-to)
(mutagenic AND after)
(mutagenic AND following)
(mutagenic AND related-to)
(mutagenic AND resulting-from)
(mutagenic AND due-to)
(adverse-outcome AND after)*
(adverse-outcome AND following)*
(adverse-outcome AND related-to)*
(adverse-outcome AND resulting-from)*
(adverse-outcome AND due-to)*
(life-threatening AND after)
(life-threatening AND following)
(life-threatening AND related-to)
(life-threatening AND resulting-from)
(life-threatening AND due-to)
(lung-injury AND after)
(lung-injury AND following)
(lung-injury AND related-to)
(lung-injury AND resulting-from)
(lung-injury AND due-to)
(renal-injury AND after)
(renal-injury AND following)
(renal-injury AND related-to)
(renal-injury AND resulting-from)
(renal-injury AND due-to)
(susceptibility AND after)
(susceptibility AND following)
(susceptibility AND related-to)
(susceptibility AND resulting-from)
(susceptibility AND due-to)
(adverse AND after)
(adverse AND following)
(adverse AND related-to)
(adverse AND resulting-from)
(adverse AND due-to)
(allergic-reaction AND after)*
(allergic-reaction AND following)*
(allergic-reaction AND related-to)*
(allergic-reaction AND resulting-from)*
(allergic-reaction AND due-to)*
(anaphyla AND after)*
(anaphyla AND following)*
(anaphyla AND related-to)*
(anaphyla AND resulting-from)*
(anaphyla AND due-to)*
(cognitive-dysfunction AND after)
(cognitive-dysfunction AND following)
(cognitive-dysfunction AND related-to)
(cognitive-dysfunction AND resulting-from)
(cognitive-dysfunction AND due-to)
(cardiac-dysfunction AND after)
(cardiac-dysfunction AND following)
(cardiac-dysfunction AND related-to)
(cardiac-dysfunction AND resulting-from)
(cardiac-dysfunction AND due-to)
((dysfunction AND in-rats) AND after)
((dysfunction AND in-rats) AND following)
((dysfunction AND in-rats) AND related-to)
((dysfunction AND in-rats) AND resulting-from)
((dysfunction AND in-rats) AND due-to)
(erectile-dysfunction AND after)
(erectile-dysfunction AND following)
(erectile-dysfunction AND related-to)
(erectile-dysfunction AND resulting-from)
(erectile-dysfunction AND due-to)
(renal-dysfunction AND after)
(renal-dysfunction AND following)
(renal-dysfunction AND related-to)
(renal-dysfunction AND resulting-from)
(renal-dysfunction AND due-to)
(mitochondrial-dysfunction AND after)
(mitochondrial-dysfunction AND following)
(mitochondrial-dysfunction AND related-to)
(mitochondrial-dysfunction AND resulting-from)
(mitochondrial-dysfunction AND due-to)
(endothelial-dysfunction AND after)
(endothelial-dysfunction AND following)
(endothelial-dysfunction AND related-to)
(endothelial-dysfunction AND resulting-from)

(endothelial-dysfunction AND due-to)
 (sexual-dysfunction AND after)
 (sexual-dysfunction AND following)
 (sexual-dysfunction AND related-to)
 (sexual-dysfunction AND resulting-from)
 (sexual-dysfunction AND due-to)
 (ventricular-dysfunction AND after)
 (ventricular-dysfunction AND following)
 (ventricular-dysfunction AND related-to)
 (ventricular-dysfunction AND resulting-from)
 (ventricular-dysfunction AND due-to)
 (allograft-dysfunction AND after)
 (allograft-dysfunction AND following)
 (allograft-dysfunction AND related-to)
 (allograft-dysfunction AND resulting-from)
 (allograft-dysfunction AND due-to)
 (thyroid-dysfunction AND after)
 (thyroid-dysfunction AND following)
 (thyroid-dysfunction AND related-to)
 (thyroid-dysfunction AND resulting-from)
 (thyroid-dysfunction AND due-to)
 (graft-dysfunction AND after)
 (graft-dysfunction AND following)
 (graft-dysfunction AND related-to)
 (graft-dysfunction AND resulting-from)
 (graft-dysfunction AND due-to)
 (liver-dysfunction AND after)
 (liver-dysfunction AND following)
 (liver-dysfunction AND related-to)
 (liver-dysfunction AND resulting-from)
 (liver-dysfunction AND due-to)
 (diastolic-dysfunction AND after)
 (diastolic-dysfunction AND following)
 (diastolic-dysfunction AND related-to)
 (diastolic-dysfunction AND resulting-from)
 (diastolic-dysfunction AND due-to)
 (vascular-dysfunction AND after)
 (vascular-dysfunction AND following)
 (vascular-dysfunction AND related-to)
 (vascular-dysfunction AND resulting-from)
 (vascular-dysfunction AND due-to)
 (organ-dysfunction AND after)
 (organ-dysfunction AND following)
 (organ-dysfunction AND related-to)
 (organ-dysfunction AND resulting-from)
 (organ-dysfunction AND due-to)
 (barrier-dysfunction AND after)
 (barrier-dysfunction AND following)
 (barrier-dysfunction AND related-to)
 (barrier-dysfunction AND resulting-from)
 (barrier-dysfunction AND due-to)
 (myocardial-dysfunction AND after)
 (myocardial-dysfunction AND following)

(myocardial-dysfunction AND related-to)
 (myocardial-dysfunction AND resulting-from)
 (myocardial-dysfunction AND due-to)
 (systolic-dysfunction AND after)
 (systolic-dysfunction AND following)
 (systolic-dysfunction AND related-to)
 (systolic-dysfunction AND resulting-from)
 (systolic-dysfunction AND due-to)
 (voiding-dysfunction AND after)
 (voiding-dysfunction AND following)
 (voiding-dysfunction AND related-to)
 (voiding-dysfunction AND resulting-from)
 (voiding-dysfunction AND due-to)
 (hepatic-dysfunction AND after)
 (hepatic-dysfunction AND following)
 (hepatic-dysfunction AND related-to)
 (hepatic-dysfunction AND resulting-from)
 (hepatic-dysfunction AND due-to)
 (bladder-dysfunction AND after)
 (bladder-dysfunction AND following)
 (bladder-dysfunction AND related-to)
 (bladder-dysfunction AND resulting-from)
 (bladder-dysfunction AND due-to)
 (bowel-dysfunction AND after)
 (bowel-dysfunction AND following)
 (bowel-dysfunction AND related-to)
 (bowel-dysfunction AND resulting-from)
 (bowel-dysfunction AND due-to)
 (urinary-dysfunction AND after)
 (urinary-dysfunction AND following)
 (urinary-dysfunction AND related-to)
 (urinary-dysfunction AND resulting-from)
 (urinary-dysfunction AND due-to)
 (swallowing-dysfunction AND after)
 (swallowing-dysfunction AND following)
 (swallowing-dysfunction AND related-to)
 (swallowing-dysfunction AND resulting-from)
 (swallowing-dysfunction AND due-to)
 (anorectal-dysfunction AND after)
 (anorectal-dysfunction AND following)
 (anorectal-dysfunction AND related-to)
 (anorectal-dysfunction AND resulting-from)
 (anorectal-dysfunction AND due-to)
 (cardiopulmonary-dysfunction AND after)
 (cardiopulmonary-dysfunction AND following)
 (cardiopulmonary-dysfunction AND related-to)
 (cardiopulmonary-dysfunction AND resulting-from)
 (cardiopulmonary-dysfunction AND due-to)
 (fatal AND after)
 (fatal AND following)
 (fatal AND related-to)
 (fatal AND resulting-from)
 (fatal AND due-to)

(fibrosis AND after)
(fibrosis AND following)
(fibrosis AND related-to)
(fibrosis AND resulting-from)
(fibrosis AND due-to)
(high-incidence AND after)
(high-incidence AND following)
(high-incidence AND related-to)
(high-incidence AND resulting-from)
(high-incidence AND due-to)
(iatrogenic AND after)
(iatrogenic AND following)
(iatrogenic AND related-to)
(iatrogenic AND resulting-from)
(iatrogenic AND due-to)
(mortality AND after)
(mortality AND following)
(mortality AND related-to)
(mortality AND resulting-from)
(mortality AND due-to)
(morbidity AND after)
(morbidity AND following)
(morbidity AND related-to)
(morbidity AND resulting-from)
(morbidity AND due-to)
(risk AND after)*
(risk AND following)*
(risk AND related-to)*
(risk AND resulting-from)*
(risk AND due-to)*

7C2b. Diseases

Each of these linking terms below were combined with each of the diseases listed below.

7C2b1. Linking Terms

*Expos**
induce
induced
induces
incarceration
*occupation**
*pathogen**
*pollut**
poverty
socioeconomic
*worker**

Each of these diseases is combined with each of the linking terms listed above.

7C2b2. Diseases

Abdominal-Pregnancy
Aberrant-Crypt-Foci
Abnormal-Karyotype
Abnormal-Reflex
Abnormalities
Abnormality
Abortion
Abruptio-Placentae
*Abscess**
Acalculous-Cholecystitis
Acanthamoeba-Keratitis
Acantholysis
Acanthosis-Nigricans
Acatalsia
Accelerated-Idioventricular-Rhythm
Accessory-Atrioventricular-Bundle
Achlorhydria
Achondroplasia
*Acid-Base-Imbalance**
Acidosis
Acne-Keloid
Acne-Vulgaris
Acrocephalosyndactylia
Acrodermatitis
Acrodynia
Acromegaly
Acro-Osteolysis
Acrospiroma
Actinomycosis
Activated-Protein-C-Resistance
Acute-Abdomen

Acute-Generalized-Exanthematous-Pustulosis
Acute-Kidney-Injury
Acute-Lung-Injury
Acute-Phase-Reaction
*Adenocarcinoma**
Adenofibroma
Adenolymphoma
*Adenoma**
Adenomyoma
Adenomyosis
Adenosarcoma
Adiposis-Dolorosa
Adrenal-Insufficiency
Adrenocortical-Hyperfunction
Adrenoleukodystrophy
Aerophagy
Afibrinogenemia
African-Horse-Sickness
Agammaglobulinemia
Agenesis-of-Corpus-Callosum
Ageusia
Aggressive-Periodontitis
Agnosia
Agranulocytosis
Agraphia
AIDS-Arteritis
AIDS-Dementia-Complex
AIDS-Related-Complex
*Airway-Obstruction**
Airway-Remodeling
Akathisia
Akinetic-Mutism
Albinism
Albuminuria
Alcohol-Withdrawal-Delirium
Alcohol-Withdrawal-Seizures
Alcoholism
Alexia
Alkalosis
Alkaptonuria
Alopecia
alpha-1-Antitrypsin-Deficiency
alpha-Mannosidosis
alpha-Thalassemia
Alternariosis
Altitude-Sickness
Alveolar-Bone-Loss
Alveolitis
Amaurosis-Fugax
Amblyopia
Amebiasis
Ameloblastoma
Amelogenesis-Imperfecta

Amenorrhea
Amino-Acid-Metabolism
Amnesia
amyloid-Plaque
Amyloidosis
Anaemia
Anaphylaxis
Anaplasia
Anaplasmosis
Anastomotic-Leak
Ancylostomiasis
Anemia
Anencephaly
Anetoderma
Aneurysm
Angina
Angiodysplasia
*Angioedema**
Angiofibroma
Angioid-Streaks
Angiokeratoma
Angiolipoma
Angiomatosis
Angiomyolipoma
Anhedonia
Aniridia
Anisakiasis
Aniseikonia
Anisocoria
Anisometropia
Ankylosis
Anodontia
Anomia
Anophthalmos
Anorexia
Anovulation
Anoxia
Anthracosilicosis
Anthracosis
Anthrax
Antithrombin-III-Deficiency
Anuria
Aortic-Coarctation
Aortic-Valve-Insufficiency
Aortic-Valve-Prolapse
Aortitis
Aphakia
Aphasia
Aphonia
Aplasia
Apnea
Apoptosis
Appendicitis

Apraxia
Apraxias
*Arachnoid-Cyst**
Arachnoiditis
Arcus-Senilis
Argininosuccinic-Aciduria
Argyria
Arnold-Chiari-Malformation
*Arrhythmia**
Arterial-Stiffness
Arterio-Arterial-Fistula
Arteriosclerosis
Arteriosclerosis
Arteriovenous-Fistula
Arteriovenous-Malformations
Arteritis
Arthralgia
Arthritis
Arthrogryposis
Arthropathy
Arthus-Reaction
Artificial-Lens-Implant-Migration
Asbestosis
Ascariasis
Ascariasis
Ascites
Ascorbic-Acid-Deficiency
Aspergillosis
Asphyxia
Asthenia
Asthenopia
Asthenozoospermia
Asthma
Astigmatism
Astrocytoma
Ataxia
Atherosclerosis
atherosclerotic-plaque
Athetosis
Atrial-Fibrillation
Atrial-Flutter
Atrial-Premature-Complexes
Atrial-Remodeling
Atrioventricular-Block
Atrophic-Vaginitis
Atrophy
Autolysis
Autonomic-Dysreflexia
Avian-Leukosis
Avitaminosis
Azoospermia
Azotemia
Babesiosis

babinski-Reflex
Bacteremia
Bacteriuria
Balanitis
Balanitis-Xerotica-Obliterans
Balantidiasis
Barrett-Esophagus
Bell-Palsy
Bell's-Palsy
Beriberi
Berylliosis
beta-Thalassemia
Bile-Reflux
Biliary-Atresia
Biliary-Dyskinesia
Biliary-Fistula
Binge-Drinking
Biotinidase-Deficiency
Bird-Fancier's-Lung
Birth-Injuries
Birth-Weight
Bladder-Exstrophy
Blast-Crisis
Blastomycosis
Blepharitis
Blepharoptosis
Blepharospasm
Blindness
*Blister**
Blood-Group-Incompatibility
Blood-Loss
Bluetongue
Body-Weight
Bone-Anteversion
Bone-Cysts
Bone-Demineralization
Bone-Malalignment
Bone-Resorption
Bone-Retroversion
Botulism
Brachial-Plexus-Neuritis
Brachydactyly
Bradycardia
Brain-Concussion
Brain-Damage
Brain-Death
*Brain-Injur**
Brain-Ischemia
Branchioma
*Breast-Cyst**
Breech-Presentation
*Brenner-Tumor**
Bronchial-Fistula

Bronchial-Hyperreactivity
Bronchial-Spasm
Bronchiectasis
Bronchiolitis
Bronchitis
*Bronchogenic-Cyst**
Bronchomalacia
Bronchopneumonia
Bronchopulmonary-Sequestration
Brucellosis
Bruxism
Bulbar-Palsy
Bulbo-Spinal-Atrophy
Bulimia
Bundle-Branch-Block
Burkitt-Lymphoma
Bursitis
*Buschke-Lowenstein-Tumor**
Byssinosis
Cachexia
CADASIL
Cafe-au-Lait-Spots
Calcification
Calcinosis
Calciophylaxis
Calculi
Callosities
*Cancer**
Candidemia
Candidiasis
Capsule-Opacification
Carbohydrate-Metabolism
Carbonyl-Stress
Carboxymethyllysine
Carcinogenesis
*Carcinoid-Tumor**
*Carcinoma**
*Carcinosarcoma**
Cardiac-Arrest
Cardiac-Complexes
Cardiac-Output
Cardiac-Tamponade
Cardiogenic-Shock
Cardiomegaly
*Cardiomyopath**
cardiovascular-health
*cardiovascular-outcome**
cardiovascular-risk
Carney-Complex
Carotid-Artery-Dissection
Carotid-Artery-Injuries
*Carotid-Body-Tumor**
Carotid-Cavernous-Sinus-Fistula

Catalepsy
Cataplexy
*Cataract**
Catatonia
Causalgia
Cellulitis
*Central-Nervous-System-Cyst**
Central-Nervous-System-Helminthiasis
*Central-Nervous-System-Vascular-Malformation**
Central-Serous-Chorioretinopathy
Cephalopelvic-Disproportion
Cerebellar-Ataxia
Cerebral-Amyloid-Angiopathy
Cerebral-Palsy
Cerebral-Phaeohyphomycosis
Cerebral-Ventriculitis
Cerebrospinal-Fluid-Otorrhea
Cerebrospinal-Fluid-Rhinorrhea
Cerebrovascular-Trauma
Cervical-Intraepithelial-Neoplasia
Chagas-Cardiomyopathy
Chalazion
Chancre
Chancroid
Channelopathies
Cheilitis
Cheyne-Stokes-Respiration
Chickenpox
Chills
Chloracne
Choanal-Atresia
Cholangiocarcinoma
Cholangitis
Cholecystitis
Cholecystolithiasis
*Choledochal-Cyst**
Choledocholithiasis
Cholelithiasis
Cholera
Cholestasis
Cholesteatoma
Choline-Deficiency
Chondroblastoma
Chondrocalcinosis
Chondrodysplasia-Punctata
Chondroma
Chondromalacia-Patellae
Chondrosarcoma
Chordoma
Chorea
Chorioamnionitis
Choriocarcinoma
Chorioretinitis

Choristoma
Choroidal-Neovascularization
Choroiditis
Chromoblastomycosis
Chromosomal-Instability
*Chromosome-Aberration**
Chromosome-Breakage
Chromosome-Fragility
Chromosome-Inversion
Chylothorax
Chylous-Ascites
Cicatrix
Citrullinemia
Cleft-Lip
Cleft-Palate
Clonorchiasis
Clubfoot
*Cluster-Headache**
Coccidioidomycosis
Coccidiosis
Colic
Colitis
Collagenous-Sprue
Colloid-Cysts
Coloboma
Colonic-Polyps
Colonic-Pseudo-Obstruction
Color-Vision-Defects
Coma
Common-Cold
Common-Variable-Immunodeficiency
Commotio-Cordis
*Complication**
Condylomata-Acuminata
Confusion
Congenital-Hyperinsulinism
Congenital-Hypothyroidism
Conjoined-Twins
Conjunctivitis
Constipation
Constriction
Contracture
Coproporphyrria
Cor-Triatriatum
Corneal-Dystrophies
Corneal-Endothelial-Cell-Loss
Corneal-Neovascularization
Corneal-Opacity
Corneal-Perforation
Corneal-Wavefront-Aberration
*Coronary-Aneurysm**
Coronary-Occlusion
*Coronary-Vasospasm**

Coronary-Vessel-Anomalies
Cough
Cowpox
Coxa-Valga
Coxa-Vara
Craniocerebral-Trauma
Craniofacial-Dysostosis
Craniopharyngioma
Craniosynostoses
Croup
Cryoglobulinemia
Cryptococcosis
Cryptogenic-Organizing-Pneumonia
Cryptorchidism
Cryptosporidiosis
Cutaneous-Fistula
Cutis-Laxa
Cyanosis
Cyclosporiasis
Cystadenocarcinoma
Cystadenoma
Cystic-Fibrosis
Cysticercosis
Cystinosis
Cystinuria
Cystitis
Cystocele
Cysts
Cytochrome-c-Oxidase-Deficiency
Cytomegalovirus-Retinitis
Dacryocystitis
Dandruff
Deafness
Decalcification
Decerebrate-State
Dehydration
Delayed-Emergence-from-Anesthesia
Delayed-Graft-Function
Delayed-Puberty
Delirium
Delta-Thalassemia
Dementia
Dendritic-Cell-Sarcoma
Dengue
Dental-Calculus
Dental-Caries
Dental-Deposits
Dental-Enamel-Hypoplasia
Dental-Fissures
Dental-Fistula
Dental-Leakage
Dental-Occlusion
Dental-Plaque

Dental-Pulp-Calcification
Dental-Pulp-Exposure
Dental-Pulp-Necrosis
Dentigerous-Cyst
Dentin-Sensitivity
Dentinogenesis-Imperfecta
Dentofacial-Deformities
Depression
Dermatitis
Dermatofibrosarcoma
Dermatomycoses
Dermatomyositis
Dermoid-Cyst
*Desmoplastic-Small-Round-Cell-Tumor**
Dextrocardia
Diabetes
Diabetic
Diaper-Rash
Diaphragmatic-Eventration
Diarrhea
Diastema
Dicrocoeliasis
Dientamoebiasis
Diffuse-Axonal-Injury
Digestive-System-Fistula
Dihydropyrimidine-Dehydrogenase-Deficiency
Dilatation
Diphtheria
Diphyllobothriasis
Diplopia
Dirofilariasis
Discitis
*Disease**

*Disorder**
Disseminated-Intravascular-Coagulation
Distemper
Diurnal-Enuresis
Diverticulitis
Diverticulosis
Diverticulum
Dizziness
Double-Outlet-Right-Ventricle
Dracunculiasis
Drowning
Drug-Hypersensitivity
Drug-Overdose
Drug-Induced-Liver-Injury
Dry-Socket
Ductus-Arteriosus
*Duodenal-Obstruction**
Duodenitis
Duodenogastric-Reflux

Dupuytren-Contracture
Dwarfism
Dysarthria
Dysautonomia
Dysbiosis
Dyscalculia
Dysentery
*Dysfunction**
Dysgammaglobulinemia
Dysgerminoma
Dysgeusia
Dyskeratosis-Congenita
*Dyskinesia**
Dyslexia
*Dyslipid**
Dysmenorrhea
Dysostoses
Dyspareunia
Dyspepsia
Dysphonia
Dysplasia
Dyspnea
Dyssomnias
Dystocia
Dystonia
Dysuria
Ear-Deformities
Earache
Ebstein-Anomaly
Ecchymosis
Eccrine-Porocarcinoma
Echinococcosis
Echinostomiasis
Eclampsia
Ecthyma
Ectoparasitic-Infestations
Ectopia-Cordis
Ectopia-Lentis
ectopic-Pregnancy
Ectromelia
Ectropion
Eczema
*Edema**
edentulous-Mouth
Egg-Hypersensitivity
Ehrlichiosis
Eisenmenger-Complex
Elephantiasis
Elliptocytosis
Emaciation
*Embolism**
Embryo-Loss
Emergencies

Emphysema
Emphysematous-Cholecystitis
Empyema
Encephalitis
Encephalitozoonosis
Encephalocele
Encephalomalacia
Encephalomyelitis
Encephalopathy
Enchondromatosis
Endarteritis
Endocardial-Cushion-Defects
Endocardial-Fibroelastosis
Endocarditis
*Endodermal-Sinus-Tumor**
Endoleak
Endolymphatic-Hydrops
*Endometrial-Stromal-Tumors**
Endometriosis
Endometritis
Endophthalmitis
Endotoxemia
Enophthalmos
Entamoebiasis
Enteritis
Enterobiasis
Enterocolitis
Enterotoxemia
Entropion
Enuresis
Enzootic-Bovine-Leukosis
Eosinophilia
Eosinophilic-Granuloma
Ependymoma
*Epidermal-Cyst**
Epidermodysplasia-Verruciformis
Epidermolysis-Bullosa
Epididymitis
Epiglottitis
Epilepsia-Partialis-Continua
Epilepsies
Epilepsy
Epiphyse
Epiretinal-Membrane
Epispadias
Epistaxis
Equinus-Deformity
Erectile-Dysfunction
Ergotism
Eructation
*Eruption**
Erysipelas
Erysipeloid

*Erythema**
Erythroblastosis
Erythrokeratoderma-Variabilis
Erythromelalgia
Erythroplasia
Esophageal-Achalasia
Esophageal-and-Gastric-Varices
Esophageal-Atresia
*Esophageal-Cyst**
Esophageal-Fistula
*Esophageal-Perforation**
*Esophageal-Spasm**
Esophagitis
Esotropia
*Essential-Tremor**
Esthesioneuroblastoma
Ethmoid-Sinusitis
Exanthema
Exocrine-Pancreatic-Insufficiency
Exophthalmos
Exostoses
Exotropia
Exsanguination
Eye-Injuries
Facial-Asymmetry
Facial-Dermatoses
Facial-Hemiatrophy
Facial-Neuralgia
Facial-Paralysis
Factor-V-Deficiency
Factor-VII-Deficiency
Factor-X-Deficiency
Factor-XI-Deficiency
Factor-XII-Deficiency
Factor-XIII-Deficiency
Failure-to-Thrive
Familial-Hypophosphatemic-Rickets
Fanconi-Anemia
Farmer's-Lung
Fasciculation
Fasciitis
Fascioliasis
Fascioloidiasis
Fatigue
Fatty-Liver
Favism
Febrile-Neutropenia
Fecal-Impaction
Fecal-Incontinence
Feline-Panleukopenia
Feminization
Femoracetabular-Impingement
*Fetal-Death**

Fetal-Distress
Fetal-Growth-Retardation
Fetal-Hypoxia
Fetal-Macrosomia
Fetal-Membranes
Fetal-Resorption
Fetal-Weight
Fetofetal-Transfusion
Fetomaternal-Transfusion
Fever
*Fibroadenoma**
*Fibroma**
Fibromatosis
Fibromyalgia
Fibrosarcoma
Fibrosis
*Fibrous-Tumor**
Filariasis
Fissure-in-Ano
Fissured-Tongue
Fistula
Flatfoot
Flatulence
*Flea-Infestation**
Fluorosis
Flushing
Focal-Dermal-Hypoplasia
Folic-Acid-Deficiency
*Follicular-Cyst**
Folliculitis
Food-Hypersensitivity
Foot-Deformities
Foot-Dermatoses
Foramen-Ovale
*Foreign-Body-Reaction**
Fournier-Gangrene
Fowlpox
Freemartinism
Friedreich-Ataxia
Frontal-Sinusitis
Frontotemporal-Dementia
Frontotemporal-Lobar-Degeneration
Fructose-Intolerance
Fructose-1,6-Diphosphatase-Deficiency
Fuchs'-Endothelial-Dystrophy
Fucosidosis
Fungemia
Funnel-Chest
Furcation-Defects
Furunculosis
Fusariosis
Gagging
Gait-Apraxia

Gait-Ataxia
Galactorrhea
*Galactosemia**
*Gallstone**
Ganglioglioma
*Ganglion-Cyst**
Ganglioneuroblastoma
*Ganglioneuroma**
Gangliosidosis
Gangrene
Gastric-Antral-Vascular-Ectasia
Gastric-Dilatation
Gastric-Fistula
*Gastric-Outlet-Obstruction**
Gastrinoma
Gastritis
Gastroenteritis
Gastroesophageal-Reflux
*Gastrointestinal-Stromal-Tumor**
Gastroparesis
Gastroschisis
Genomic-Instability
Genu-Valgum
Genu-Varum
Geographic-Atrophy
Geotrichosis
Germinoma
Giant-Cell-Arteritis
Giant-Cell-Tumor-of-Bone
*Giant-Cell-Tumor**
Giardiasis
Gigantism
Gingival-Hypertrophy
Gingival-Overgrowth
*Gingival-Pocket**
Gingival-Recession
Gingivitis
Glanders
Glaucoma
Glioblastoma
Glioma
Gliosarcoma
Gliosis
Glomerulonephritis
Glomerulosclerosis
*Glomus-Jugulare-Tumor**
*Glomus-Tumor**
*Glomus-Tympanicum-Tumor**
Glossalgia
Glossitis
Glucagonoma
Glucose-Intolerance
Glucosephosphate-Dehydrogenase-Deficiency

*Glycat**
Glycemia
Glycosuria
*Glycosylat**
Glycoxidation
Gnathostomiasis
Goiter
Gonadal-Dysgenesis
Gonorrhea
Gout
*Graft-Occlusion**
*Granular-Cell-Tumor**
*Granuloma**
Granulomatosis
Granulomatous-Mastitis
*Granulosa-Cell-Tumor**
Graves-Ophthalmopathy
Gynatresia
Gynecomastia
Gyrate-Atrophy
Haematuria
Haemonchiasis
Hairy-Tongue
Halitosis
*Hallucination**
Hallux-Rigidus
Hallux-Valgus
Hallux-Varus
Hamartoma
Hand-Deformities
Hand-Dermatoses
Haploinsufficiency
*Hazard**
*Head-Injur**
*Headache**
Hearing-Loss
*Heart-Aneurysm**
Heart-Arrest
*Heart-Block**
*Heart-Defect**
Heart-Failure
*Heart-Murmur**
*Heart-Septal-Defect**
Heartburn
*Heel-Spur**
Helminthiasis
Hemangioblastoma
Hemangioendothelioma
*Hemangioma**
Hemangiopericytoma
Hemangiosarcoma
Hemarthrosis
Hematemesis

Hematocele
Hematocolpos
*Hematoma**
Hematometra
Hematuria
Hemianopsia
*Hemifacial-Spasm**
Hemiplegia
Hemobilia
Hemochromatosis
Hemoglobinopathies
Hemoglobinuria
Hemolysis
Hemoperitoneum
Hemophilia
Hemopneumothorax
Hemoptysis
*Hemorrhag**
Hemorrhoids
Hemosiderosis
Hemospermia
Hemothorax
Hepatic-Encephalopathy
Hepatic-Insufficiency
Hepatitis
Hepatoblastoma
Hepatolenticular-Degeneration
Hepatomegaly
Hereditary-Angioedema
*Hernia**
Heroin-Dependence
Herpangina
Herpes-Genitalis
Herpes-Labialis
Herpes-Simplex
Herpes-Zoster
Heterotopic-Pregnancy
*Hiccup**
Hidradenitis
Hidrocystoma
Hip-Contracture
*Hip-Dislocation**
Hirsutism
Histiocytic-Necrotizing-Lymphadenitis
Histiocytic-Sarcoma
Histiocytoma
Histiocytosis
Histoplasmosis
HIV-Enteropathy
HIV-Seropositivity
HIV/AIDS
Hoarseness
Holoprosencephaly

Homocystinuria
Hot-Flashes
Hutchinson's-Melanotic-Freckle
Hyalohyphomycosis
Hydatidiform-Mole
Hydranencephaly
Hydroa-Vacciniforme
Hydrocephalus
Hydronephrosis
Hydrophthalmos
Hydropneumothorax
Hydrops-Fetalis
Hydrothorax
Hymenolepiasis
Hyperacusis
Hyperaldosteronism
Hyperalgesia
Hyperammonemia
Hyperamylasemia
Hyperandrogenism
Hyperargininemia
Hyperbilirubinemia
*Hypercalcemi**
Hypercalciuria
Hypercapnia
Hypercellularity
Hypercementosis
*Hypercholesterol**
*Hypercoagul**
Hyperemesis-Gravidarum
*Hyperemi**
Hyperesthesia
Hypergammaglobulinemia
*Hyperglyc**
Hyperhidrosis
*Hyperhomocystein**
*Hyperinsulin**
*Hyperkal**
Hyperkeratosis
*Hyperkinesi**
*Hyperleptinemia**
*Hyperlipid**
*Hyperlipoproteinemia**
Hyperlysinemias
*Hypermagnesemi**
Hypernatremia
Hyperopia
Hyperostosis
Hyperoxaluria
Hyperoxia
*Hyperparathyroid**
Hyperphagia
*Hyperphosphat**

Hyperpigmentation
Hyperpituitarism
Hyperplasia
Hyperprolactinemia
Hypersecretion
Hypersensitivity
Hypersomnolence
Hypersplenism
Hypertelorism
Hypertension
Hypertensive-Encephalopathy
Hypertensive-Retinopathy
Hyperthyroidism
Hyperthyroxinemia
Hypertrichosis
*Hypertriglycerid**
Hypertrophy
*Hyperuric**
Hyperventilation
Hypervitaminosis
Hypervolemia
Hypesthesia
Hyphema
Hypoalbuminemia
Hypoaldosteronism
*Hypoalphalipoproteinemia**
*Hypobetalipoproteinemia**
*Hypocalcemi**
Hypocapnia
Hypodermiiasis
*Hypoglyc**
Hypogonadism
Hypohidrosis
*Hypokalemi**
*Hypokinesi**
*Hypolipid**
Hypolipoproteinemias
*Hypomagnesemi**
Hypomethylation
*Hyponatremi**
Hypoparathyroidism
Hypoperfusion
*Hypophosphat**
Hypopigmentation
Hypopituitarism
Hypoplasia
*Hypoprothrombinemia**
Hypospadias
Hypotension
Hypothermia
*Hypothyroid**
Hypotrichosis
Hypoventilation

Hypovolemia
Hypoxemia
Hypoxia
Ichthyosis
IgA-Deficiency
IgG-Deficiency
Ileitis
Ileus
Iliac-Aneurysm
Illness
Illusions
Immersion-Foot
Immunoblastic-Lymphadenopathy
Impacted-Tooth
Imperforate-Anus
Impetigo
Implant-Capsular-Contracture
Impotence
Incontinentia-Pigmenti
Inert-Gas-Narcosis
*Infarction**
*Infect**
Infertility
Inflammation
Inflammatory
Influenza
Ingrown-Nails
*Inhalant-Abuse**
(Injury-in
AND Mice [ti]) (injury-in
*AND rats [ti]) Insect-Bite**
*Insect-Sting**
*Insomnia**
Insulin-Coma
Insulin-Resistance
Insulinoma
Intellectual-Disability
Intermittent-Claudication
Interstitial-Pneumonias
Intertrigo
Intervertebral-Disc-Degeneration
Intervertebral-Disc-Displacement
Intestinal-Atresia
*Intestinal-Fistula**
*Intestinal-Obstruction**
*Intestinal-Perforation**
Intestinal-Polyposis
Intestinal-Polyps
Intestinal-Pseudo-Obstruction
Intestinal-Volvulus
Intracranial-Arteriosclerosis
Intracranial-Arteriovenous-Malformations
*Intracranial-Embolism**

Intracranial-Hypotension
Intraoperative-Awareness
Intraoperative-Complications
Intussusception
Iridocyclitis
Iritis
Iron-Overload
Ischemia
Ischemic-Attack
Ischemic-Contracture
Isolated-Noncompaction-of-the-Ventricular-Myocardium
Isosporiasis
Jaundice
*Jaw-Cyst**
Joint-Deformities
Joint-Instability
Joint-Loose-Bodies
Keloid
Keratitis
Keratoacanthoma
Keratoconjunctivitis
Keratoconus
Keratoderma
Keratosi
Kernicterus
Ketosis
Kidney-Calculi
Kidney-Failure
Klatskin's-Tumor
Krukenberg-Tumor
Kuru
Kwashiorkor
Kyphosis
Labyrinthitis
*Lacrimal-Duct-Obstruction**
Lactose-Intolerance
Larva-Migrans
Laryngismus
Laryngitis
Laryngomalacia
Laryngopharyngeal-Reflux
Laryngostenosis
Latex-Hypersensitivity
Lathyrism
Leber-Congenital-Amaurosis
Lecithin-Acyltransferase-Deficiency
Leg-Dermatoses
Leg-Length-Inequality
Legionellosis
Leiomyoma
Leiomyomatosis
Leiomyosarcoma
*Leishmania**

Lens-Subluxation
Lentigo
Leprosy
Leptospirosis
Lethargy
Leukemia
Leukemic-Infiltration
Leukemoid-Reaction
Leukoaraiosis
Leukocytosis
Leukodystrophy
Leukoedema
Leukoencephalitis
*Leukoencephalopath**
Leukokeratosis
Leukomalacia
Leukopenia
Leukoplakia
Leukorrhoea
Leukostasis
Leydig-Cell-Tumor
*Lice-Infestation**
Lichen-Nitidus
Lichen-Planus
Lichen-Sclerosus-et-Atrophicus
*Limb-Deformit**
Linear-IgA-Bullous-Dermatosis
Lingual-Thyroid
Linitis-Plastica
Lipid-Metabolism
Lipidoses
*Lipid-Peroxid**
Lipodystrophy
Lipoma
Lipomatosis
Lipoperoxidation
Liposarcoma
Lipoxidation
Lissencephalies
Lissencephaly
Listeriosis
Lithiasis
Livedo-Reticularis
Liver-Cirrhosis
Liver-Failure
Liver-Injury
Loiasis
Lordosis
Low-Tension-Glaucoma
*Lower-Extremity-Deformit**
*Lower-Urinary-Tract-Symptom**
Ludwig's-Angina
Lung-Injury

Lupus-Erythematosus
Lupus-Nephritis
Lupus-Vulgaris
Lyme-Neuroborreliosis
Lymphadenitis
Lymphangiectasis
Lymphangioliomyomatosis
Lymphangioma
Lymphangiomyoma
Lymphangiosarcoma
Lymphangitis
*Lymphatic-Metastas**
Lymphedema
Lymphocele
Lymphocytic-Choriomeningitis
Lymphocytosis
Lymphogranuloma-Venereum
Lymphohistiocytosis
Lymphoma
Lymphomatoid-Granulomatosis
Lymphomatoid-Papulosis
Lymphopenia
Macroalbuminuria
Macrocephaly
Macroglossia
Macular-Degeneration
Magnesium-Deficiency
Malacoplakia
Malaria
Malformations-of-Cortical-Development
Malformed-Nails
Malignant-Catarrh
Malignant-Hyperthermia
Malnutrition
Malocclusion
Mandibulofacial-Dysostosis
Mansonelliasis
Marijuana-Abuse
Mast-Cell-Sarcoma
Mastitis
Mastocytoma
Mastocytosis
Mastodynia
Mastoiditis
Maternal-Death
Maxillary-Sinusitis
Measles
Meckel-Diverticulum
Mediastinal-Cyst
Mediastinal-Emphysema
Mediastinitis
Medullary-Sponge-Kidney
Medulloblastoma

Megacolon
*Melanoma**
Melanosis
Melena
Melioidosis
Meningeal-Carcinomatosis
*Meningioma**
Meningism
Meningitis
Meningocele
Meningoencephalitis
Meningomyelocele
Menopause
Menorrhagia
Menstruation-Disturbances
Mental-Fatigue
Mental-Retardation
Mesenchymoma
*Mesenteric-Cyst**
Mesenteric-Lymphadenitis
Mesenteric-Vascular-Occlusion
Mesial-Movement-of-Teeth
Mesothelioma
Metabolic-Acidosis
Metabolic-Syndrome
Metabolism
Metal-Metabolism
Metaplasia
Metatarsalgia
Methemoglobinemia
Metrorrhagia
Mevalonate-Kinase-Deficiency
Microalbuminuria
Microcephaly
Micrognathism
Microinflammation
Micronuclei
Microphthalmos
Microsatellite-Instability
Microscopic-Polyangiitis
Microsporidiosis
Microstomia
Microvascular-Angina
*Migraine**
Miliaria
Milk-Hypersensitivity
Milk-Sickness
Mink-Viral-Enteritis
Miosis
*Mite-Infestation**
*Mitochondrial-Encephalomyopath**
*Mitochondrial-Myopath**
Mitral-Valve-Insufficiency

Mitral-Valve-Prolapse
*Mixed-Tumor**
Molluscum-Contagiosum
Monieziasis
Monilethrix
Monkeypox
Monoclonal-Gammopathy
*Mononeuropath**
Morning-Sickness
Morphine-Dependence
Motion-Sickness
Mouth-Breathing
Mucinoses
Mucinosis
Mucocele
Mucolipidoses
Mucopolysaccharidoses
Mucopolysaccharidosis
Mucormycosis
Mucositis
Multicystic-Dysplastic-Kidney
Multiple-Acyl-Coenzyme-A-Dehydrogenase-Deficiency
Multiple-Carboxylase-Deficiency
Multiple-Chemical-Sensitivity
Multiple-Myeloma
*Multiple-Organ-Failure**
Multiple-Pulmonary-Nodules
Multiple-System-Atrophy
Mumps
*Muscle-Cramp**
Muscle-Hypertonia
Muscle-Hypotonia
Muscle-Rigidity
Muscle-Spasticity
Muscle-Weakness
Muscular-Atrophy
*Muscular-Dystroph**
Mutism
Myalgia
Myasthenia-Gravis
Mycetoma
Mycoses
Mycosis-Fungoides
Mycotoxicosis
Mydriasis
Myelinolysis
Myelitis
Myelolipoma
Myiasis
Myocardial-Bridging
Myocardial-Ischemia
Myocardial-Reperfusion-Injury
Myocardial-Stunning

Myocarditis
Myoclonic-Cerebellar-Dyssynergia
*Myoclonic-Epileps**
Myoclonus
Myoepithelioma
Myoglobinuria
Myokymia
Myoma
*Myopath**
Myopia
Myositis
Myotonia
Myotonic-Dystrophy
Myringosclerosis
Myxedema
Myxoma
Myxomatosis
Myxosarcoma
Narcolepsy
*Nasal-Obstruction**
*Nasal-Polyp**
Nasal-Septal-Perforation
Nasopharyngitis
Nausea
Necatoriasis
Necrobiosis-Lipoidica
Necrobiotic-Xanthogranuloma
Necrolytic-Migratory-Erythema
Necrosis
Neointima
Neoplasia
*Neoplasm**
*Neoplastic-Cell**
Neovascularization
Nephritis
Nephrocalcinosis
Nephrogenic-Fibrosing-Dermopathy
Nephrolithiasis
Nephroma
*Nephropath**
Nephrosclerosis
Nephrosis
Nerve-Degeneration
*Nerve-Injur**
*Nervous-System-Malformation**
Nesidioblastosis
*Neural-Tube-Defect**
Neuralgia
Neurilemmoma
Neuritis
Neuroacanthocytosis
Neuroaspergillosis
*Neuroaxonal-Dystroph**

Neuroblastoma
Neurocysticercosis
Neurocytoma
*Neuroectodermal-Tumor**
*Neuroendocrine-Tumor**
Neurofibroma
*Neurofibromatos**
Neurofibrosarcoma
Neurogenic-Bowel
Neurogenic-Inflammation
Neurogenic-Urinary-Bladder
Neuroma
Neuromyelitis-Optica
Neuronal-Ceroid-Lipofuscinoses
*Neuropath**
Neuroschistosomiasis
Neurosyphilis
Neurothekeoma
Neutropenia
Nevus
Night-Blindness
*Night-Terror**
Nocturia
Nocturnal-Enuresis
Nocturnal-Paroxysmal-Dystonia
Noma
Nondisjunction
Nonodontogenic-Cysts
Nonvital-Tooth
No-Reflow-Phenomenon
Nose-Deformities
Nut-Hypersensitivity
Nystagmus
Obesity
Obstetric-Labor-Complications
Ochronosis
Ocular-Hypotension
*Odontogenic-Cyst**
*Odontogenic-Tumor**
Odontoma
Oedema
Oligodendroglioma
Oligohydramnios
Oligomenorrhea
Oligospermia
Oliguria
Olivopontocerebellar-Atrophies
Onchocerciasis
Onycholysis
Onychomycosis
Oophoritis
Open-Bite
Ophthalmia

Ophthalmoplegia
Opisthorchiasis
Optic-Atrophy
Optic-Disk-Drusen
Optic-Nerve-Glioma
Optic-Neuritis
*Oral-Fistula**
Orbital-Cellulitis
Orbital-Myositis
*Orbital-Pseudotumor**
Orchitis
*Oroantral-Fistula**
Orthostatic-Intolerance
Ossification
Osteitis
Osteoarthritis
*Osteoarthropath**
Osteoblastoma
Osteochondritis
Osteochondrodysplasias
Osteochondroma
Osteochondrosis
Osteodystrophy
Osteogenesis-Imperfecta
Osteolysis
Osteoma
Osteomalacia
Osteomyelitis
Osteonecrosis
Osteopenia
Osteopetrosis
Osteophyte
Osteoporosis
Osteosarcoma
Osteosclerosis
Ostertagiasis
Otitis
Otomycosis
Otosclerosis
*Ovarian-Cyst**
Overactive-Urinary-Bladder
Overbite
Overnutrition
Overweight
Oxidative-Stress
Oxyuriasis
Pachyonychia-Congenita
Pain
Pallor
*Pancreatic-Cyst**
*Pancreatic-Fistula**
Pancreatic-Insufficiency
Pancreatic-Pseudocyst

Pancreatitis
Pancytopenia
Panniculitis
Panuveitis
Papilledema
Papilloma
Paracoccidioidomycosis
Paraganglioma
Paragonimiasis
Parakeratosis
Paralyses
Paralysis
Paraneoplastic
Paraparesis
Paraphimosis
Paraplegia
Paraproteinemias
Parapsoriasis
Parasitemia
Parasomnias
Parasystole
Paratuberculosis
Paresis
Paresthesia
Paronychia
Parotitis
Paroxysmal-Hemicrania
Pars-Planitis
Pasteurellosis
Peanut-Hypersensitivity
Pediatric-Obesity
Pelger-Huet-Anomaly
Peliosis-Hepatis
Pellagra
Pelvic-Organ-Prolapse
Pemphigoid
Pemphigus
Penile-Induration
*Periapical-Granuloma**
Periarthritis
Pericardial-Effusion
Pericarditis
Pericoronitis
Peri-Implantitis
Perinephritis
Periodontal-Atrophy
Periodontal-Attachment-Loss
*Periodontal-Cyst**
Periodontal-Pocket
Periodontitis
Periostitis
Peritonitis
Periventricular-Nodular-Heterotopia

Persistent-Hyperplastic-Primary-Vitreous
Persistent-Vegetative-State
Peste-des-Petits-Ruminants
Phaeohyphomycosis
Phantom-Limb
Pharyngitis
*Phencyclidine-Abuse**
*Phenylketonuria**
Pheochromocytoma
Phimosis
Phlebitis
Photophobia
Phyllodes-Tumor
Piebaldism
Piedra
Pilomatrixoma
Pilonidal-Sinus
Pinealoma
Pinguecula
Pituitary-ACTH-Hypersecretion
Pituitary-Apoplexy
Pityriasis
Placenta
Placental-Insufficiency
Plagiocephaly
Plague
*Plasma-Cell-Granuloma**
Plasmacytoma
Platelet-Storage-Pool-Deficiency
Platybasia
Pleural-Effusion
Pleurisy
Pleurodynia
Pleuropneumonia
Pneumatosis-Cystoides-Intestinalis
Pneumocephalus
Pneumoconiosis
Pneumonia
Pneumopericardium
Pneumoperitoneum
Pneumorrhachis
Pneumothorax
Poliomyelitis
Polyarteritis-Nodosa
Polychondritis
Polycystic-Kidney
Polycythemia
Polydactyly
Polydipsia
Polyendocrinopathies
Polyhydramnios
Polymyalgia-Rheumatica
Polymyositis

Polyneuropathies
Polyps
Polyradiculopathy
Polyuria
*Popliteal-Cyst**
Porokeratosis
Poroma
*Porphyria**
Port-Wine-Stain
Positive-Pressure-Respiration
Posterior-Tibial-Tendon-Dysfunction
Post-Exercise-Hypotension
Postoperative-Complications
Postoperative-Nausea
postoperative-vomiting
Postpartum-Thyroiditis
Potassium-Deficiency
Pouchitis
Precancerous
Precocious-Puberty
Prediabetic-State
Pre-Eclampsia
Pre-Excitation
Pregnancy-Complications
Pregnancy-in-Diabetics
Prehypertension
Preleukemia
Premature-Aging
Premature-Birth
Premature-Ejaculation
Premature-Obstetric-Labor
*Prenatal-Injur**
Presbycusis
Presbyopia
Priapism
Primary-Dysautonomias
*Primary-Graft-Dysfunction**
Primary-Myelofibrosis
Primary-Ovarian-Insufficiency
Proctitis
Proctocolitis
Progeria
Prognathism
Prolactinoma
Prolonged-Pregnancy
Propionic-Acidemia
Prosopagnosia
Prostatism
Prostatitis
*Prosthesis-Failure**
Protein-C-Deficiency
Protein-Deficiency
Protein-S-Deficiency

Protein-Energy-Malnutrition
Protein-Losing-Enteropathies
Proteinuria
Proteostasis-Deficiencies
Protoporphyrria
Prurigo
Pruritus
Pseudobulbar-Palsy
Pseudohypoaldosteronism
Pseudohypoparathyroidism
Pseudolymphoma
Pseudomyxoma-Peritonei
Pseudophakia
Pseudorabies
Pseudotumor-Cerebri
Pseudoxanthoma-Elasticum
Psittacosis
Psoriasis
Psychomotor-Agitation
Psychoses
Pterygium
Pubic-Symphysis-Diastasis
Pudendal-Neuralgia
Pulmonary-Alveolar-Proteinosis
Pulmonary-Aspergillosis
Pulmonary-Atelectasis
Pulmonary-Atresia
Pulmonary-Blastoma
Pulmonary-Embolism
Pulmonary-Emphysema
Pulmonary-Eosinophilia
*Pulmonary-Nodule**
Pulmonary-Sclerosing-Hemangioma
Pulmonary-Valve-Insufficiency
Pulpitis
Pure-Autonomic-Failure
Purine-Pyrimidine-Metabolism
Purpura
Pyelitis
Pyelonephritis
Pyoderma
Pyometra
Pyomyositis
Pyonephrosis
Pythiosis
Pyuria
Quadriplegia
Rabies
Radiation-Pneumonitis
*Radicular-Cyst**
Radiculopathy
Ranula
Reactive-Oxygen-Species

Rectal-Fistula
Rectal-Prolapse
Rectocele
Rectovaginal-Fistula
Recurrence
Red-Cell-Aplasia
Reflex-Sympathetic-Dystrophy
Refractive-Errors
Renal-Aminoacidurias
Renal-Artery-Obstruction
Renal-Colic
Renal-Injury
Renal-Insufficiency
Renal-Osteodystrophy
Renal-Tubular-Transport
Reperfusion-Injury
Respiratory-Aspiration
Respiratory-Hypersensitivity
Respiratory-Insufficiency
Respiratory-Paralysis
Respiratory-Sounds
Respiratory-Tract-Fistula
Restenosis
Reticulocytosis
Retinal-Artery-Occlusion
Retinal-Degeneration
Retinal-Detachment
Retinal-Drusen
Retinal-Neovascularization
Retinal-Perforations
Retinal-Telangiectasis
Retinal-Vein-Occlusion
Retinitis
Retinoblastoma
Retinopathy
Retinoschisis
Retrognathia
Retrograde-Degeneration
Retropneumoperitoneum
Rh-Isoimmunization
*Rhabdoid-Tumor**
Rhabdomyolysis
Rhabdomyoma
Rhabdomyosarcoma
*Rheumatic-Nodule**
*Rheumatoid-Nodule**
Rhinitis
Rhinophyma
Rhinoscleroma
Rhinosporidiosis
Riboflavin-Deficiency
Rickets
Rigor-Mortis

Rinderpest
Root-Caries
Root-Resorption
Rosacea
Rubella
Rupture
Sacroiliitis
Salivary-Duct-Calculi
Salivary-Gland-Calculi
Salivary-Gland-Fistula
Salpingitis
Sarcocystosis
Sarcoidosis
Sarcoma
Sarcopenia
Scabies
Scalp-Dermatoses
Schistosomiasis
Sciatica
Scleredema-Adultorum
Sclerema-Neonatorum
Scleritis
Scleroderma
Scleromyxedema
Sclerosis
Scoliosis
*Scorpion-Sting**
Scotoma
Scrapie
Scrub-Typhus
Scurvy
Seizures
Seminoma
Sepsis
Septic-Shock
Seroma
Serositis
*Sertoli-Cell-Tumor**
Sertoli-Leydig-Cell-Tumor
Serum-Sickness
Severe-Combined-Immunodeficiency
Severe-Dengue
Sex-Chromosome-Aberrations
*Sex-Cord-Gonadal-Stromal-Tumor**
Sexual-Dysfunction
Shwartzman-Phenomenon
Sialadenitis
Sialometaplasia
Sialorrhoea
Sickle-Cell-Trait
Siderosis
Silicosis
Silicotuberculosis

Single-Umbilical-Artery
Sinoatrial-Block
Sinus-Arrest
Sinus-Pericranii
Sinusitis
Situs-Inversus
*Skull-Fracture**
Sleep-Apnea
Sleep-Bruxism
Sleep-Deprivation
Sleep-Paralysis
Slipped-Capital-Femoral-Epiphyse
Smallpox
*Smooth-Muscle-Tumor**
*Snake-Bite**
Sneezing
Snoring
Somatostatinoma
Somnambulism
Space-Motion-Sickness
Sparganosis
Spasm
Spasms
Spastic-Paraplegia
Spermatic-Cord-Torsion
Spermatocele
Sphenoid-Sinusitis
Spherocytosis
Sphincter-of-Oddi-Dysfunction
Sphingolipidoses
*Spider-Bite**
Spina-Bifida
Spinal-Cord-Compression
*Spinal-Cord-Injur**
Spinal-Cord-Ischemia
*Spinal-Curvature**
Spinal-Dysraphism
Spinal-Muscular-Atrophies-of-Childhood
Spinal-Osteophytosis
Spinocerebellar-Ataxias
*Spinocerebellar-Degeneration**
Splenomegaly
Splenosis
Spondylarthritis
Spondylarthropathies
Spondylitis
Spondylolisthesis
Spondylolysis
Spondylosis
Sporotrichosis
Sprue
Starvation
Status-Asthmaticus

Status-Epilepticus
Steatitis
Steatorrhea
Stenosis
Steroid-Metabolism
Stings
Stomach-Volvulus
Stomatitis
Strabismus
Striae-Distensae
Striatonigral-Degeneration
*Stricture**
Stroke
Strongyloidiasis
Stupor
Stuttering
Subacute-Combined-Degeneration
Subacute-Sclerosing-Panencephalitis
Subcutaneous-Emphysema
Subdural-Effusion
*Substance-Abuse**
Sudden-Death
*Sudden-Infant-Death**
Sulfhemoglobinemia
Sunburn
Supernumerary-Tooth
Suppuration
Supranuclear-Palsy
Surgical-Shock
Surgical-Wound-Dehiscence
Sweating
Swine-Erysipelas
Syncope
Syndactyly
*Syndrome**
Synkinesis
Synostosis
*Synovial-Cyst**
Synovitis
Syphilis
Syringoma
Syringomyelia
Systolic-Murmurs
Tabes-Dorsalis
Tachycardia
Tachypnea
Taeniasis
Takayasu-Arteritis
Takotsubo-Cardiomyopathy
Tarlov-Cysts
Tauopathies
Tauopathy
TDP-43-Proteinopathies

Telangiectasia
Telangiectasis
*Tendinopath**
Tendon-Entrapment
Tennis-Elbow
Tenosynovitis
*Teratocarcinoma**
Teratogenesis
Teratoma
*Testicular-Hydrocele**
Tetanus
Tetany
Tetralogy-of-Fallot
Thalassemia
Thecoma
Theileriasis
Thiamine-Deficiency
Thinness
Thrombasthenia
Thromboangiitis-Obliterans
Thrombocythemia
Thrombocytopenia
Thrombocytosis
Thromboembolism
Thrombophilia
Thrombophlebitis
Thrombosis
Thrombotic-Microangiopathies
Thymoma
*Thyroglossal-Cyst**
Thyroid-Crisis
Thyroid-Dysgenesis
*Thyroid-Nodule**
Thyroiditis
Thyrotoxicosis
*Tick-Bite**
*Tick-Infestation**
Tick-Paralysis
Tick-Toxicoses
Tics
Tinea
Tinnitus
Tissue-Adhesions
T-Lymphocytopenia
Tonic-Pupil
Tonsillitis
Tooth-Abrasion
Tooth-Ankylosis
Tooth-Attrition
Tooth-Avulsion
Tooth-Demineralization
*Tooth-Discoloration**
Tooth-Erosion

*Tooth-Fracture**
*Tooth-Injur**
Tooth-Loss
Tooth-Migration
Tooth-Mobility
Tooth-Resorption
Tooth-Wear
*Toothache**
Torsades-de-Pointes
Torticollis
Toxascariasis
Toxemia
Toxic-Shock
Toxocariasis
Toxoplasmosis
Tracheitis
Tracheobronchomalacia
Tracheobronchomegaly
Tracheoesophageal-Fistula
Tracheomalacia
Trachoma
Transient-Tachypnea
Translocation
Transposition-of-Great-Vessels
Trauma
Traumatic-Shock
*Tremor**
Trichiasis
Trichinellosis
Trichomonas-Vaginitis
Trichosporonosis
Trichostrongyloidiasis
Trichostrongylosis
Trichuriasis
Tricuspid-Atresia
Tricuspid-Valve-Insufficiency
Trigeminal-Autonomic-Cephalalgias
Trigeminal-Neuralgia
Trilogy-of-Fallot
Trismus
Trisomy
Trombiculiasis
*Trophoblastic-Tumor**
Trypanosomiasis
Tubal-Pregnancy
Tuberculoma
Tuberculosis
Tularemia
Tungiasis
Tympanic-Membrane-Perforation
Typhlitis
Typhus
Tyrosinemias

*Ulcer**
Unconsciousness
Uniparental-Disomy
Upper-Extremity-Deformities
*Urachal-Cyst**
Uraemia
Uremia
Ureteral-Calculi
*Ureteral-Obstruction**
Ureterocele
Ureterolithiasis
*Urethral-Obstruction**
Urethritis
Urinary-Bladder-Calculi
*Urinary-Bladder-Fistula**
*Urinary-Bladder-Neck-Obstruction**
Urinary-Calculi
Urinary-Fistula
Urinary-Incontinence
Urinary-Retention
Urinoma
Urolithiasis
Urticaria
Urticaria-Pigmentosa
Uterine-Cervical-Erosion
Uterine-Cervical-Incompetence
Uterine-Cervicitis
Uterine-Inertia
Uterine-Inversion
*Uterine-Perforation**
Uterine-Prolapse
Uterine-Retroversion
Uveitis
Vaccinia
*Vaginal-Discharge**
*Vaginal-Fistula**
Vaginismus
Vaginitis
Vaginosiis
Varicocele
Varicose-Veins
Vasa-Previa
Vascular-Calcification
Vascular-Fistula
Vascular-Malformations
Vascular-Resistance
Vascular-Stiffness
*Vascular-System-Injur**
Vasculitis
Vasoconstriction
Vasoplegia
Vasospasm
Vein-of-Galen-Malformations

Velopharyngeal-Insufficiency
Venous-Insufficiency
*Venous-Thromboembolism**
Ventilator-Induced-Lung-Injury
*Ventricular-Dysfunction**
*Ventricular-Fibrillation**
*Ventricular-Outflow-Obstruction**
Ventricular-Premature-Complexes
Ventricular-Remodeling
Vertebral-Artery-Dissection
Vertebrobasilar-Insufficiency
Vertigo
Vesico-Ureteral-Reflux
*Vesicovaginal-Fistula**
Vesicular-Stomatitis
Vestibular-Neuronitis
VIRAL-Cell-Transformation
Viremia
Virilism
Visceral-Prolapse
Visna
Vitamin-A-Deficiency
Vitamin-B-12-Deficiency
Vitamin-B-6-Deficiency
Vitamin-B-Deficiency
Vitamin-D-Deficiency
Vitamin-E-Deficiency
Vitamin-K-Deficiency
Vitiligo
Vitreoretinopathy
Vitreous-Detachment
Vocal-Cord-Dysfunction
Vocal-Cord-Paralysis
Vomiting
Vulvar-Lichen-Sclerosus
Vulvar-Vestibulitis
Vulvitis
Vulvodynia
Vulvovaginitis
Waldenstrom-Macroglobulinemia
Wallerian-Degeneration
Wandering-Spleen
Warts
Water-Electrolyte-Imbalance
Wegener-Granulomatosis
Wernicke-Encephalopathy
Wet-Macular-Degeneration
Wheat-Hypersensitivity
Whooping-Cough
Wilms-Tumor
*Xanthogranuloma**
Xanthomatosis
Xeroderma-Pigmentosum

Xerophthalmia
Xerostomia
Yang-Deficiency
Yaws
Yin-Deficiency
Zenker-Diverticulum
Zoonoses
Zoster-Sine-Herpete
Zygomycosis

7C6. Acknowledgement

I acknowledge and appreciate the contribution of Michael B. Briggs in constructing the quick reference listing of query terms from the previous section.

Chapter 8

TAXONOMY OF PERVASIVE CAUSES WITH EXAMPLES

8A. Overview

[Table 8-1](#) is a taxonomy that categorizes the different types of pervasive foundational causes, and contains many illustrative examples of pervasive causes linked to diseases. It is similar in structure to [Table 3-1](#) in the main text ([Chapter 3](#)), but far more detailed with the illustrative examples. The format in describing results in each category/ sub-category is to present some of the leading MeSH terms, Title text terms, and CRN terms that were identified in the study as pervasive causes, highlighted to distinguish levels of pervasiveness.

A threshold of two papers or more was used for computational purposes; there had to be at least two papers in which the foundational cause co-occurred with the disease in order for it to be considered to have an impact. Had only one paper been used as the threshold, the number of diseases impacted by a given foundational cause would have *increased by anywhere from 50% to 150%*.

For each sub-category shown, the MeSH, Title, and CRN pervasive cause terms appear in parentheses after the sub-category heading, followed by record Titles selected to show the breadth of diseases impacted by the pervasive 'cause'. These Titles will (in most cases) then be followed by a brief discussion of the findings. The interested reader can insert the Title of the illustrative example in Pubmed, and retrieve the full record. The main objective of showing the foundational 'causes' terms and Titles is to convey the breadth of potential pervasive foundational causes (that need to be eliminated for maximal restorative treatment effectiveness) to the reader.

The pervasive foundational causes were further arbitrarily divided into highly pervasive, moderately pervasive, and pervasive. Numbers of diseases/ symptoms/ conditions impacted by each type were: highly pervasive, >100; moderately pervasive, 70-100; pervasive, 30-70. In the taxonomy presentation of causes, the highly pervasive causes are **bolded**, *italicized*, and underlined, the moderately pervasive causes are *italicized* and underlined, and the pervasive causes are underlined.

There is a caveat here. For those causes that are important and ubiquitous, there tend to be multiple MeSH terms (and Title terms) that describe different aspects. Each MeSH term has its unique aspects, and cannot typically be combined with other seemingly related terms. As an example, the MeSH term Smoking co-occurred with 1498 Disease MeSH terms in the MeSH Qualifiers-derived database. By any measure, this is a highly pervasive foundational cause. Very related terms include Tobacco Smoke Pollution (467), Tobacco (565), Tobacco Products (43), and Nicotine (305). So, the numbers associated with the leading MeSH term for a highly pervasive foundational cause (such as Smoking) should be viewed as the lower level of its true impact. The same is true for Title text phrases.

Further, as [Chapter 9](#) shows in far more detail, given the imperfections in

1) the queries,

2) the MeSH Headings and Qualifiers assignment process, and

3) the (in)ability to extract causes from the Abstracts for these retrievals due to computer memory limitations,

it is clear that the true impact of the foundational causes presented here will be quantitatively ***much higher*** than the numbers suggest. For this reason, the results in this book should be viewed as a *proof-of-principle demonstration*. To enhance the numbers of foundational causes, an adequately resourced study (with an in-house copy of Medline, along with access to the Science Citation Index journals) should be performed to gain a better understanding of the actual quantitative impact of large numbers of foundational causes on disease (based on the published literature).

The pervasive foundational causes identified are at different levels of importance to the diseases identified, and are at different levels of verification/ validation. In the literature examined, some foundational causes were identified through in vitro cell or tissue tests. Some foundational causes were identified through animal experiments, and other foundational causes through epidemiological studies. Some foundational causes were based on individual case studies, while others were based on trials with large numbers of subjects. By and large, those foundational causes associated with large numbers of papers published and large numbers of test subjects would have greater credibility. However, as shown in [Chapter 9](#), there may be (many) important foundational causes being withheld from the literature deliberately, so numbers of papers is not a definitive metric for credibility.

8B. Taxonomy with Illustrative Examples

8B1. Format

In the table below, as stated previously, each sub-category heading will typically be followed by a parenthesis containing pervasive Title text terms, MeSH terms, or CRN terms to effectively define the category. The parenthesis will then be followed by article Titles that relate some of the foundational causes in the category to diseases or symptoms. Each Title will be preceded by an asterisk (*). These Titles are illustrative examples only, and represent a very small sample of the true impacts of the myriad foundational causes.

A word about the content of Titles. There are two major problems I have encountered with biomedical article Titles, especially compared to the Titles of non-biomedical technical articles. The biomedical Titles can be misleading. Also, the biomedical Titles, especially for the larger-scale studies, tend to emphasize what was done rather than the significant results. Thus, one reason many examples presented below use Titles reflecting case studies is that these types of studies tend to be more forthright in presenting unambiguous significant results. The most egregious examples of misleading Titles were in the Occupational/ Environmental and Iatrogenic categories, and to some degree in the Food Additives component of the Lifestyle category, where the potential causes were mainly the products of high technology.

What do I mean by misleading? A Title might have the form 'Association between Substance X and leukemia'. In the Abstract, however, the conclusion may be 'this study found no association between Substance X and leukemia'. This may be the tradition among biomedical article authors; however, I find it disingenuous, and it limits the value of Titles for identifying potential foundational causes or other important factors. Any Titles shown in the illustrative examples in this chapter of the capitalized form 'ASSOCIATION BETWEEN SUBSTANCE X AND LEUKEMIA' should be interpreted as 'there was an association between substance X and Leukemia'. These types of Titles are CAPITALIZED for further emphasis.

What do I mean by emphasizing what was done rather than significant results? Most large-scale studies' Titles would be of the form 'a risk assessment of cancer for coke oven workers'. In the Abstract, the conclusion might be 'there was an increased incidence of lung and bladder cancer with OR 2.5.' Why is that not in the Title?

Because of these Title limitations, an adequately-resourced study would need to examine the Abstracts for foundational causes to get a fuller picture. Using Titles only for text information extraction provides the tip of a much larger iceberg.

8B2. Table 8-1 - Categories, Sub-Categories, and Illustrative Examples

1. Lifestyle

Lifestyle includes choices mainly under individual control, and is divided arbitrarily into Diet, Activity, Substance Abuse, Other.

1A. Diet

Poor diet is ubiquitous. It is used to induce myriad diseases in test animals, and it is a critical disease factor from many epidemiological and case studies. Components of poor diet include:

1A1. Excesses

-High salt/sodium (e.g., Dietary Sodium Chloride)

- *Telmisartan improves survival and ventricular function in SHR rats with extensive cardiovascular damage induced by dietary salt excess.
- *A CASE-CONTROL STUDY ON THE RELATIONSHIP BETWEEN SALT INTAKE AND SALTY TASTE AND RISK OF GASTRIC CANCER.
- *A high-salt diet further impairs age-associated declines in cognitive, behavioral, and cardiovascular functions in male Fischer brown Norway rats.
- *A randomized trial of dietary sodium restriction in CKD.
- *A 5-component mathematical model for salt-induced hypertension in Dahl-S and Dahl-R rats.
- *Dietary sodium restriction: a neglected therapeutic opportunity in chronic kidney disease.

-High sugar/sucrose/glycemic load (e.g., High Fructose; High Glucose; Dietary Sucrose; Sweetening Agents)

- *Cardiovascular disease mortality: the deleterious effects of excess dietary sugar intake.
- *Mammalian target of rapamycin hyperactivity mediates the detrimental effects of a high sucrose diet on Alzheimer's disease pathology.
- *SUCROSE, HIGH-SUGAR FOODS, AND RISK OF ENDOMETRIAL CANCER--A POPULATION-BASED COHORT STUDY.
- *A causal role for uric acid in fructose-induced metabolic syndrome.
- *Adrenomedullin protects against fructose-induced insulin resistance and myocardial hypertrophy in rats.
- *Adverse effects of dietary fructose.
- *A dose of fructose induces oxidative stress during endurance and strength exercise.
- *A high-fructose diet induces hippocampal insulin resistance and exacerbates memory deficits in male Sprague-Dawley rats.
- *Androgens are necessary for the development of fructose-induced hypertension.

- *A high-sucrose diet induces fatty liver, but not deterioration of diabetes mellitus in Zucker diabetic fatty rats.
- *A high-sucrose isocaloric pair-fed model induces obesity and impairs NDUF6 gene function in rat adipose tissue.
- *A sucrose-rich diet affects triglyceride metabolism differently in pregnant and nonpregnant rats and has negative effects on fetal growth.
- *3,4,5,6-Tetrahydroxyxanthone prevents vascular endothelial cell apoptosis induced by high glucose.
- *3-Hydroxy-3-methylglutaryl CoA reductase inhibitors prevent high glucose-induced proliferation of mesangial cells via modulation of Rho GTPase/ p21 signaling pathway: Implications for diabetic nephropathy.
- *Accelerated premature stress-induced senescence of young annulus fibrosus cells of rats by high glucose-induced oxidative stress.
- *Advanced glycation end products (AGE) induce the receptor for AGE in the colonic mucosa of azoxymethane-injected Fischer 344 rats fed with a high-linoleic acid and high-glucose diet.
- *Adverse effects of high-intensity sweeteners on energy intake and weight control in male and obesity-prone female rats.
- *Artificial sweeteners induce glucose intolerance by altering the gut microbiota.
- *The potential toxicity of artificial sweeteners.
- *MAY ARTIFICIAL SWEETENERS NOT SUGAR BE THE CULPRIT OF DRAMATIC INCREASE OF INFLAMMATORY BOWEL DISEASE IN CHINA?
- High fat*** (e.g., *Dietary Fats*; *High-Fat Diet*)
- *Dietary fat without body weight gain increases in vivo MCF-7 human breast cancer cell growth and decreases natural killer cell cytotoxicity.
- *Will metformin postpone high-fat diet promotion of TRAMP mouse prostate cancer development and progression?
- *High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity.
- *Insulin reverses the high-fat diet-induced increase in brain abeta and improves memory in an animal model of Alzheimer disease.
- *12/15-lipoxygenase is required for the early onset of high fat diet-induced adipose tissue inflammation and insulin resistance in mice.

*12/15-Lipoxygenase mediates high-fat diet-induced endothelial tight junction disruption and monocyte transmigration: a new role for 15(S)-hydroxyeicosatetraenoic acid in endothelial cell dysfunction.

*17alpha-Estradiol and genistein inhibit high fat diet induced prostate gene expression and prostate growth in the rat.

*17beta-Estradiol attenuates saturated fatty acid diet-induced liver injury in ovariectomized mice by up-regulating hepatic senescence marker protein-30.

*A high fat diet in CF-1 mice: An experimental model for metabolic syndrome.

*A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice.

*A high-fat diet during rat pregnancy or suckling induces cardiovascular dysfunction in adult offspring.

-High protein/tryptophan (e.g., *High Meat; Milk; Dairy; Purines; High Dietary Proteins; Seafood*)

*Advanced glycation end products and nephrotoxicity of high-protein diets.

*DIETARY MEAT, ENDOGENOUS NITROSATION AND COLORECTAL CANCER.

*Resistant starch may reduce colon cancer risk from red meat.

*Higher red meat intake in young women increases breast cancer risk.

*Red meat consumption is associated with an increased overall cancer risk: a prospective cohort study in Korea.

*RED MEAT CONSUMPTION AND STOMACH CANCER RISK: A META-ANALYSIS.

*INTAKE OF RED MEAT AND HETEROCYCLIC AMINES, METABOLIC PATHWAY GENES AND BLADDER CANCER RISK.

*High meat consumption linked to gastric-cancer risk.

*2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, a carcinogen in high-temperature-cooked meat, and breast cancer risk.

*Association of meat intake and meat-derived mutagen exposure with the risk of colorectal polyps by histologic type.

*Carcinogenicity of mutagens from cooked meats.

*High-protein-low-carbohydrate diet: deleterious metabolic and cardiovascular effects depend on age.

*Dietary protein restriction and preservation of kidney function in chronic kidney disease.

*Central vein occlusion caused by high-protein diet.

*High dietary protein intake induces endothelial dysfunction in uninephrectomized rats.

*Delayed anaphylaxis after ingestion of meat : Carbohydrate epitope galactose-alpha-1,3-galactose as cause of severe anaphylactic reactions.

Most of the articles related to meat consumption emphasized adverse effects. Unfortunately, in most of these meat studies, especially epidemiological studies on humans, there was no separation of confounding effects.

Most meat available to the American public comes from CAFO (confined animal feeding operations). These animals are raised confined in very close quarters. To reduce infections from such close confinement, animals are given antibiotics, and to increase growth more rapidly, animals are given synthetic growth hormones. Their feed is grain-based, not the grass they would have if pasture-raised.

In addition to the various chronic diseases associated with meat consumption, there were also many articles related to adverse effects of meat contamination. Is the direct cause of resulting disease mentioned in the articles the meat (the carrier), or (typically) the bacteria?

Would the various infectious and chronic diseases associated with meat consumption in the articles be as copious and serious for pasture/ grass-fed animals not raised under confined conditions, and not given antibiotics and synthetic growth hormones?

Finally, most meat eaten is cooked, much of it at high temperatures, sometimes in the presence of additional fats. High-temperature cooking, especially of animal foods that are high in protein and fat, results in substantial production of advanced glycation end products and other harmful substances. How are the harmful effects of the cooking separated from the harmful effects of the meat? I didn't see the separation in any papers I examined.

I accept the implications of the bulk of the literature on the adverse effects of meat consumption given what is consumed by the public today, especially the American public. However, it has not been demonstrated to my satisfaction that meat from 'organic' pasture-raised grass-fed animals not fed antibiotics and growth hormones and not cooked at high temperatures is equally harmful, and there is some evidence that a moderate amount may be beneficial.

-High Cholesterol (e.g., Dietary Cholesterol)

*Researchers find link between high cholesterol and breast cancer.

*DIETARY CHOLESTEROL INTAKE AND CANCER.

*Dietary cholesterol increases ventricular volume and narrows cerebrovascular diameter in a rabbit model of Alzheimer's disease.

- *High cholesterol levels are associated with coronary microvascular dysfunction.
- *A cloned pig model for examining atherosclerosis induced by high fat, high cholesterol diets.
- *A guanidinylated bioreducible polymer as a novel gene carrier to the corpus cavernosum of mice with high-cholesterol diet-induced erectile dysfunction.
- *A novel antihypoglycemic role of inducible nitric oxide synthase in liver inflammatory response induced by dietary cholesterol and endotoxemia.
- *Cardiac systolic and diastolic dysfunction after a cholesterol-rich diet.
- *Cholesterol accumulation caused by low density lipoprotein receptor deficiency or a cholesterol-rich diet results in ectopic bone formation during experimental osteoarthritis.
- *Combined effect of probucol and insulin on renal damage in diabetic rats fed a high cholesterol diet.
- High Refined Carbohydrates** (e.g., **Dietary Carbohydrates**; **High Carbohydrate Diet**; **Wheat**)
- *A high carbohydrate diet induces insulin resistance through decreased glucose utilization in ovariectomized rats.
- *DIETARY CARBOHYDRATES, REFINED GRAINS, GLYCEMIC LOAD, AND RISK OF CORONARY HEART DISEASE IN CHINESE ADULTS.
- *Nutrition and Alzheimer's disease: the detrimental role of a high carbohydrate diet.
- *HIGH CARBOHYDRATE DIETS AND ALZHEIMER'S DISEASE.
- *Naringin improves diet-induced cardiovascular dysfunction and obesity in high carbohydrate, high fat diet-fed rats.
- *A high carbohydrate meal yields a lower ischemic threshold than a high fat meal in patients with stable coronary disease.
- *A high fat/high carbohydrate diet induces aortic valve disease in C57BL/6J mice.
- *A high-carbohydrate diet in the immediate postnatal life of rats induces adaptations predisposing to adult-onset obesity.
- *Caffeine prevents cognitive impairment induced by chronic psychosocial stress and/or high fat-high carbohydrate diet.
- *Sudden cardiac death may be caused by malnutrition. High carbohydrate diet may cause energy imbalance in athletes.
- *Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment.

*Increasing evidence that diet impacts cognitive function. Reduce refined carbohydrates and sugar intake, increase protein and "good" fats consumption to help prevent cognitive impairment.

-High temperature (e.g., Advanced glycation end products; Nitrosamines; Cooking)

*A STATISTICAL REGRESSION MODEL FOR THE ESTIMATION OF ACRYLAMIDE CONCENTRATIONS IN FRENCH FRIES FOR EXCESS LIFETIME CANCER RISK ASSESSMENT.

*DIETARY ACRYLAMIDE INTAKE AND THE RISK OF LYMPHATIC MALIGNANCIES: THE NETHERLANDS COHORT STUDY ON DIET AND CANCER.

*NITROSAMINE AND RELATED FOOD INTAKE AND GASTRIC AND OESOPHAGEAL CANCER RISK: A SYSTEMATIC REVIEW OF THE EPIDEMIOLOGICAL EVIDENCE.

*EXPOSURE TO N-NITROSO COMPOUNDS IN A POPULATION OF HIGH LIVER CANCER REGIONS IN THAILAND: VOLATILE NITROSAMINE (VNA) LEVELS IN THAI FOOD.

*CONSUMPTION OF DEEP-FRIED FOODS AND RISK OF PROSTATE CANCER

*Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines, and selected foods.

*Advanced glycation end products increase carbohydrate responsive element binding protein expression and promote cancer cell proliferation.

*Possible participation of advanced glycation end products in the pathogenesis of colorectal cancer in diabetic patients.

*DIETARY CONSUMPTION OF MEAT, FAT, ANIMAL PRODUCTS AND ADVANCED GLYCATION END-PRODUCTS AND THE RISK OF BARRETT'S OESOPHAGUS.

*A developmental nephron deficit in rats is associated with increased susceptibility to a secondary renal injury due to advanced glycation end-products.

*Advanced glycation end product accumulation: a new enemy to target in chronic kidney disease?

*A role for advanced glycation end products in diminished bone healing in type 1 diabetes.

*Dietary advanced glycation end products are associated with decline in memory in young elderly

*Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans

*A study on serum advanced glycation end products and its association with oxidative stress and paraoxonase activity in type 2 diabetic patients with vascular complications.

***ADVANCED GLYCATION END PRODUCTS AND DIABETIC CARDIOVASCULAR DISEASE**

- *Abnormalities in platelets and vascular endothelial cells induced by glycated lipoproteins.
- *Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis.

***ADVANCED GLYCATION END PRODUCTS AND CARDIOVASCULAR DISEASE.**

***DIETARY ADVANCED GLYCATION END PRODUCTS AND AGING.**

-High/altered soy (e.g., Genistein)

- *Adverse effects on female development and reproduction in CD-1 mice following neonatal exposure to the phytoestrogen genistein at environmentally relevant doses.
- *A possible cause of Alzheimer's dementia - industrial soy foods.
- *Altered mammary gland development in male rats exposed to genistein and methoxychlor.
- *Change in mutagenic activity of genistein after a nitrite treatment.
- *Chronic dietary exposure to a low-dose mixture of genistein and vinclozolin modifies the reproductive axis, testis transcriptome, and fertility.
- *Early life exposure to genistein and daidzein disrupts structural development of reproductive organs in female mice.
- *Allergy or histamine intolerance? Cheilitis caused by soy sauce.
- *A soy diet accelerates renal damage in autoimmune MRL/Mp-lpr/lpr mice.
- *Anaphylaxis caused by hidden soybean allergens in pillows.
- *Baker's asthma related to soybean lecithin exposure.

The soybean results were mixed. While Genistein had numerous adverse effects, there were also many papers describing its use to retard cancer.

-High Supplements/Plant Extracts (e.g., Phytotherapy; N-Acetylcysteine; Capsaicin; Caffeine; Herbs/Chinese Herbal Medicine)

- *Multi-organ toxicity following ingestion of mixed herbal preparations: an unusual but dangerous adverse effect of phytotherapy.
- *Fatal renal failure due to the Chinese herb "GuanMu Tong" (*Aristolochia manshuriensis*): Autopsy findings and review of literature

- *A case of drug induced hepatitis and interstitial pneumonia caused by a herbal drug, Dai-saikoto.
- *A case of drug induced liver injury caused by a herbal drug, bofu-tsu-sho-san.
- *A case of hepatitis and pneumonitis caused by Bofutsusyo-san herbal medicine.
- *Acute exposure to caffeine selectively disrupts context conditioning in rats.
- *Acute hemorrhagic myocardial necrosis and sudden death of rats exposed to a combination of ephedrine and caffeine.
- *Life-threatening cardiovascular toxicity following ingestion of Chinese herbal medicine.
- *Increased risk of urinary tract cancer in ESRD patients associated with usage of Chinese herbal products suspected of containing aristolochic acid.
- *Anaphylaxis due to caffeine.
- *A bradykinin (BK)1 receptor antagonist blocks capsaicin-induced ear inflammation in mice.
- *Age-related differences in the time course of capsaicin-induced hyperalgesia.
- *A new model for inflammatory colonic disease induced by capsaicin in rats.
- *Anaphylactic reaction to N-acetylcysteine after poisoning with paracetamol.
- *DMPS and N-acetylcysteine induced renal toxicity in mice exposed to mercury.

Another category where the results are mixed. Variants of phytotherapy and Herbal Medicine have shown many positive benefits in the research literature, but they are not without their adverse impacts as well.

-High selenium

- *A case-control study of the risk of cutaneous melanoma associated with three selenium exposure indicators.
- *Accidental death from acute selenium poisoning.
- *SELENIUM LEVELS IN RICE SAMPLES FROM HIGH AND LOW RISK AREAS FOR ESOPHAGEAL CANCER.
- *PROSTATE CANCER: NEW DATA ON RISKS OF SELENIUM AND VITAMIN E.
- *SELENIUM EXPOSURE AND DEPRESSIVE SYMPTOMS: THE CORONARY ARTERY RISK DEVELOPMENT IN YOUNG ADULTS TRACE ELEMENT STUDY.
- *Active oxygen generation as a possible mechanism of selenium toxicity.

*Acute selenium poisoning by paradise nuts (*Lecythis ollaria*).

*The toxicity of combination of selenium, fluoride and arsenic on rat embryos.

More mixed results. Many papers on selenium toxicity were reported, but the larger fraction dealt with selenium in its anti-cancer role and protective role in metal poisoning. Selenium deficiency led to many problems. Balance appears to be the key here; neither too much nor too little.

-Food poisoning/Food Toxicity (e.g., *Areca*; *Plant Oils*; *Yeast*; *Mushroom*)

*A case of anaphylactic reaction following matsutake mushroom ingestion: demonstration of histamine release reaction of basophils.

*A case of chronic hypersensitivity pneumonitis induced by shiitake mushroom spores.

*Acute encephalopathy caused by cyanogenic fungi in 2004, and magic mushroom regulation in Japan.

*Acute renal failure as a sequela of mushroom poisoning with *Cortinarius speciocissimus*.

*Areca nut extract induces pyknotic necrosis in serum-starved oral cells via increasing reactive oxygen species and inhibiting GSK3beta: an implication for cytopathic effects in betel quid chewers.

*Betel quid and areca nut are carcinogenic without tobacco.

*Genetic damage in cultured human keratinocytes stressed by long-term exposure to areca nut extracts.

*A striking and frequent cause of premature thelarche in children: *Foeniculum vulgare*.

*Accelerated atherosclerosis in apolipoprotein E-deficient mice fed Western diets containing palm oil compared with extra virgin olive oils: a role for small, dense high-density lipoproteins.

*ASSOCIATION OF MUSTARD OIL AS COOKING MEDIA WITH CARCINOMA OF THE GALLBLADDER.

The sub-category above reflects the adverse effects of excesses of dietary components. Excesses of these components in both directions, both too much and too little, can be harmful. In particular, excesses of fat, sugar/ glycemic loading, salt, protein, meat, calories, cholesterol, soy, herbs (especially Chinese herbs and the accompanying aristolochic acids), and processing/ cooking temperatures had adverse impacts across the disease spectrum. The highly pervasive components of this diet sub-category tend to be high-fat, high-sugar, high-salt, high-meat, and the high-temperature cooking that results in harmful products (e.g., advanced glycation end products, heterocyclic amines and nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides).

1A2. Deficiencies

Many deficiencies listed in the literature are symptoms, not foundational causes in the present sense. Thus, a Vitamin A deficiency may be due to insufficient Vitamin A intake (foundational cause), or some metabolic problem that results in reduced Vitamin A (symptom).

(e.g., Malnutrition; Starvation; Dehydration)

- *Anaphylactic reaction in experimental malnutrition.
- *Chronic malnutrition caused by a corn-based diet lowers the threshold for pentylentetrazol-induced seizures in rats.
- *Chronic moderate hypoxia and protein malnutrition both induce growth retardation, but have distinct effects on arterial endothelium-dependent reactivity in the chicken embryo.
- *Coerulear activation by crh and its role in hypertension induced by prenatal malnutrition in the rat.
- *Cognitive function of children with cystic fibrosis: deleterious effect of early malnutrition.
- *Acute diaphragmatic changes induced by starvation in rats.
- *Energy-preserving effects of IGF-1 antagonize starvation-induced cardiac autophagy.
- *Osteoporosis in survivors of early life starvation.
- *A case of acute renal failure, rhabdomyolysis and disseminated intravascular coagulation associated with severe exercise-induced hypernatremic dehydration.
- *A convenient rabbit model of ocular epithelium damage induced by osmotic dehydration.
- *Aortic and cerebral thrombosis caused by hypernatremic dehydration in an exclusively breast-fed infant.
- *Dehydration from outdoor work and urinary stones in a tropical environment.

Deficiencies of water, fiber, protein, legumes/ pulses, minerals, melatonin, selenium, iron, zinc, and other nutrients (sunlight, selenium in soil, germs/ hygiene hypothesis) had adverse effects, but the only deficiencies that reached the pervasive threshold were the more general ones listed above. Even then, two of them, malnutrition and dehydration, could include both foundational causes (poor diet, insufficient water) and symptoms due to other foundational causes. This is a problem that underlies most of the deficiencies mentioned above: is the deficiency due to low intake (a foundational cause) or is it a symptom of e.g. metabolic dysfunction resulting from other foundational causes? This is one case where an improved query might be able to separate out the foundational causes, and raise some of the above substances to pervasive status.

1A3. Food Additives/ Pollutants

Foods are modified from their original state to enhance taste, appearance, and shelf life, among other characteristics. While some additives are harmless, many are accompanied by adverse effects. Adverse reactions to additives may be underdiagnosed and under-researched. Many of the excesses and deficiencies mentioned in 1A1 and 1A2 are the result of substances being added or removed from the fresh whole food. The large number of additives include phosphates/ phosphorous, glycerin, sodium glutamate, palmitate, 2,3-pentanedione, etc. None of the specific additives reached the level of pervasive in the present study. Depending on how one defines 'food additives', those with the widest impacts tend to include the major items listed under excesses in 1A1, such as fat, sugar, and salt, which tend to be added to foods for taste enhancement.

*Phosphate additives in food a potential public health risk. High phosphate levels can lead to cardiovascular disease.

*Bioavailable dietary phosphate, a mediator of cardiovascular disease, may be decreased with plant-based diets, phosphate binders, niacin, and avoidance of phosphate additives.

*THE IMPACT OF PROCESSING MEAT AND FISH PRODUCTS ON PHOSPHORUS INTAKE IN CHRONIC KIDNEY DISEASE PATIENTS.

*POTENTIAL HEALTH CONCERNS OF DIETARY PHOSPHORUS: CANCER, OBESITY, AND HYPERTENSION.

*Induction of kidney and liver cancers by the natural food additive madder color in a two-year rat carcinogenicity study.

*CARCINOGENIC RISK OF COPPER GLUCONATE EVALUATED BY A RAT MEDIUM-TERM LIVER CARCINOGENICITY BIOASSAY PROTOCOL.

*EVALUATION OF THE BUTTER FLAVORING CHEMICAL DIACETYL and a fluorochemical paper additive FOR MUTAGENICITY AND TOXICITY USING THE MAMMALIAN CELL GENE MUTATION ASSAY IN L5178Y MOUSE LYMPHOMA CELLS.

*Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease.

*Low-concentration capsaicin promotes colorectal cancer metastasis by triggering ROS production and modulating Akt/mTOR and STAT-3 pathways.

*Molecular mechanism of mutagenesis induced by olaquinox using a shuttle vector pSP189/mammalian cell system.

*Monosodium glutamate neonatal treatment induces cardiovascular autonomic function changes in rodents.

*Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin.

***SMOKED SAUSAGES AND FOOD ADDITIVES: EVALUATION OF TOTAL MUTAGENIC ACTIVITY.**

*Mutagenicity and DNA-damaging activity caused by decomposed products of potassium sorbate reacting with ascorbic acid in the presence of Fe salt.

INTERPRETATION OF DIET RESULTS

There are a number of caveats to be used in interpreting the results of the section on diet above (1A). Many of these caveats also apply to interpreting the other sections in this taxonomy. First, the results reflect what is published in the Medline database. As is pointed out repeatedly in [Chapter 9](#), many foundational causes may not have reached the literature, or a skewed representation of foundational causes may have been placed into the literature. Of those papers published on a topic, it is difficult to know which papers are credible. The fact that a concept appears to meet one of the Gold Standards of research, namely, reproducibility/repeatability, may or may not be relevant. If a sponsor wants to distort a literature, it can fund diverse performers to arrive at similar conclusions.

For diet in particular, these caveats are crucial. In the USA (and other countries as well), we have large industries that support grains, animal husbandry, fruits, vegetables, etc, and government agencies that promote many of these products as well. In many of e.g. the phytotherapy studies I examined in previous LRDI studies (focused on treatments), I noticed that

- 1) publications from specific countries would tend to
- 2) emphasize the positive effects on treatments from plants et al native to that country and
- 3) de-emphasize the negative.

Any adverse effects would typically come from research performed by scientists from other countries. Then, the question arose whether these adverse effects were the result of good objective science or one competitor subjectively evaluating another competitor. All these industries and governments have an interest in promoting their products, both for domestic use and export, and have 'deep pockets' for supporting research that could potentially influence the salability of their products.

For example, under the diet category above, I concluded in part: "The highly pervasive components of this diet sub-category tended to be high-fat, high-sugar, high-salt, high-meat, and the high-temperature cooking that resulted in harmful products (e.g., advanced glycation end products, heterocyclic amines and nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides)." Each potential foundational cause on that list was based on there being more articles published in the literature on the adverse effects of the potential cause, more articles showing impacts across myriad diseases, high credibility articles, etc. The list does not imply absolute consensus; for most of these foundational causes, there were always some articles stating a non-effect or positive effect. There were just far less stating a positive effect than a negative effect.

How do I interpret these differences? Are they the results of good research, and just reflect

different experimental conditions, or are they the results of manufactured research, cherry-picking, and deliberate selection of windows of parameter space that will yield a desired answer? Absent conducting my own experiments on each substance to validate the results, I need to make a judgment on what appears to be most credible given the weight of the evidence.

As a specific example, there is much disagreement in the biomedical literature and the popular press as to what constitutes an optimal, or even desirable, diet for humans. Two major and diametrically opposing camps today are the high-carb low-fat (and, in many cases, low animal protein) diets and the low-carb high-fat (and, in many cases, high animal protein) diets. Each camp has published best-selling books on the NYT list, with each book containing hundreds of references in 'prestigious' medical journals purporting to show the benefits of the book's approach. These books remind me of expert witnesses in a trial, with each side presenting its expert witnesses stating completely opposing viewpoints. Unfortunately, we the public are forced to act like the judge and jury in deciding which set of dietary witnesses is more credible.

The strong numerical preponderance of evidence published in the medical literature is on the side of high-fat high-meat high-refined-carbohydrates low-complex-carbohydrates as the culprits. Other than the high-refined-carbohydrates being problematical, on which both camps seem to agree, disagreement is complete on the value of the other three types of food.

The evidence for both sides is shaky. Long-term effects (of these potential pervasive foundational causes) on humans in the context of exposure to the myriad other potential foundational causes have not been done. To support their arguments, many researchers and clinicians refer to how our ancestors lived (e.g., Paleo diets, Hunter-Gatherers, etc), or how similar animal species live in the wild, in hopes of identifying more 'natural' and traditional diets. However, many foods have been so grossly altered since the days of our primitive ancestors that their resemblance to foods available now is in name only, and usually the diets of similar species are 'cherry-picked' so the total combination of foods in their diet is not extrapolated to recommendations for human diets.

Fruits and plant foods have been continuously altered for many decades to improve yield, taste, and appearance, to the point where pictures of these foods now compared to many thousands of years ago are entirely unrecognizable. Animals for consumption are raised and fed under circumstances unrecognizable compared to centuries ago. Cattle are raised in confined areas without exercise, fed grains rather than grass, and given growth hormones and antibiotics to increase weight and maintain 'health' over shorter periods of time until slaughter. The meat is then cooked at high temperatures in the presence of additional fats, producing large amounts of advanced glycation end products and other harmful substances. It's unclear whether any basis for consensus is possible, given the lack of credible data upon which to base a decision.

The USDA, as well as many other diet authors, have taken a somewhat middle ground. The USDA displays its recommendations graphically with a four level pyramid, with grains constituting the base, fruits and vegetables the second level, mainly high protein foods constituting the third level, and fats and sugars capping the pyramid. Not surprisingly, the

findings in this book are somewhat reflective of the pyramid structure.

So, for readers who are proponents of the high-fat high-animal protein low-carb diet, and who see the different results presented in this book and in the USDA pyramid, you need to interpret the diet results based on the discussion and caveats above.

The differences in the other taxonomy categories are not quite as polarized. For example, most studies might conclude that e.g. Cadmium exposure causes serious diseases, and perhaps a few might not see an association with serious diseases. Probably none would conclude that Cadmium has positive effects. With the two diet extremes described above, we see a strong swing of the pendulum to each side.

1B. Activity1B1. Sedentary Lifestyle

(e.g., Immobile; Bed Rest; Restraint)

*ASSOCIATION OF SEDENTARY BEHAVIOUR WITH COLON AND RECTAL CANCER: A META-ANALYSIS OF OBSERVATIONAL STUDIES.

*TELEVISION VIEWING AND TIME SPENT SEDENTARY IN RELATION TO CANCER RISK: A META-ANALYSIS.

*SEDENTARY BEHAVIOR AND INCIDENT CANCER: A META-ANALYSIS OF PROSPECTIVE STUDIES.

*A comparative bear model for immobility-induced osteopenia.

*A gravitational hypothesis of essential hypertension as a natural adaptation to increased gravitational stress caused by regular, prolonged sitting typical of modern life.

*Anemia of immobility: caused by adipocyte accumulation in bone marrow.

*SEDENTARY LIFESTYLE AND ITS RELATION TO CARDIOVASCULAR RISK FACTORS, INSULIN RESISTANCE AND INFLAMMATORY PROFILE.

*Two-week cast immobilization induced chronic widespread hyperalgesia in rats.

*TIME TREND OF PREVALENCE OF SELF-REPORTED CATARACT AND ITS ASSOCIATION WITH PROLONGED SITTING IN TAIWAN FROM 2001 AND 2013.

*PROLONGED SITTING: IS IT A DISTINCT CORONARY HEART DISEASE RISK FACTOR?

*"eThrombosis" - venous thromboembolism provoked by prolonged sitting position by a computer. A case series report of six patients.

1B2. Exercise/Overexercise

(e.g., Physiological Stress; Diving)

*3-min step test and treadmill exercise for evaluating exercise-induced asthma.

*40-year-old athlete with exercise-induced angina pectoris.

*A case of acute renal failure, rhabdomyolysis and disseminated intravascular coagulation associated with severe exercise-induced hypernatremic dehydration.

*Acute care for exercise-induced hyperthermia to avoid adverse outcome from exertional heat stroke.

*Exercise-induced atrioventricular block. Significance of the ischemic component. Report of 4 new cases.

*A case of anterior cerebral artery dissection caused by scuba diving.

*Facial baroparesis caused by scuba diving.

*Oxygen toxicity in recreational and technical diving.

1B3. Sleep

(e.g., Sleep Deprivation)

*Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles.

*SLEEP DEPRIVATION, SLEEP APNEA AND CARDIOVASCULAR DISEASES.

*A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects.

*Cardiovascular function alterations induced by acute paradoxical sleep deprivation in rats.

*Paradoxical sleep deprivation potentiates epilepsy induced by homocysteine thiolactone in adult rats.

*Sleep deprivation after septic insult increases mortality independent of age.

The main sub-categories of Activity were exercise, sedentary, and sleep. Exercise in the right amounts at the right intensity was viewed as beneficial, but excessive exercise in time and intensity (as well as related heat stroke) could be harmful. Sedentary lifestyle (lack of exercise) was problematic, and mentioned quite often. Prolonged sitting in all its variants appeared to be an under-recognized factor contributing to many diseases. Its importance will probably increase substantially, with the advent of increased computer use for work and recreation and the attendant prolonged sitting required. Insufficient sleep, both in quality and duration, was a problem area as well. The effects of sedentary lifestyle on many diseases may be heavily under-researched.

1C. Substance Abuse

1C1. Recreational Drugs

(e.g., Substance Abuse; Smokeless Tobacco; Narcotics; Cocaine; Cannabis; Methamphetamine; Street Drugs; N-Methyl-3,4-methylenedioxyamphetamine; Marijuana Smoking; Hallucinogens)

- *Recent cocaine use is a significant risk factor for sudden cardiovascular death in 15-49-year-old subjects: a forensic case-control study.
- *Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana: what cardiologists need to know.
- *MARIJUANA USE AND RISK OF LUNG CANCER: A 40-YEAR COHORT STUDY.
- *Cocaine-induced vasoconstriction in the human coronary microcirculation: new evidence from myocardial contrast echocardiography.
- *Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk.
- *Cocaine-induced coronary stent thrombosis.
- *Cocaine is a major risk factor for antipsychotic induced akathisia, parkinsonism and dyskinesia.
- *Chronic manganese toxicity due to substance abuse in Turkish patients.
- *Chronic non-neurological toxicity from volatile substance abuse.
- *Digestive system damage caused by substance abuse.
- *Substance abuse and toxicity. Fetal drug syndrome.
- *Carcinogenic components of smokeless tobacco and tobacco-free cigarettes.
- *Possible carcinogenicity of smokeless tobacco.
- *SMOKELESS TOBACCO AND THE RISK OF STROKE.
- *Kidney diseases caused by contrast media and narcotics.
- *Rhabdomyolysis during acute poisoning with drugs and narcotics. Experience with 7 clinical cases.
- *A case of cocaine-induced basilar artery thrombosis.
- *A problem of physiology. Cardiac toxicity of cocaine.
- *Acute angle closure glaucoma precipitated by intranasal application of cocaine.
- *Cluster headache induced by cocaine.
- *A novel cause of eosinophilic pneumonia: recreational marijuana exposure.
- *A case of cannabis-induced pancreatitis.
- *Acute and chronic cognitive disorders caused by cannabis use.

*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine pretreatment attenuates methamphetamine-induced dopamine toxicity.

*A fatal case of myocardial damage due to misuse of the "designer drug" MDMA.

*Acute hepatitis induced by Ecstasy.

1C2. Smoking

(e.g. Tobacco Smoke Pollution; Nicotine; Smoke)

*A Bayesian approach to assess interaction between known risk factors: the risk of lung cancer from exposure to asbestos and smoking.

*A case of smoking-induced chest pain improved with beta2-stimulant.

*A modified Ames assay reveals the mutagenicity of native cigarette mainstream smoke and its gas vapour phase.

*A new experimental model of cigarette smoke-induced emphysema in Wistar rats.

*META-ANALYSIS OF PROSPECTIVE COHORT STUDIES OF CIGARETTE SMOKING AND THE INCIDENCE OF COLON AND RECTAL CANCERS.

*Oral cancer in young Jordanians: potential association with frequency of narghile smoking.

*Smoking at diagnosis is an independent prognostic factor for cancer-specific survival in head and neck cancer: findings from a large, population-based study.

*CIGARETTE SMOKING AND THE RISK OF PANCREATIC CANCER: A CASE-CONTROL STUDY.

*THE RELATION BETWEEN CIGARETTE SMOKING AND RISK OF ACUTE MYELOID LEUKEMIA: AN UPDATED META-ANALYSIS OF EPIDEMIOLOGICAL STUDIES.

*SMOKING AND INCREASED ALZHEIMER'S DISEASE RISK: A REVIEW OF POTENTIAL MECHANISMS.

*Smoking exacerbates amyloid pathology in a mouse model of Alzheimer's disease.

1C3. Alcohol

(e.g., Ethanol)

*TLR4-Dependent Tumor-Initiating Stem Cell-Like Cells (TICs) in Alcohol-Associated Hepatocellular Carcinogenesis.

*Fetal alcohol exposure increases susceptibility to carcinogenesis and promotes tumor progression in prostate gland.

*THE INTERPLAY BETWEEN ALCOHOL CONSUMPTION, ORAL HYGIENE, ALDH2 AND ADH1B IN THE RISK OF HEAD AND NECK CANCER.

*ALCOHOL DRINKING AND THE RISK OF COLORECTAL CANCER DEATH: A META-ANALYSIS.

*LIFETIME RISK OF DISTINCT UPPER AERODIGESTIVE TRACT CANCERS AND CONSUMPTION OF ALCOHOL, betel AND CIGARETTE.

*ALCOHOL USE DISORDERS AND RISK OF PARKINSON'S DISEASE: FINDINGS FROM A SWEDISH NATIONAL COHORT STUDY 1972-2008.

*A case of acute pancreatitis with hyperlipemia and hyperglycemia induced by alcohol abuse.

*A cocktail for skin cancer: why alcohol and sun exposure do not mix.

*Abdominal pain and renal failure after alcoholic intoxication. Intraperitoneal urinary bladder rupture after alcohol excess.

*Acute esophageal necrosis caused by alcohol abuse.

*Alcohol induced myocardial infarction in two young brothers.

Excessive alcohol use was implicated as a contributor to myriad diseases. Results for very moderate use, especially beer and red wine, were somewhat mixed. There may be a hormetic (beneficial) effect operating at very low doses (~ one drink per day), although consensus does not exist on that point.

Substance abuse included 'recreational' drugs of all types (cocaine, methamphetamine, etc), other substances such as laxatives, common household products not usually identified as recreational drugs (such as mothballs), and especially excessive cigarette smoking and alcohol. There were a large number of MeSH terms covering these substances, especially smoking and alcohol, only a very few of which are shown here. Excess smoking and drinking are among the most highly pervasive of all foundational causes.

1D. Other

(e.g., Tattooing; Body Piercing)

*Adverse effects of cosmetic tattooing: an illustrative case of granulomatous dermatitis following the application of permanent makeup.

*Colonic abscess induced by India ink tattooing.

*Tattoo Ink-Related Cutaneous Pseudolymphoma: A Rare but Significant Complication. Case Report and Review of the Literature

*Melanoma on Tattoos: Two Finnish Cases

*Light-induced mutagenicity in Salmonella TA102 and genotoxicity/cytotoxicity in human T-cells by 3,3'-dichlorobenzidine: a chemical used in the manufacture of dyes and pigments and in tattoo inks.

*A case of Staphylococcus aureus endocarditis after ear piercing in a patient with normal cardiac valve and a questionnaire survey on adverse events of body piercing in college students of Korea.

*Dental and buccal complications of lip and tongue piercing.

*Ear piercing as a risk factor for contact allergy to nickel.

The individual foundational causes identified with Lifestyle are usually studied in isolation, and ***synergistic*** effects are typically not identified. Given the number of Lifestyle component combinations that could be synergistic, and adding in

1) the foundational causes from the remaining categories identified here to the potential combinations and

2) foundational causes that surface only when operating in synergy but which have not yet been identified here as individual foundational causes,

it is clear that only the tip of the foundational causes iceberg is being exposed in this book.

2. IATROGENIC

The 'side-effects' from drugs and the complications from surgery and invasive treatments predominated in this category. One needs to be careful here. The more frequently a drug is used, or the more frequently surgery or invasive treatments are employed, the more opportunity for side-effects and complications, and the more opportunity for publications describing these side-effects and complications. This book does not provide an indication of how often such side-effects and complications would occur as a percentage of use.

However, diseases resulting from Iatrogenic causes have been estimated independently, and appear quite large. For example, the report Death by Medicine (<http://www.webdc.com/pdfs/deathbymedicine.pdf>) estimates: "the number of people having in-hospital, adverse reactions to prescribed drugs to be 2.2 million per year. The number of unnecessary antibiotics prescribed annually for viral infections is 20 million per year. The number of unnecessary medical and surgical procedures performed annually is 7.5 million per year. The number of people exposed to unnecessary hospitalization annually is 8.9 million per year.

The most stunning statistic, however, is that the total number of deaths caused by conventional medicine is an astounding 783,936 per year. It is now evident that the American medical system is the leading cause of death and injury in the US. (By contrast, the number of deaths attributable to heart disease in 2001 was 699,697, while the number of deaths attributable to cancer was 553,251.5)"

Other statistics on Iatrogenic disease are available; the numbers tend to be large. The main categories of drugs and surgeries are presented in this section, along with illustrative examples of adverse effects from members of these drug and surgery categories. Large numbers of substances were found in the drug class sub-categories highlighted below, and far more would be expected in the recommended follow-on study.

Specific drugs that are pervasive foundational causes are not listed within the parentheses following the drug category. Because of the myriad reasons listed in [Chapter 9](#), I believe there are many more substances (especially drugs and chemicals) that are pervasive foundational causes operationally that have either not appeared, or have not been adequately represented, in the published literature. I did not want to leave the impression that the drug classes listed represent the totality of pervasive foundational causes that are drugs, which can sometimes be the (erroneous) message that readers remember after viewing a list in print. In the illustrative Titles following each category, any specific drugs listed may or may not be pervasive foundational causes. The illustrative Titles were selected to represent the *pervasive drug class*, not any specific pervasive drug.

The Iatrogenic drug sub-category differed from the two categories that follow: biotoxic and environmental/ occupational exposure. For drugs that addressed symptoms related to a given disease, the Iatrogenic effects ranged in publication frequency from rare to modest (in the disease core literature), and for drugs that primarily addressed symptoms not related to the disease of interest, publication frequency related to Iatrogenic effects was high (in the disease core literature).

Thus, for example, an antineoplastic drug that co-occurred with a cancer sub-type would rarely be shown having an adverse impact on the cancer, and would most frequently be shown as having a side-effect causing some other disease/ symptom. An antineoplastic drug that co-occurred with a non-cancer disease would almost always be a side-effect from the drug used for treating cancer (unless the drug's application to the non-cancer disease was being explored in the study).

Thus, an antineoplastic drug/ drug category that co-occurred with Mild Cognitive Impairment (MCI) would almost always, if not always, reflect an MCI side effect resulting from cancer treatment. Almost every paper (in the disease core literature) dealing with biotoxic and environmental/ occupational exposure is related to causing one or more disease-related symptoms.

Finally, for purposes of brevity, each drug was assigned to one class only. However, some drugs could have been placed in multiple categories. 'Monoclonal antibodies', for example, were placed under Antineoplastic Agents, but are used in treatment of cancer, inflammation, autoimmune, and viral, to name a few.

2A. Drugs

2A1. *Antineoplastic Agents*

This is a very large category, both in sub-categories and numbers of specific drugs. However, these drugs are mainly used to treat life-threatening diseases, and the risks must be weighed against the benefits.

(e.g., Monoclonal Antibodies; Antineoplastic Antimetabolites; Antineoplastic Antibiotics; Phytogetic Antineoplastic Agents; Hormonal Antineoplastic Agents; Cancer Chemotherapy; Cancer Therapy; Adjuvant Chemotherapy; Alkylating Antineoplastic Agents; Pyridines; Angiogenesis Inhibitors; Indoles; Protein Kinase Inhibitors; Taxoids; Quinazolines; Transplantation Conditioning; Organometallic Compounds; Organoplatinum Compounds; Nitriles; Recombinant Fusion Proteins; Pyrazines; Neoadjuvant Therapy; Anthracyclines; Photochemotherapy; Boronic Acids; Aromatase Inhibitors; Alkylating Agents; Hydroxyurea; Neoplasm Antibodies; Induced Hyperthermia; Benzamides; Arsenic Trioxide)

*Adverse effects on cardiovascular status and lipid levels of albino Wistar rats treated with cisplatin and oxaliplatin in combination with 5 Fluorouracil.

*Persistence of cisplatin-induced mutagenicity in hematopoietic stem cells: implications for secondary cancer risk following chemotherapy.

*Prolonged use of bevacizumab may cause extensive coronary artery thrombosis.

*Severe exacerbation of Crohn's disease during sunitinib treatment.

*Selected nutraceutic screening by therapeutic effects on doxorubicin-induced chronic kidney disease.

*Proanthocyanidins produce significant attenuation of doxorubicin-induced mutagenicity via suppression of oxidative stress.

*Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis.

*Acute infusion reactions induced by monoclonal antibody therapy.

*Anti-CTLA4 monoclonal antibody induced sarcoidosis in a metastatic melanoma patient.

*Cutaneous adverse reactions to therapeutic monoclonal antibodies for cancer.

*Immunotoxicity of monoclonal antibodies.

*A biochemical perspective of methotrexate neurotoxicity with insight on nonfolate rescue modalities.

*6-Gingerol prevents cisplatin-induced acute renal failure in rats.

*5-Fluorouracil can cross brain-blood barrier and cause encephalopathy: should we expect the same from capecitabine? A case report on capecitabine-induced central neurotoxicity progressing to coma.

- *6-Thioguanine and S(6)-methylthioguanine are mutagenic in human cells.
- *A case of epirubicin-associated cardiotoxicity progressing to life-threatening heart failure and splenic thromboembolism.
- *A case of interstitial lung disease due to sunitinib.
- *A case of adenomyomatous polyp of the uterus associated with tamoxifen therapy.
- *A case of therapy for bevacizumab-induced hypertension.
- *Acute lung injury induced by arsenic trioxide in a patient with refractory myelodysplastic syndrome.
- *Acute ototoxicity from a single infusion of oxaliplatin.
- *Acute renal failure, gastrointestinal bleeding, and cardiac arrhythmia after administration of arsenic trioxide for acute promyelocytic leukemia.
- *Acute severe cardiac failure in a myeloma patient due to proteasome inhibitor bortezomib.
- *A case of sclerosing cholangitis caused by oral chemotherapy with S-1.
- *A case of secondary leukemia induced by chemotherapy with a CDDP-based regimen for gastric cancer 5 years following radical resection.
- *A case of severe enteritis induced by adjuvant chemotherapy for colon cancer.
- *A database for mucositis induced by cancer chemotherapy.

2A2. Anti-Infective Agents

This also was a very large class.

2A2a. Anti-Bacterial Agents/Anti-Fungal Agents/Anti-Parasite Agents

(e.g., Sulfonamides; Imidazoles; Triazoles; Antitubercular Agents; Quinolines; Benzimidazoles; Local Anti-Infective Agents; Antimalarials; Quinolones; Fluoroquinolones; Oxazolidinones; Cephalosporins; Aminoglycosides; Anthelmintics; Antibiotic Prophylaxis)

- *A case of acute generalized exanthematous pustulosis due to amoxicillin-clavulanate with multiple positivity to beta-lactam patch testing.
- *Minocycline-induced arthritis.
- *A case of amoxicillin-induced hepatocellular liver injury with bile-duct damage.
- *LONG-TERM VORICONAZOLE AND SKIN CANCER: IS THERE CAUSE FOR CONCERN?

- *Retrospective review of vancomycin-induced nephrotoxicity in patients with leukemia.
- *An overlooked complication of vancomycin induced acute flaccid paralysis in a child with acute leukemia: a case report.
- *Voriconazole-induced pancreatitis in a patient of acute myeloid leukemia and invasive aspergillosis.
- *A case of anaphylaxis to oral minocycline.
- *Toxic epidermal necrolysis caused by cetuximab plus minocycline in head and neck cancer.
- *MINOCYCLINE-INDUCED BLACK THYROID GLAND: MEDICAL CURIOSITY OR A MARKER FOR PAPILLARY CANCER?
- *Minocycline-induced hyperpigmentation in rheumatoid arthritis.
- *Ofloxacin induced Sweet's syndrome in a patient with Crohn's disease.
- *A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use.
- *A Mexican population-based study on exposure to paracetamol and the risk of wheezing, rhinitis, and eczema in childhood.
- *A probable association of acute dystonia with gemifloxacin administration.
- *A rare case of hepatitis associated with cefprozil therapy.
- *Acetaminophen and/or antibiotic use in early life and the development of childhood allergic diseases.
- *Acute eosinophilic pneumonia secondary to daptomycin: a report of three cases.
- *Ciprofloxacin-induced nephrotoxicity in patients with cancer.
- *Acute hepatitis associated with the use of levofloxacin.
- *Acute interstitial nephritis due to cefoperazone.
- *Acute myocardial infarction in a young male on methylphenidate, bupropion, and erythromycin.
- *Acute neurological deficits caused by cefipime: a case report and review of literature.
- *Chronic minocycline-induced autoimmunity in children.
- *Neuralgic amyotrophy associated with antibiotic therapy.

2A2b. Antiviral/Antiretroviral Agents

(e.g., Recombinant Proteins; Anti-HIV Agents; Highly Active Antiretroviral Therapy; Interferon-alpha; Polyethylene Glycols/PEGylated; Interferon alfa-2b; Peginterferon alfa-2a; Interferon alfa-2a; Peginterferon alfa-2b; Immunoglobulin G; Reverse Transcriptase Inhibitors; Organophosphonates; Protease Inhibitors)

*A case of Bell's palsy associated with peginterferon Alfa-2a and ribavirin therapy for chronic hepatitis C virus infection.

*Recovery after L-DOPA treatment in peginterferon and ribavirin induced parkinsonism.

*Prolonged treatment with interferon alpha and peginterferon induces rheumatoid arthritis syndrome and erythema nodosum.

*Arthritis induced by interferon-alpha therapy in a patient with essential thrombocythemia.

*Ginsenosides block HIV protease inhibitor ritonavir-induced vascular dysfunction of porcine coronary arteries.

*Gender differences in adenine-induced chronic kidney disease and cardiovascular complications in rats.

*Interferon-alpha-induced thrombotic microangiopathy in patients with chronic myelogenous leukemia.

*Efavirenz directly modulates the oestrogen receptor and induces breast cancer cell growth.

*A case of gynecomastia due to entecavir.

*Acute hemorrhagic colitis associated with oral administration of oseltamivir for the treatment of influenza A.

*Acute renal failure related to intravenous acyclovir.

*A case of visual hypoemotionality induced by interferon alpha-2b therapy in a patient with chronic myeloid leukemia.

*Acute portal thrombosis in patients with hepatitis C treated with pegylated interferon and ribavirin.

*Acyclovir-induced nephrotoxicity: the role of the acyclovir aldehyde metabolite.

*Adefovir dipivoxil-induced Fanconi syndrome and hypophosphatemic osteomalacia associated with muscular weakness in a patient with chronic hepatitis B.

*Anemia associated with antiviral therapy in chronic hepatitis C: incidence, risk factors, and impact on treatment response.

*Autoimmune thyroiditis and delayed onset psoriasis in association with combination therapy for chronic hepatitis C infection.

- *A case of lactic acidosis caused by stavudine in an AIDS patient.
- *Absence seizures associated with efavirenz initiation.
- *Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy.
- *Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study.
- *Antiretroviral-therapy-associated lipodystrophy: current status and future directions.

2A3. Anti-Inflammatory Agents

(e.g., Non-Steroidal Anti-Inflammatory Agents; Pyrazoles; Cyclooxygenase Inhibitors; Lactones)

- *Acetaminophen increases blood pressure in patients with coronary artery disease.
- *A case of acute pancreatitis caused by 5-aminosalicylic acid suppositories in a patient with ulcerative colitis.
- *A NSAID-associated alimentary tract disease in patients with rheumatism in Russia.
- *Acute coronary syndrome after diclofenac induced coronary spasm.
- *Acute Delta(9)-tetrahydrocannabinol blocks gastric hemorrhages induced by the nonsteroidal anti-inflammatory drug diclofenac sodium in mice.
- *Acute interstitial nephritis due to mesalazine.
- *Celecoxib exacerbates hepatic fibrosis and induces hepatocellular necrosis in rats treated with porcine serum.
- *Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract.
- *Adverse respiratory reactions to aspirin and nonsteroidal anti-inflammatory drugs.
- *A case of peritoneal TB causing renal failure in a patient with rheumatoid arthritis and initial negative PPD after treatment with infliximab.
- *Infliximab-induced psoriasis in treatment of Crohn's disease-associated ankylosing spondylitis: case report and review of 142 cases.
- *Adenosine-induced coronary vasospasm following drug-eluting stent implantation.
- *Adverse effects of nonsteroidal anti-inflammatory drugs on the colon.
- *Acute coronary syndrome caused by infliximab in a patient with ankylosing spondylitis.

- *Hepatitis B virus reactivation induced by infliximab administration in a patient with Crohn's disease.
- *Aggravation of exercise-induced intestinal injury by Ibuprofen in athletes.
- *Analgesic use and the risk of hearing loss in women.
- *Adalimumab-induced acute interstitial lung disease in a patient with rheumatoid arthritis.
- *Aspirin-induced asthma: clinical aspects, pathogenesis and management.
- *Probable diffuse retinopathy caused by adalimumab in a patient with Crohn's disease.

2A4. Cardiovascular Agents

(e.g., Anti-Arrhythmia Agents; Vasodilator Agents; Phosphodiesterase Inhibitors; Cardiotonic Agents; Vasopressin)

- *Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E2 through reduced NK activity.
- *Bilateral injection of isoproterenol into hippocampus induces Alzheimer-like hyperphosphorylation of tau and spatial memory deficit in rat.
- *24 h-kinetics of iodide uptake in amiodarone induced hypothyroidism.
- *A characterization of amiodarone-induced pulmonary toxicity in F344 rats and identification of surfactant protein-D as a potential biomarker for the development of the toxicity.
- *Acute amiodarone hepatotoxicity.
- *Amiodarone-induced liver cirrhosis and parkinsonism: a case report.
- *Acute Amiodarone-induced Lung Toxicity.
- *Amiodarone-induced delirium in advanced cancer: a case report.
- *Amiodarone-induced thyrotoxicosis with thyroid papillary cancer in multinodular goiter: case report.
- *Adenosine deaminase and adenosine attenuate ventricular arrhythmias caused by norepinephrine.
- *A calcium stimulated cysteine protease involved in isoproterenol induced cardiac hypertrophy.
- *Aegle marmelos fruit extract attenuates isoproterenol-induced oxidative stress in rats.
- *Cardio protective effect of vitamin A against isoproterenol-induced myocardial infarction.
- *Isoproterenol-induced myocardial fibrosis in relation to myocyte necrosis.

- *A case of dobutamine-induced coronary arterial spasm with ST-segment elevation.
- *Dermal cellulitis--a hypersensitivity reaction from dobutamine hydrochloride.
- *Dobutamine induced cardiogenic shock due to systolic anterior motion after mitral valve repair.
- *Dobutamine-induced eosinophilia.
- *ADVERSE EFFECTS OF PROPRANOLOL ON REPRODUCTIVE FUNCTION IN ADULT MALE MICE.
- *Musical hallucinations induced by propranolol.
- *Severe asthma attack induced by propranolol.
- *Severe hyperkalemia induced by propranolol.

2A5. Central Nervous System Agents

This is a very large category of both sub-categories and specific agents.

2A5a. Analgesics and Pain Relievers

(e.g., Aspirin; Analgesics; Opioid Analgesics; Local Anesthetics; General Anesthesia; Psychotropic Drugs; Acetaminophen; Non-Narcotic Analgesics; Anesthesia; Nerve Block; Inhalation Anesthetics; Vasoconstrictor Agents; Spinal Anesthesia; Epidural Analgesia; Amides; Conscious Sedation; Dental Anesthesia; Methyl Ethers)

- *Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia-inducible factor cellular signaling pathway in vitro.
- *ASSOCIATION OF INTENSIVE MORPHINE TREATMENT AND INCREASED STROKE INCIDENCE IN PROSTATE CANCER PATIENTS: A POPULATION-BASED NESTED CASE-CONTROL STUDY.
- *Propofol induces proliferation and invasion of gallbladder cancer cells through activation of Nrf2.
- *Regulatory T cells: a possible promising approach to cancer recurrence induced by morphine.
- *Anesthetic sevoflurane causes neurotoxicity differently in neonatal naive and Alzheimer disease transgenic mice.
- *A case of aspirin-induced cough without bronchoconstriction. A new type of aspirin hypersensitivity.
- *A clinical study of Japanese patients with ulcer induced by low-dose aspirin and other non-steroidal anti-inflammatory drugs.

- *A disease marker for aspirin-induced chronic urticaria.
- *Insulin Facilitates the Recovery of Myocardial Contractility and Conduction during Cardiac Compression in Rabbits with Bupivacaine-Induced Cardiovascular Collapse.
- *A severe inflammatory cutaneous reaction after continuous epidural analgesia.
- *A case of hepatitis attributable to repeated exposure to methoxyflurane during its use for procedural analgesia.
- *Acute analgesic-induced renal papillary necrosis.
- *Modest increase in risk of acute coronary syndrome associated with morphine use in cancer patients: a population-based nested case-control study.
- *Pre-treatment of bupivacaine-induced cardiovascular depression using different lipid formulations of propofol.
- *Subdural haemorrhage is associated with recent morphine treatment in patients with cancer: a retrospective population-based nested case-control study.
- *Anesthetic induction with etomidate, rather than propofol, is associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery.
- *A case of liver dysfunction after isoflurane anesthesia.
- *A fatal case of fulminant hepatic necrosis following sevoflurane anesthesia.
- *Allergic reaction to local anesthetic agents of the amide group.
- *Anesthetic-induced neurotoxicity of the neonate: time for clinical guidelines?
- *Anesthetic-induced myocardial ischemia: the isoflurane-coronary steal controversy.
- *Cerebral and cardiac toxicity of locoregional anaesthetics.

2A5b. Movement Stabilizers

(e.g., Central Muscle Relaxants; Neuromuscular Agents)

- *A case of eperisone hydrochloride (myonal)--induced drug eruption leading to erythema and angioedema.
- *A case of torsades de pointes induced by severe QT prolongation after an overdose of eperisone and triazolam in a patient receiving nifedipine.
- *A case report of unusual vasculitic reaction after Methocarbamol injection.
- *Acute intoxications with carisoprodol.

- *Acute pancreatitis in the course of meprobamate poisoning.
- *Eosinophilic pleurisy induced by dantrolene.
- *A case report of acute polyradiculoneuritis developing after multiple injections of botulinum toxin for cervical dystonia.
- *Acute deterioration of bulbar function after botulinum toxin treatment for sialorrhoea in amyotrophic lateral sclerosis.
- *Hourglass deformity after botulinum toxin type A injection.

2A5c. Depressants/Antidepressants and Stimulants

(e.g., Depressants; Central Nervous System Depressants; Antidepressants; Serotonin Uptake Inhibitors; Tricyclic Antidepressive Agents; Cyclohexanols; Serotonin Receptor Agonists; Stimulants; Benzhydryl Compounds)

- *The role of adenosine receptors and endogenous adenosine in citalopram-induced cardiovascular toxicity.
- *Propafenone associated severe central nervous system and cardiovascular toxicity due to mirtazapine: a case of severe drug interaction.
- *Citalopram-induced hyponatraemia and parkinsonism: potentially fatal side-effects not to be missed.
- *Fluoxetine-induced tardive dyskinesia in a patient with Parkinson's disease.
- *Delirium associated with duloxetine in a depressed patient with Alzheimer's dementia.
- *Venlafaxine induced acute myocardial infarction with normal coronary arteries.
- *Topiramate-associated acute glaucoma in a migraine patient receiving concomitant citalopram therapy: a case-report.
- *Methylphenidate (Ritalin)-associated cataract and glaucoma.
- *A metric of maternal prenatal risk drinking predicts neurobehavioral outcomes in preschool children.
- *Acute paternal alcohol use affects offspring development and adult behavior.
- *Adult rats prenatally exposed to ethanol have increased gluconeogenesis and impaired insulin response of hepatic gluconeogenic genes.
- *A case of prolonged seizure activity after combined use of bupropion and clomipramine.
- *A case of SSRI-induced hyponatremia.

- *Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis.
- *Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction.
- *Cellular correlates of enhanced anxiety caused by acute treatment with the selective serotonin reuptake inhibitor fluoxetine in rats.
- *A fatal case of hyperthermia due to tricyclic antidepressant intoxication.
- *Antidepressant drugs: disturbing and potentially dangerous adverse effects.
- *Antidepressant-induced liver injury.
- *Antidepressant-induced sexual dysfunction in men.
- *Antidepressant-induced mania in obsessive compulsive disorder.
- *Nephropathy induced by stimulants and narcotics (heroin, amphetamine, etc).
- *A case of acute cardiomyopathy and pericarditis associated with methylphenidate.
- *Adverse effects of methylphenidate on the reproductive axis of adolescent female rats.
- *Acute myocardial infarction related to methylphenidate for adult attention deficit disorder.
- *Methylphenidate induces lipid and protein damage in prefrontal cortex, but not in cerebellum, striatum and hippocampus of juvenile rats.

2A5d. Mood Stabilizers

(e.g., Anticonvulsants; Neuroprotective Agents; Lithium Compounds; Histone Deacetylase Inhibitors; Antipsychotic Agents; Piperazines; Piperidines; Thiazoles; Antimanic Agents; Dibenzothiazepines; Anti-Anxiety Agents; Hypnotic Agents; Benzodiazepines; Neurotransmitters; Dopamine; Acetylcholine; Cholinesterase Inhibitors; Antiparkinson Agents; Cholinergic Antagonists; Dopamine Agonists; Gamma-Aminobutyric Acid/ GABA; Anti-Asthmatic Agents; Bronchodilator Agents; Nicotinic Agonists; Muscarinic Antagonists; Dopamine Uptake Inhibitors; Adrenergic Uptake Inhibitors; Dopamine Agents)

- *Clozapine treatment associated with increased risk of acute myeloid leukemia (AML).
- *Thalidomide induced acute worsening of Parkinson's disease.
- *Neuroleptic malignant syndrome induced by phenytoin in a patient with drug-induced Parkinsonism.
- *Antiepileptic drug-induced encephalopathy.
- *Myocarditis associated with clozapine studied by cardiovascular magnetic resonance.

- *Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer.
- *Aripiprazole associated with severe exacerbation of Parkinson's disease.
- *Delayed topiramate-induced bilateral angle-closure glaucoma.
- *Acute dystonia, akathisia, and parkinsonism induced by ziprasidone.
- *VALPROIC ACID-INDUCED PARKINSONISM IN THE ELDERLY: A COMPREHENSIVE REVIEW OF THE LITERATURE.
- *Anticonvulsant-induced rickets and nephrocalcinosis.
- *A case of drug-induced interstitial pneumonia due to phenytoin.
- *A case of fetal carbamazepine syndrome with right hemihypoplasia of the entire body.
- *Acute childhood pancreatitis caused by valproate.
- *A case of clozapine-induced paralytic ileus.
- *Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia.
- *Clozapine-related myocarditis and cardiomyopathy in an Australian metropolitan psychiatric service.
- *Quetiapine-induced leucopenia and thrombocytopenia.
- *Quetiapine-induced diabetes with metabolic acidosis.
- *Olanzapine-induced vasculitis.
- *Olanzapine-induced eccrine squamous syringometaplasia.
- *Thalidomide neuropathy in childhood.
- *Amantadine-induced livedo reticularis: a report of two cases.
- *Bradykinesia in patients with Parkinson's disease having levodopa-induced dyskinesias.
- *Orexins cause epileptic activity.
- *Substance P accelerates hypercellularity and angiogenesis in tendon tissue and enhances paratendinitis in response to Achilles tendon overuse in a tendinopathy model.

2A6. Immunologic Factors

2A6a. Immunosuppressive Agents/Immunosuppression

(e.g., Immunotherapy; Mycophenolic Acids)

- *Cyclosporin-induced toxic neuromyopathy.
- *Cyclosporin-induced sebaceous hyperplasia in renal transplant patients.
- *mTOR inhibitor-associated stomatitis (mIAS) in three patients with cancer treated with everolimus.
- *Mammalian target of rapamycin (mTOR) inhibitor-associated non-infectious pneumonitis in patients with renal cell cancer: predictors, management, and outcomes.
- *Increased risk of everolimus-associated acute kidney injury in cancer patients with impaired kidney function.
- *Lymphomatoid granulomatosis associated with azathioprine therapy in Crohn disease.
- *HEMATOLOGIC TOXICITIES ASSOCIATED WITH MTOR INHIBITORS TEMSIROLIMUS AND EVEROLIMUS IN CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.
- *Azathioprine-induced hepatotoxicity in a patient with Crohn's disease.
- *Acute Pancreatitis Induced by Azathioprine and 6-mercaptopurine Proven by Single and Low Dose Challenge Testing in a Child with Crohn Disease.
- *Azathioprine-induced carcinogenesis in mice according to Msh2 genotype.
- *AZATHIOPRINE: ASSOCIATION WITH THERAPY-RELATED MYELOYDYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA.
- *Significant association of coronary artery calcification in stent delivery route with restenosis after sirolimus-eluting stent implantation.
- *Prednisone-induced osteoporosis: an overlooked and undertreated adverse effect.
- *Prednisone induces cognitive dysfunction, neuronal degeneration, and reactive gliosis in rats.
- *Tacrolimus induced diabetic ketoacidosis in nephrotic syndrome.
- *Tacrolimus induced subacute cerebellar ataxia.
- *Sirolimus (rapamycin) induced proteinuria in a patient undergoing allogeneic hematopoietic stem cell transplant.
- *Severe sirolimus-induced acute hepatitis in a renal transplant recipient.

2A6b. Immunostimulation Agents

(Immunologic Factors; Immunologic Adjuvants; Immunization)

- *A case of imiquimod-induced alopecia.

- *Activation of psoriasis in patients undergoing treatment with interferon-beta.
- *Cardiac arrhythmia induced by interferon beta-1a.
- *Acute colchicine intoxication complicated with extramedullary hematopoiesis due to filgrastim in a child.
- *Acute myocardial infarction caused by filgrastim: a case report.

2A6b1. Vaccines/ Vaccination

(e.g., Influenza Vaccines; BCG Vaccine; Viral Vaccines; Cancer Vaccines)

- *A case of influenza vaccination induced Guillain Barre syndrome with normal cerebrospinal fluid protein and improvement on treatment with corticosteroids.
- *A case of ulcerative colitis relapsed by influenza vaccination.
- *A case series of children with apparent mercury toxic encephalopathies manifesting with clinical symptoms of regressive autistic disorders.
- *A dose-response relationship between organic mercury exposure from thimerosal-containing vaccines and neurodevelopmental disorders.
- *A positive association found between autism prevalence and childhood vaccination uptake across the U.S. population.
- *Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism.
- *Acute disseminated encephalomyelitis following 2009 H1N1 influenza vaccination.
- *Acute exacerbation of idiopathic pulmonary fibrosis after pandemic influenza A (H1N1) vaccination.
- *Acute hepatitis B in a healthcare worker: a case report of genuine vaccination failure.
- *Acute immune thrombocytopenic purpura as adverse reaction to oral polio vaccine (OPV).
- *Acute pancreatitis caused by parotiditis vaccine.
- *Acute systemic inflammation induced by influenza A (H1N1) vaccination causes a deterioration in endothelial function in HIV-infected patients.
- *Acute transverse myelitis and acute motor axonal neuropathy developed after vaccinations against seasonal and 2009 A/H1N1 influenza.
- *Adverse ocular effects following influenza vaccination.
- *Adverse reactions following immunization with MMR vaccine in children at selected provinces of Iran.

- *Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes
- *Adverse reactions to anthrax vaccine (eg, optic neuritis) may be more complex or delayed than reported initially by Payne et al (2006).
- *ALUMINUM-INDUCED ENTROPY IN BIOLOGICAL SYSTEMS: IMPLICATIONS FOR NEUROLOGICAL DISEASE
- *Anaphylactoid reaction after typhoid vaccination.
- *Arthritis induced by antihepatitis B vaccine.
- *BCG vaccine-associated suppurative lymphadenitis.
- *BCG vaccine-induced lupus vulgaris.
- *Childhood invasive pneumococcal disease caused by non-7-valent pneumococcal vaccine (PCV7) serotypes under partial immunization in Taiwan.
- *DO ALUMINUM VACCINE ADJUVANTS CONTRIBUTE TO THE RISING PREVALENCE OF AUTISM?
- *Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system.
- *HEPATITIS B TRIPLE SERIES VACCINE AND DEVELOPMENTAL DISABILITY IN US CHILDREN AGED 1–9 YEARS
- *HEPATITIS B VACCINATION OF MALE NEONATES AND AUTISM
- *Methodological issues and evidence of malfeasance in research purporting to show thimerosal in vaccines is safe.
- *Narcolepsy--rare disease that has received increased attention. Pandemrix vaccination caused a higher incidence among children and adolescents.
- *Persistent behavioral impairments and alterations of brain dopamine system after early postnatal administration of thimerosal in rats.
- *POSSIBLE IMMUNOLOGICAL DISORDERS IN AUTISM: CONCOMITANT AUTOIMMUNITY AND IMMUNE TOLERANCE.
- *RISK OF GUILLAIN-BARRE SYNDROME FOLLOWING PANDEMIC INFLUENZA A(H1N1) 2009 VACCINATION IN GERMANY.
- *SEROLOGICAL ASSOCIATION OF MEASLES VIRUS AND HUMAN HERPESVIRUS-6 WITH BRAIN AUTOANTIBODIES IN AUTISM.

*THIMEROSAL EXPOSURE IN INFANTS AND NEURODEVELOPMENTAL DISORDERS: AN ASSESSMENT OF COMPUTERIZED MEDICAL RECORDS IN THE VACCINE SAFETY DATALINK.

*Thimerosal in childhood vaccines contributes to accumulating mercury toxicity in the kidney

*Vaccination induced neutropenia.

*Vaccination-induced autoimmune hepatitis.

*Vaccination-induced autoimmune vitiligo is a consequence of secondary trauma to the skin.

*Vaccination-induced cutaneous pseudolymphoma.

*Vaccine-induced enhancement of viral infections.

*Vaccine-induced necrobiotic granuloma.

2A7. Hematologic Agents

2A7a. Coagulants

(e.g., Electrocoagulation; Hemostatics; Laser Coagulation)

*Bipolar forceps: a hemostatic tool for patients with electrocoagulation-induced dental pain.

*Ventricular fibrillation caused by electrocoagulation during laparoscopic surgery.

*Ameliorative effect of NAP on laser-induced retinal damage.

*Gas embolism following bronchoscopic argon plasma coagulation: a case series.

*A case of thrombocytopenia after microwave coagulation therapy for multiple metastatic liver tumors.

*Acute ischemic cholecystitis after transarterial chemoembolization with drug-eluting beads.

*Aprotinin in lung transplantation is associated with an increased incidence of primary graft dysfunction.

*Hydronephrosis after embolization of internal iliac artery aneurysms.

2A7b. Anticoagulants

(e.g., Platelet Aggregation Inhibitors; Fibrinolytic Agents; Thiophenes; Low-Molecular-Weight Heparin)

*A case of drug-induced pneumonia caused by clopidogrel.

- *Combined clopidogrel and proton pump inhibitor therapy is associated with higher cardiovascular event rates after percutaneous coronary intervention: a report from the BASKET trial.
- *Warfarin induces cardiovascular damage in mice.
- *Clopidogrel-induced hepatotoxicity and fever.
- *Clopidogrel-associated acute migratory arthritis following kidney-pancreas transplantation.
- *DABIGATRAN ETEXILATE AND RISK OF MYOCARDIAL INFARCTION, OTHER CARDIOVASCULAR EVENTS, MAJOR BLEEDING, AND ALL-CAUSE MORTALITY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.
- *Dabigatran-induced upper intestinal bleeding in a patient with chronic kidney disease.
- *A case of heparin-induced thrombocytopenia that worsened preexisting cerebral infarction.
- *Heparin-induced aldosterone suppression and hyperkalemia.
- *Heparin-induced life-threatening hyperkalemia.
- *Impact of heparin-induced thrombocytopenia on acute coronary artery thrombosis in patients undergoing PCI.
- *Acute renal failure due to hypersensitivity interstitial nephritis induced by warfarin sodium.
- *Fatal warfarin-induced skin necrosis after total hip arthroplasty.
- *Warfarin-induced brachytelephalangi chondrodysplasia punctata.
- *Warfarin-induced Venous Limb Gangrene.
- *Agranulocytosis caused by ticlopidine and its mechanism.
- *Cholestatic hepatitis and anemia induced by ticlopidine.
- *Ticlopidine-induced lymphocytic colitis.

2A7c. Other

(e.g., Angiogenesis Inhibitors; Erythropoietin; Hematinics; Folic Acid; Chelating Agents; Platelet Transfusion; Benzoates)

- *A model of hypertension and proteinuria in cancer patients treated with the anti-angiogenic drug E7080.
- *A case of erythropoietin induced hypertension in a bilaterally nephrectomized patient.

- *Epoetin-induced autoimmune pure red cell aplasia.
- *Erythropoietin induced visual hallucinations after bone marrow transplantation.
- *Erythropoietin-induced deep vein thrombosis in myelodysplastic syndrome.
- *Epoetin alpha-induced acute generalized exanthematous pustulosis and desensitisation.

2A8. Steroids/ Hormones

(e.g., Glucocorticoids; Adrenal Cortex Hormones; Angiotensin; Estrogens; Insulin; Estradiol; Insulin-Like Growth Factor; Growth Hormone; Estrogen Replacement Therapy; Hormone Replacement Therapy; Hydrocortisone/ Cortisol; Anabolic Agents; Human Growth Hormone; Testosterone; Androgens; Triamcinolone Acetonide; Diethylstilbestrol)

- *Natural Antioxidants Exhibit Chemopreventive Characteristics through the Regulation of CNC b-Zip Transcription Factors in Estrogen-Induced Breast Carcinogenesis.
- *Bisphenol-A and diethylstilbestrol exposure induces the expression of breast cancer associated long noncoding RNA HOTAIR in vitro and in vivo.
- *Steroid-induced androgen receptor-oestradiol receptor beta-*Src* complex triggers prostate cancer cell proliferation.
- *Long-term follow-up of bilateral steroid-induced osteonecrosis of the lateral femoral condyles in a patient with Crohn's disease.
- *DNA diploidy in AIDS-related and steroid-induced Kaposi's sarcoma.
- *Molecular mechanisms of sex steroid-induced growth of cancer cells.
- *17Beta-estradiol promotes aggressive laryngeal cancer through membrane-associated estrogen receptor-alpha 36.
- *A case of steroid-induced glaucoma after radial keratotomy.
- *Management of steroid-induced hyperglycemia in hospitalized patients with cancer: a review.
- *Steroid induced atrial fibrillation.
- *Steroid induced diabetes mellitus in patients receiving prednisolone for haematological disorders.
- *Steroid induced glaucoma and cataract.
- *Alendronate for steroid-induced osteopenia in children with acute lymphoblastic leukaemia or non-Hodgkin's lymphoma: results of a pilot study.
- *Steroid induced osteoporosis.

*Steroid induced psychosis in systemic lupus erythematosus: a possible role of serum albumin level.

*Glucocorticoid Induced Cerebellar Toxicity in the Developing Neonate: Implications for Glucocorticoid Therapy during Bronchopulmonary Dysplasia.

*Glucocorticoid induces micro-fat embolism in the rabbit: a scanning electron microscopic study.

*Insulin increases retinal hemorrhage in mild oxygen-induced retinopathy in the rat: inhibition by riluzole.

*Insulin induced fetal hypoglycaemia and fetal and maternal plasma prostaglandin concentrations in sheep in late gestation.

*Insulin-induced proliferation of bladder cancer cells is mediated through activation of the epidermal growth factor system.

*Insulin-induced renal dysfunction in regular Sabra rats.

*Insulin: a novel agent in the pathogenesis of prostate cancer.

*Insulin therapy contributes to the increased risk of colorectal cancer in diabetes patients: a meta-analysis.

*Acromegaly induced by growth hormone replacement therapy.

*Cardiovascular risk associated with hormone replacement therapy: some critical questions about the type of estrogen used in most clinical trials.

*Growth hormone treatment induces mammary gland hyperplasia in aging primates.

*Diethylstilbestrol liver carcinogenicity and modification of DNA in rats.

*Diethylstilbestrol-induced uterine sarcoma in mice.

2A9. Antihypertensive Agents

(e.g., Enzyme Inhibitors; Adrenergic beta-Antagonists; Angiotensin-Converting Enzyme Inhibitors; Calcium Channel Blockers; Diuretics; Tetrazoles; Angiotensin II Type 1 Receptor Blockers; Benzazepines)

*Nifedipine promotes the proliferation and migration of breast cancer cells.

*Verapamil is associated with an increased risk of cancer in the elderly: the Rotterdam study.

*ASSOCIATION OF CALCIUM CHANNEL BLOCKER USE WITH LOWER HEMOGLOBIN LEVELS IN CHRONIC KIDNEY DISEASE.

- *Treatment of calcium channel blocker-induced cardiovascular toxicity with drug scavenging liposomes.
- *Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery.
- *Acebutolol-induced subacute cutaneous lupus erythematosus.
- *Sildenafil induced choreoathetosis in men with Parkinson's disease.
- *Atenolol hepatotoxicity: report of a complicated case.
- *Beta-blocker use is associated with fragility fractures in postmenopausal women with coronary heart disease.
- *ACE inhibitor-induced angioedema.
- *ACE inhibitor-induced hypoglycemia.
- *Angiotensin converting enzyme inhibitor toxicity causing interstitial pneumonitis and cholestatic hepatitis.
- *Angiotensin converting enzyme inhibitor induced hyperkalaemic paralysis.
- *Acute toxic effects of sustained-release verapamil in chronic renal failure.
- *Verapamil-induced hepatotoxicity.
- *Verapamil-induced acute right heart failure.
- *Agranulocytosis induced by captopril.
- *Captopril-induced acute pancreatitis.
- *Captopril-induced cholestatic jaundice.
- *Captopril-induced bone marrow suppression in two cardiac patients with trisomy 21.
- *Follicular mucinosis secondary to captopril-induced photoallergy.

2A10. Gastrointestinal Agents

(e.g., Proton Pump Inhibitors; Anti-Ulcer Agents; Cathartics; Phosphates)

- *Gastric acid blockade with omeprazole promotes gastric carcinogenesis induced by duodenogastric reflux.
- *Acute kidney injury following proton pump inhibitor therapy.

- *Long-term proton pump inhibitor use is associated with vascular calcification in chronic kidney disease: a cross-sectional study using propensity score analysis.
- *Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study.
- *A case series of proton pump inhibitor-induced hypomagnesemia.
- *Agranulocytosis induced by proton pump inhibitors.
- *Central nervous system side effects after proton pump inhibitor treatment.
- *Acute pancreatitis associated with omeprazole.
- *Autoimmune haemolytic anaemia due to Omeprazole.
- *Esomeprazole-induced photoallergic dermatitis.
- *Lansoprazole-induced microscopic colitis: an increasing problem? Results of a prospective case-series and systematic review of the literature.
- *Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns.
- *Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure.
- *Severe hyperphosphatemia and hypocalcemia following the rectal administration of a phosphate-containing Fleet pediatric enema.

2A11. Lipid Regulating Agents

(e.g., Hydroxymethylglutaryl-CoA Reductase Inhibitors; Pyrrroles; Hypolipidemic Agents; Anticholesteremic Agents; Heptanoic Acids)

- *Atorvastatin-induced early-onset rhabdomyolysis in a patient with nephrotic syndrome.
- *ASSOCIATION OF STATIN USE WITH CATARACTS: A PROPENSITY SCORE-MATCHED ANALYSIS.
- *Atorvastatin associated liver disease.
- *Atorvastatin induced multiple organ failure.
- *Piriformis muscle syndrome: an unusual adverse effect of atorvastatin.
- *Simvastatin-induced rhabdomyolysis in an HIV-infected patient with coronary artery disease.
- *Current overview of statin-induced myopathy.

- *Adverse drug reaction: rosuvastatin as a cause for ischaemic colitis in a 64-year-old woman.
- *Side effects of the HMG-CoA reductase inhibitors (statins). Lupus erythematosus induced by Atorvastatin therapy.
- *Cytogenetic status and oxidative DNA-damage induced by atorvastatin in human peripheral blood lymphocytes: standard and Fpg-modified comet assay.
- *Pityriasis lichenoides chronica associated with use of HMG-CoA reductase inhibitors.
- *Pravastatin-induced colitis.
- *Rosuvastatin-induced pemphigoid.
- *Rosuvastatin-induced thrombocytopenia.
- *Severe acute cholestatic hepatitis with prolonged cholestasis and bile-duct injury following atorvastatin therapy: a case report.
- *Simvastatin has deleterious effects on human first trimester placental explants.
- *Statin induced diabetes and its clinical implications.
- *Statin-induced fibrotic nonspecific interstitial pneumonia.
- *Statins accelerate the onset of collagen type II-induced arthritis in mice.
- *Statins can induce myasthenia gravis.

2A12. *Dermatologic Agents*

(e.g., Photosensitizing Agents; Hyaluronic Acid/ Hyaluronan; Salicylic Acid)

- *A cerebellar demyelinating lesion following treatment of acne with isotretinoin.
- *Allergic contact dermatitis to pimecrolimus.
- *Contact allergy from vitamins in cosmetic products.
- *Drug-induced ocular side-effects with isotretinoin.
- *Efalizumab-induced autoimmune pancytopenia.
- *Exogenous ochronosis and striae atrophicae following the use of bleaching creams.
- *Infliximab associated new-onset psoriasis.
- *Isotretinoin (Ro-Accutane) teratogenesis. A case report.
- *Imiquimod: liver damage: topical use, systemic effects.

*Imiquimod-induced vitiligo after treatment of nodular basal cell carcinoma.

*Imiquimod 5% cream induced psoriasis: a case report, summary of the literature and mechanism.

*Severe systemic reaction to topical imiquimod.

2A13. Anti-Bone-Loss Agents

(e.g., Bone Density Conservation Agents; Diphosphonates; Zoledronic acid)

*A case of zoledronate-induced tubulointerstitial nephritis with Fanconi syndrome.

*SALMON CALCITONIN USE AND ASSOCIATED CANCER RISK.

*Innegligible musculoskeletal disorders caused by zoledronic acid in adjuvant breast cancer treatment: a meta-analysis.

*Pamidronate-induced kidney injury in a patient with metastatic breast cancer.

*Oral osteonecrosis associated with the use of zoledronic acid: first case of a patient with advanced pancreatic cancer and bone metastases.

*A case report: zoledronic acid-induced anterior uveitis.

*Acute retinal pigment epithelial detachment secondary to pamidronate administration.

*Alendronate-associated femoral insufficiency fractures and femoral stress reactions.

*Alendronate-associated ulnar and tibial fractures: a case report.

*Alendronate-induced synovitis.

*Biphosphonate-induced osteonecrosis of the jaws: CT and MRI spectrum of findings in 32 patients.

*Bisphosphonate-associated arthritis.

*Bisphosphonates and risk of upper gastrointestinal cancer--a case control study using the General Practice Research Database (GPRD).

*Oral ulcers, a little known adverse effect of alendronate: review of the literature.

*Seizures associated with zoledronic acid for osteoporosis.

*Zoledronic acid-induced transient hepatotoxicity in a patient effectively treated for Paget's disease of bone.

2A14. Antidiabetic Agents

(e.g., Hypoglycemic Agents; Thiazolidinediones; Pyrrolidines)

*ASSESSING THE ASSOCIATION OF PIOGLITAZONE USE AND BLADDER CANCER THROUGH DRUG ADVERSE EVENT REPORTING.

*Rosiglitazone, a PPAR gamma agonist: potent promoter of hydroxybutyl(butyl)nitrosamine-induced urinary bladder cancers.

*EFFECT OF ROSIGLITAZONE ON THE RISK OF MYOCARDIAL INFARCTION AND DEATH FROM CARDIOVASCULAR CAUSES.

*Antihyperglycemic treatment in diabetics with coronary disease: increased metformin-associated mortality over a 5-year follow-up.

*A case of drug-induced hepatic injury associated with sitagliptin.

*A case of fatal intoxication from metformin.

*A case of glyburide-induced leukocytoclastic vasculitis.

*A case of lipoatrophy with insulin detemir.

*Acute pulmonary edema due to rosiglitazone use in a patient with diabetes mellitus.

*Acute tubulointerstitial nephritis following treatment with exenatide.

*Metformin-associated lactic acidosis.

*Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy.

*Pemphigus vulgaris triggered by glibenclamide and cilazapril.

*Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies.

*Pneumatosis coli induced by acarbose administration for diabetes mellitus. Case report and literature review.

2A15. Antirheumatic Agents

*A case of cavitating pneumococcal pneumonia developed during the treatment with etanercept for rheumatoid arthritis.

*A case of cervical spine meningioma following etanercept use in a patient with RA.

*A case of tuberculous arthritis following the use of etanercept.

*Acute coronary syndrome after infliximab infusion.

*Acute development of multiple keratoacanthomas and squamous cell carcinomas after treatment with infliximab.

- *Acute encephalomyelitis with multiple herpes viral reactivations during abatacept therapy.
- *Acute myeloid leukemia after infliximab: a case report.
- *Adalimumab-induced acute myelogenous leukemia.
- *Adalimumab-induced autoimmune hepatitis.
- *Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment.
- *Leflunomide-induced DRESS syndrome with renal involvement and vasculitis.
- *Leflunomide-induced peripheral neuropathy.
- *Leflunomide-induced pulmonary hypertension in a young woman with rheumatoid arthritis: a case report.
- *Acute renal and hepatic failure associated with allopurinol treatment.
- *Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel.

2A16. Anti-Allergic Agents

(e.g., Androstadienes)

- *Acute asthma attack caused by ophthalmic application of antiallergic agents.
- *Use of cetirizine in a 23-month-old male causes insomnia.
- *Cetirizine-induced dystonic reaction in a 6-year-old boy.
- *Delayed hypersensitivity reactions to corticosteroids.
- *Epinephrine-induced myocardial infarction in severe anaphylaxis: is nonselective beta-blockade a contributory factor?
- *Exogenous Cushing's syndrome as a serious side-effect of therapy with ritonavir and inhaled fluticasone.
- *First-generation H1 antihistamines found in pilot fatalities of civil aviation accidents, 1990-2005.
- *Inflammation and neurological adverse drug reactions: a case of long lasting impaired consciousness after oxatomide administration in a patient with gastroenteritis.
- *Inhaled corticosteroid-induced hair depigmentation in a child.
- *Oculogyric crisis in patients taking cetirizine.

*Steroid-induced ocular hypertension with loteprednol etabonate 0.2%--a case report.

2A17. Anti-Hypotensive Agents

(e.g., Norepinephrine)

*Cardiogenic shock with stunned myocardium during triple-H therapy treated with intra-aortic balloon pump counterpulsation.

*High-dose norepinephrine induces disruption of myocardial extracellular matrix and left ventricular dilatation and dysfunction in a novel feline model.

*Intracerebral haemorrhage and postpartum cerebral angiopathy associated with the administration of sulprostone and norepinephrine.

*IS NOREPINEPHRINE AN ETIOLOGICAL FACTOR IN SOME TYPES OF CANCER?

*Major haemodynamic incident during continuous norepinephrine infusion: Beware of the infusion line. An avoidable postoperative hypertensive peak?.

*Norepinephrine-induced pressor diuresis blockade as a possible cause of hypertension.

2A18. Antithyroid Agents

(e.g., Propylthiouracil)

*A case of MPO-ANCA positive vasculitis associated with diffuse alveolar hemorrhage and various cardiac conducting system abnormalities following propylthiouracil treatment.

*A case of hypersensitivity syndrome induced by methimazole for Graves' disease.

*A serious adverse effect: sepsis due to carbimazole.

*Acute agranulocytosis from thiamazole: points for improvement in daily practice.

*Acute pancreatitis induced by methimazole in a patient with Graves' disease.

*Acute-on-chronic liver failure due to thiamazole in a patient with hyperthyroidism and trilogy of Fallot: case report.

*Antenatal carbimazole and choanal atresia: a new embryopathy.

*Antineutrophil cytoplasmic antibody (Anca)-associated autoimmune disease induced by propylthiouracil.

*Antithyroid drug-induced aplastic anemia.

*Aplasia cutis congenita and other anomalies associated with methimazole exposure during pregnancy.

*Carbimazole-induced lupus.

*Propylthiouracil-induced overt hepatic injury in patients with hyperthyroidism.

2B. Radiotherapy

(e.g., Radiosurgery; Brachytherapy; Adjuvant Radiotherapy; Cranial Irradiation; Conformal Radiotherapy; Intensity-Modulated Radiotherapy; Radiopharmaceuticals; Iodine Radioisotopes; Chemoradiotherapy; Whole-Body Irradiation)

*A case of delayed facial palsy following gamma knife radiosurgery for intractable trigeminal neuralgia.

*A nonhuman primate model of human radiation-induced venoocclusive liver disease and hepatocyte injury.

*Acute neurological complications following gamma knife surgery for vestibular schwannoma. Case report.

*Delayed radiation-induced vasculitic leukoencephalopathy.

*Adult survivors of childhood acute lymphoblastic leukaemia with GH deficiency have normal self-rated quality of life but impaired neuropsychological performance 20 years after cranial irradiation.

*Cerebral cavernoma: an emerging long-term consequence of external beam radiation in childhood.

*Chemotherapy- and radiotherapy-induced oral mucositis: pathobiology, epidemiology and management.

*Cranial irradiation as an additional risk factor for anthracycline cardiotoxicity in childhood cancer survivors: an analysis from the cardiac risk factors in childhood cancer survivors study.

*Acute cardiac impairment associated with concurrent chemoradiotherapy for esophageal cancer: magnetic resonance evaluation.

*Chemoradiotherapy for anal cancer in HIV patients causes prolonged CD4 cell count suppression.

*Delayed carotid blow-out syndrome: a new complication of chemoradiotherapy treatment in pharyngolaryngeal carcinoma.

*Murine acute leukemia cell line with megakaryocytic differentiation (MK-8057) induced by whole-body irradiation in C3H/He mice: cytological properties and kinetics of its leukemic stem cells.

*The differences between interstitial pneumonia following whole-body irradiation and radiation-induced pneumonitis.

*10 Gy total body irradiation increases risk of coronary sclerosis, degeneration of heart structure and function in a rat model.

*Basal cell skin cancer after total-body irradiation and hematopoietic cell transplantation.

*Chondrosarcoma arising within a radiation-induced osteochondroma several years following childhood total body irradiation: case report.

2C. Surgery; Invasive Treatments

The following categorization is not unique. Some procedures could be assigned to multiple categories.

2C1. Transplantation

(e.g., Transplantation; Kidney Transplantation; Liver Transplantation; Hematopoietic Stem Cell Transplantation; Bone Marrow Transplantation; Heart Transplantation; Stem Cell Transplantation; Lung Transplantation; Organ Transplantation; Homologous Transplantation; Cell Transplantation; Peripheral Blood Stem Cell Transplantation; Pancreas Transplantation; Bone Transplantation; Cord Blood Stem Cell Transplantation)

Transplantation is an extremely large category of foundational causes, and these foundational causes operate on different levels. There are foundational causes due to the transplant preparation process, due to the surgery, due to the immune suppression drugs, and enabled by the transplant (the transplant left the person more susceptible to disease).

*13-cis-retinoic acid-induced eosinophilia following autologous bone marrow transplantation for neuroblastoma.

*2 fatal cases of pneumococcal septicemia after bone marrow transplantation.

*A case of bronchiolitis obliterans caused by allogeneic hematopoietic stem cell transplantation diagnosed with a body plethysmograph.

*A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation.

*A retrospective study of ocular side effects in children undergoing bone marrow transplantation.

*Abdominal complications after bone marrow transplantation in children: sonographic and CT findings.

*Accelerated bone mineral density loss occurs with similar incidence and severity, but with different risk factors, after autologous versus allogeneic hematopoietic cell transplantation.

*Acute and chronic pulmonary complications following autologous bone marrow transplantation in non-Hodgkin's lymphoma.

- *Acute leukemia, a rare but fatal complication after liver transplantation.
- *Acute neurological complications after hematopoietic stem cell transplantation in children.
- *Acute renal failure following lung transplantation: risk factors, mortality, and long-term consequences.
- *Cardiac morbidity and mortality related to orthotopic liver transplantation.
- *Chronic graft-versus-host disease and late effects after hematopoietic stem cell transplantation.
- *Chronic kidney disease after lung transplantation: incidence, risk factors, and treatment.
- *Fatal Kaposi sarcoma after allogeneic stem cell transplant.

2C2. CardioVascular

(e.g., Stents; Cardiac Surgical Procedures; Heart Surgery; Catheterization; Bypass; Coronary Artery Bypass; Vascular Surgical Procedures; Blood Vessel Prosthesis Implantation; Central Venous Catheterization; Therapeutic Embolization; Cardiopulmonary Bypass; Heart Valve Prosthesis Implantation; Angioplasty; Coronary Balloon Angioplasty; Blood Vessel Prosthesis; Endovascular Procedures; Balloon Angioplasty; Artificial Pacemaker; Thrombolytic Therapy; Peripheral Catheterization; Heart-Assist Devices; Angiography; Atrial Pacing; Carotid Endarterectomy; Implantable Defibrillators; Cardiovascular Surgical Procedures; Fontan Procedure; Drug-Eluting Stents; Balloon Occlusion; Sclerotherapy; Cardiopulmonary Resuscitation; Thrombectomy; Revascularization)

Very large category.

- *Abdominal organ injury after cardiac surgery.
- *Acute kidney injury and chronic kidney disease after cardiac surgery.
- *Acute gastric volvulus: an unreported long-term complication of pericardial drainage.
- *Acute kidney injury and long-term risk of stroke after coronary artery bypass surgery.
- *Adverse cerebral outcomes after coronary bypass surgery.
- *Atrial fibrillation after coronary artery bypass grafting in elderly patients: incidence and risk factor analysis.
- *Cardiopulmonary bypass as a cause of free radical-induced oxidative stress and enhanced blood-borne isoprostanes in humans.
- *A case of contrast-induced pancreatitis following cardiac catheterization.
- *Bilateral femoral neuropathy caused by iliacus hematomas during anticoagulation after cardiac catheterization.

- *Cardiac catheterization-induced acute radiation dermatitis presenting as a fixed drug eruption.
- *Catheter-induced pulmonary artery rupture in the setting of cardiopulmonary bypass.
- *Stent-induced thromboembolism.
- *Stent-induced coronary artery stenosis characterized by multimodal nonlinear optical microscopy.
- *A hypothesis regarding vascular acoustic emission accompanying arterial injury induced by balloon angioplasty.
- *Acute myocardial ischaemia and cardiogenic shock after percutaneous transluminal coronary angioplasty; risk factors for and results of emergency coronary bypass.
- *Coronary angioplasty induces a systemic inflammatory response.

2C3. Orthopedic

(e.g., Orthopedic Procedures; Hip Replacement Arthroplasty; Prostheses and Implants; Osteotomy; Spinal Fusion; Prosthesis Implantation; Knee Replacement Arthroplasty; Surgical Decompression; Laminectomy; Discectomy; Arthroscopy; Hip Prosthesis; Bone Screws; Replacement Arthroplasty; Bioprosthesis; Internal Fixators; Prosthesis Failure; Knee Prosthesis)

- *A case of delayed recurrent hemarthrosis after posterolateral reconstruction of the knee with a staple fixation at the lateral femoral epicondyle.
- *Acute bowel ischemia following spinal surgery.
- *Acute thrombotic thrombocytopenic purpura following orthopedic surgery: case report and review of the literature.
- *Cardiac complications following hip fracture surgery.
- *Acute crystal-induced arthritis following arthroplasty.
- *Acute kidney injury following total joint arthroplasty: retrospective analysis.
- *Allergic reaction to components of bone cement after total knee arthroplasty.
- *Fatal fat embolism following femoral head resection in total hip arthroplasty.
- *Fatal massive adrenal hemorrhage after bilateral total knee arthroplasty.
- *Hyponatremia after primary hip and knee arthroplasty: incidence and associated risk factors.
- *Severe bone defects and reduced mineralization caused by massive metallosis after total knee arthroplasty: histopathologic and bone morphometric findings.
- *Anterior interosseus nerve injury following elbow arthroscopy.

*Fatal pulmonary embolus after knee arthroscopy.

*Septic arthritis following arthroscopy: clinical syndromes and analysis of risk factors.

*Life-threatening airway edema resulting from prolonged shoulder arthroscopy.

2C4. Gastrointestinal

(e.g., Laparoscopy; Digestive System Surgical Procedures; Endoscopy; Gastric Bypass; Bariatric Surgery; Esophagectomy; Gastroplasty; Gastrectomy; Colectomy; Laparotomy; Gastrointestinal Endoscopy; Gastrostomy; Gastrointestinal Intubation; Ileostomy; Colostomy; Restorative Proctocolectomy; Fundoplication; Appendectomy; Gastroscopy)

*Bile duct injury following laparoscopic cholecystectomy.

*Bladder dysfunction after gynecologic laparoscopic surgery for benign disease.

*Fatal intestinal ischaemia following laparoscopic cholecystectomy.

*Heart arrest caused by CO₂ embolism during a laparoscopic cholecystectomy.

*High incidence of trocar site hernia after laparoscopic or robotic Roux-en-Y gastric bypass.

*Malnutrition-induced myopathy following Roux-en-Y gastric bypass.

*Rectal epithelial cell mitosis and expression of macrophage migration inhibitory factor are increased 3 years after Roux-en-Y gastric bypass (RYGB) for morbid obesity: implications for long-term neoplastic risk following RYGB.

*Acute kidney injury following bariatric surgery.

*Acute liver failure after bariatric surgery. A case report and literature review.

*Anemia after bariatric surgery: more than just iron deficiency.

*Beriberi after bariatric surgery: not an unusual complication. Report of two cases and literature review.

*Dramatic reduction in sperm parameters following bariatric surgery: report of two cases.

*Liver transplantation for subacute hepatocellular failure due to massive steatohepatitis after bariatric surgery.

2C5. Kidney/ Urologic

(e.g. Renal Dialysis; Peritoneal Dialysis; Urinary Catheterization; Nephrectomy; Laparoscopic Cholecystectomy; Prostatectomy; Cholecystectomy; Urologic Surgical Procedures; Urinary Diversion; Suburethral Slings; Cystectomy; Lithotripsy; Percutaneous Nephrostomy)

- *A boy undergoing maintenance hemodialysis who developed mediastinal lymph node tuberculosis.
- *A case of phlegmesia cerulea dolens after dialysis catheter insertion.
- *Accelerated atherosclerosis in haemodialysis patients; correlation of endothelial function with oxidative DNA damage.
- *Acute calciphylaxis precipitated by the initiation of hemodialysis.
- *A case of uretero-aortic fistula after the urinary diversion.
- *Anaphylactic reactions to chlorhexidine during urinary catheterisation.
- *Catheter-associated urinary tract infection.
- *Adverse effect of radical prostatectomy on nocturia and voiding frequency symptoms.
- *A case of pulmonary embolism and a case of ileus as complications after laparoscopic radical prostatectomy.
- *Addressing and managing erectile dysfunction after prostatectomy for prostate cancer.
- *Deep vein thrombosis caused by pelvic lymphocyst following radical prostatectomy: a case report.
- *Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses.

2C6. Brain/Neural

(e.g., Neurosurgical Procedures; Ventriculoperitoneal Shunt; Craniotomy; Electric Stimulation Therapy; Deep Brain Stimulation; Spinal Puncture; Electric Stimulation; Spinal Injections)

- *Acute parotitis following sitting position neurosurgical procedures: review of five cases.
- *Analysis of the factors contributing to diabetes insipidus after surgeries for craniopharyngiomas.
- *Bilateral bulbar palsy and postural hypotension following surgery for fourth ventricle subependymoma.
- *Baroreflex failure after chemodectoma resection.
- *Brachial neuritis: an under-recognized cause of upper extremity paresis after cervical decompression surgery.
- *Acute massive pulmonary hemorrhage after craniotomy in a patient with systemic lupus erythematosus.

- *Acute respiratory arrest following partial suboccipital cranioplasty for cerebellar ptosis from Chiari malformation decompression.
- *A report of paraparesis following spinal cord stimulator trial, implantation and revision.
- *Complete heart block with ventricular asystole during left vagus nerve stimulation for epilepsy.
- *Explosive-aggressive behavior related to bilateral subthalamic stimulation.
- *Late onset cervical myelopathy secondary to fibrous scar tissue formation around the spinal cord stimulation electrode.
- *Sleep-related breathing disorder in children with vagal nerve stimulators.

2C7. Dental/ Oral/ Nose/ Ear

(e.g., Tooth Extraction; Oral Surgical Procedures; Dental Implants; Tonsillectomy; Otorhinolaryngologic Surgical Procedures; Laryngectomy; Endosseous Dental Implantation; Root Canal Therapy; Cochlear Implantation)

- *An unusual complication of osteotome sinus floor elevation: benign paroxysmal positional vertigo.
- *A case of Candida mediastinitis after dental extraction.
- *Asphyxial death related to postextraction hematoma in an elderly man.
- *Bacterial meningitis after tooth extraction.
- *Bilateral idiopathic sensorineural hearing loss following dental surgery.
- *Bell's palsy following primary tooth extraction. A case report.
- *Cervicofacial emphysema after dental treatment with emphasis on the anatomy of the cervical fascia.
- *Chronic osteomyelitis following an uncomplicated dental extraction.
- *Accidental displacement of dental implants into the maxillary sinus: a report of nine cases.
- *Dental implant failure associated with bacterial infection and long-term bisphosphonate usage: a case report.
- *Dental implants and squamous cell carcinoma in the at risk patient--report of three cases.
- *Mandibular fractures associated with endosteal implants.

2C8. Gynecologic

(e.g., Cesarean Section; Hysterectomy; Gynecologic Surgical Procedures; Ovariectomy)

- *A case of bifocal endometriosis involving a pfannenstiel incision.
- *A case of Mycoplasma hominis infection after bladder injury during cesarean section.
- *A fatal case of hypovolemic shock after cesarean section.
- *Abdominal wall mycetoma presented as obstructed incisional hernia of cesarean section in eastern Sudan.
- *Adrenal insufficiency after laparoscopic hysterectomy in a patient with primary antiphospholipid syndrome.
- *Abnormal vaginal cytology in HIV-infected and at-risk women after hysterectomy.
- *Biofeedback therapy for female patients with constipation caused by radical hysterectomy or vaginal delivery.
- *Bladder dysfunction after simple hysterectomy: urodynamic and neurological evaluation.
- *17 beta-Estradiol and tamoxifen prevent the over-glycosylation of rat trabecular bone collagen induced by ovariectomy.
- *A change in liver metabolism but not in brown adipose tissue thermogenesis is an early event in ovariectomy-induced obesity in rats.
- *A potential role for the bone marrow mesenchymal stem cell in the pathogenesis of osteoporosis by ovariectomy in rat.
- *Genistein supplementation and estrogen replacement therapy improve endothelial dysfunction induced by ovariectomy in rats.

2C9. Respiratory/Thorax

(e.g., Intratracheal Intubation; Pneumonectomy; Thoracotomy; Thoracic Surgical Procedures; Tracheostomy; Video-Assisted Thoracic Surgery; Sternotomy; Artificial Pneumoperitoneum; Mechanical Ventilation)

- *Acute lung injury and acute respiratory distress syndrome following pneumonectomy.
- *Bronchial artery dissection and fatal hemothorax following pneumonectomy.
- *Cardiovascular and respiratory complications after pneumonectomy.
- *Acute life-threatening airway obstruction with pseudomembrane formation after percutaneous dilational tracheostomy.
- *Analysis of the risk factors causing tracheal stenosis after tracheotomy for mechanical ventilation in 560 patients.

- *Bilateral pneumothoraces and pulmonary oedema following tracheostomy induced by acute tracheal obstruction.
- *Fatal re-expansion pulmonary edema in a young adult following tube thoracostomy for spontaneous pneumothorax.
- *Increased age is an independent risk factor for radiographic aspiration and laryngeal penetration after thoracotomy for pulmonary resection.
- *Lung injury after thoracotomy.
- *Cardiovascular complications after lung surgery.
- *Postoperative psychiatric disorders in general thoracic surgery: incidence, risk factors and outcomes.

2C10. Liver/ Spleen

(e.g., Hepatectomy; Splenectomy)

- *Acute iatrogenic Budd-Chiari syndrome following hepatectomy for hepatolithiasis: a report of two cases.
- *Bacterial translocation in acute liver failure induced by 90 per cent hepatectomy in the rat.
- *Bile leakage after hepatectomy for hepatolithiasis: risk factors and management.
- *Hypersplenism induced by hepatectomy.
- *Hypophosphataemia after major hepatectomy and the risk of post-operative hepatic insufficiency and mortality: an analysis of 719 patients.
- *Iron chelation prevents lung injury after major hepatectomy.
- *Adverse effect of splenectomy on recurrence in total gastrectomy cancer patients with perioperative transfusion
- *Angioedema caused by splenectomy with malignant lymphoma followed by multiple myeloma 7 years later.
- *Earlier onset of delta-retrovirus-induced leukemia after splenectomy.
- *Fatal infection after splenectomy despite reimplantation of splenic tissue.
- *Fatal venous thromboembolism after splenectomy: pathogenesis and management.
- *High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: a prospective study with contrast-enhanced CT scan.

2C11. Ocular

(e.g., Cataract Extraction; Ophthalmologic Surgical Procedures; Phacoemulsification; Vitrectomy; Laser Keratomileusis In Situ; Intraocular Lens Implantation)

- *A case of endophthalmitis associated with limbal relaxing incision.
- *A sudden total loss of vision after routine cataract surgery.
- *Adult retinopathy of prematurity: retinal complications from cataract surgery.
- *A case of acquired Brown syndrome after surgical repair of a medial orbital wall fracture.
- *Acute angle closure glaucoma after oculoplastic surgery.
- *Atypical necrotizing scleritis after strabismus surgery.
- *Binocular photophobia after surgical treatment in intermittent exotropia.
- *Corneal ectasia after LASIK despite low preoperative risk: tomographic and biomechanical findings in the unoperated, stable, fellow eye.
- *LASIK-induced optic neuropathy.
- *Bacterial contamination of the vitreous cavity associated with transconjunctival 25-gauge microincision vitrectomy surgery.
- *Factors contributing to corneal complications after vitrectomy in diabetic patients

2C12. Breast

(e.g., Mammoplasty; Mastectomy; Breast Implants)

- *Augmentation mammoplasty: postoperative cephalosporin-induced hepatitis.
- *Granulomatous pleurisy after mammoplasty, induced by polyacrylamide gel.
- *A case of toxic shock syndrome following a DIEP breast reconstruction.
- *Cardiac arrest following hydrogen peroxide irrigation of a breast wound.
- *Clarithromycin attenuates mastectomy-induced acute inflammatory response.
- *Hematoma after mastectomy with immediate reconstruction: an analysis of risk factors in 883 patients.
- *Allergic contact dermatitis to synthetic rubber following breast augmentation.
- *An uncommon complication of secondary augmentation mammoplasty: bilaterally massive engorgement of breasts after pregnancy attributable to postinfection and blockage of mammary ducts.

*Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases.

*Anaplastic large cell lymphoma and breast implants: five Australian cases.

*Galactorrhea after aesthetic breast augmentation with silicone implants: report of two cases and management of postoperative galactorrhea.

2C13. Dermal/ Tissue/ Neck

(e.g., Neck Dissection; Herniorrhaphy)

*A case of increased intracranial pressure after unilateral modified radical neck dissection.

*A new shoulder orthosis for paralysis of the trapezius muscle after radical neck dissection: a preliminary report.

*Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial.

*Bilateral chylothorax following left-sided radical neck dissection.

*A new classification for seroma after laparoscopic ventral hernia repair.

*Aortic injury during laparoscopic esophageal hiataloplasty.

*First cases of giant pseudocyst complicating inguinal hernia repair.

*Late onset mesh infection following laparoscopic inguinal hernia repair.

2C14. Thyroid

(e.g., Thyroidectomy)

*Blockage of gonadotropin-induced first ovulation caused by thyroidectomy and its possible mechanisms in rats.

*Exacerbation of idiopathic paroxysmal kinesigenic dyskinesia in remission state caused by secondary hypoparathyroidism with hypocalcemia after thyroidectomy: evidence for ion channelopathy.

*Hypothyroidism during neonatal and perinatal period induced by thyroidectomy of the mother causes depressive-like behavior in prepubertal rats.

*Hypocalcaemia following total thyroidectomy: early post-operative parathyroid hormone assay as a risk stratification and management tool.

*Hypoparathyroid risk after total thyroidectomy.

*Influence of Superior Laryngeal Nerve Injury on Glottal Configuration/Function of Thyroidectomy-Induced Unilateral Vocal Fold Paralysis.

*Respiratory complications after thyroidectomy and the need for tracheostomy in patients with a large goitre.

2C15. Pancreas

(e.g., Pancreaticoduodenectomy; Pancreatectomy)

*A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy.

*Delayed gastric emptying after pylorus-preserving pancreatoduodenectomy is strongly related to other postoperative complications.

*Haemorrhage following pancreaticoduodenectomy: risk factors and the importance of sentinel bleed

*Necrotizing pancreatitis caused by pancreatoduodenectomy.

*Pancreatic fibrosis correlates with exocrine pancreatic insufficiency after pancreatoduodenectomy.

*High surgical morbidity following distal pancreatectomy: still an unsolved problem.

*Pancreatic fistula after distal pancreatectomy: incidence, risk factors and management.

*Treatment of isolated pancreatic islets to reverse pancreatectomy-induced and insulin-dependent type I diabetes in humans: a 6-year experience.

2C16. General

(e.g., Blood Transfusion; Erythrocyte Transfusion; Reconstructive Surgical Procedures; Ablation; Catheter Ablation; Indwelling Catheters; Artificial Respiration; Surgical Anastomosis; Operative Surgical Procedures; Drainage; Minimally Invasive Surgical Procedures; Laser Therapy; Reoperation; Graft; Ligation; Shunt; Enteral Nutrition; Surgical Mesh; Lymph Node Excision; Parenteral Nutrition; Device Removal; Cryosurgery; Microsurgery; Tissue and Organ Harvesting; Sutures; Reoperation; Surgical Instruments; Intravenous Infusions; Suction; Surgical Stapling; Amputation; Resuscitation)

*Acute lung injury following blood transfusion: expanding the definition.

*A case of fatal graft-versus-host disease following blood transfusion in esophageal cancer documented by homozygous changes of HLA typing.

*Adverse effects of blood transfusion. 1. Posttransfusion hepatitis.

*A case of delayed massive hemothorax caused by the rupture of a pulmonary artery pseudoaneurysm after radiofrequency ablation of lung tumors.

- *A case of diaphragmatic hernia induced by radiofrequency ablation for hepatocellular carcinoma.
- *Acute fatal pulmonary vein occlusion after catheter ablation of atrial fibrillation.
- *A case of external iliac arteriovenous fistula and high-output cardiac failure after endovenous laser treatment of great saphenous vein.
- *Amaurosis after lower eyelid laser blepharoplasty.
- *Arterio-venous fistula following endovenous laser ablation for varicose veins.
- *Bilateral cataract and corectopia after laser eyebrow corrected epilation.
- *A case of inappropriate sinus tachycardia after atrio-ventricular nodal reentrant tachycardia cryoablation successfully treated by ivabradine.
- *Panniculitis due to alpha 1-antitrypsin deficiency induced by cryosurgery.
- *A case of delayed recurrent hemarthrosis after posterolateral reconstruction of the knee with a staple fixation at the lateral femoral epicondyle.
- *Early rectal stenosis following stapled rectal mucosectomy for hemorrhoids.
- *Cardiac morbidity and operative mortality following lower-extremity amputation: the significance of multiple Eagle criteria.
- *High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease
- *Mortality following lower extremity amputation in minorities with diabetes mellitus.

2C17. Other

(e.g., Chinese Herbal Drugs; Oral Contraceptives; Hormonal Oral Contraceptives; Vascular Endothelial Growth Factor; Fertilization in Vitro; Induced Abortion; Genetic Therapy; Assisted Reproductive Techniques; Ovulation Induction; Intrauterine Devices; Female Contraceptive Agents; Combined Oral Contraceptives; Ophthalmic Solutions; Contact Lenses; Bone Cements; Polymethyl Methacrylate; Nonprescription Drugs; Interferon-beta; Physical Stimulation; Antiemetics; Narcotic Antagonists; Prodrugs; Delayed-Action Preparations; Kainic Acid; Peroxyntirite)

- *A case of drug-induced pneumonitis associated with chinese herbal drugs and valsartan.
- *A case of ischemic colitis associated with the herbal food supplement ma huang.
- *Aconite poisoning over 5 years: a case series in Hong Kong and lessons towards herbal safety.
- *Acute hepatitis induced by Chinese hepatoprotective herb, xiao-chai-hu-tang.

- *A 21-year-old white woman diagnosed with cerebral venous sinus thrombosis related to oral contraceptive and Factor V Leiden.
- *Central retinal vein occlusion in young women: rare cases with oral contraceptive pills as a risk factor.
- *Oral contraceptive causing renal artery thrombosis.
- *A case of panic disorder induced by oral contraceptive.
- *Acute toxicity after high-dose systemic injection of helper-dependent adenoviral vectors into nonhuman primates.
- *Arthritis gene therapy's first death.
- *Genotoxicity of retroviral hematopoietic stem cell gene therapy.
- *A case report of acute interstitial nephritis associated with antibiotic-impregnated orthopedic bone-cement spacer.
- *Acute tissue toxicity of PMMA bone cements.
- *Allergic reaction to components of bone cement after total knee arthroplasty.
- *Acute respiratory distress syndrome associated with pulmonary cement embolism following percutaneous vertebroplasty with polymethylmethacrylate.
- *7-chlorokynurenic acid prevents in vitro epileptiform and neurotoxic effects due to kainic acid.
- *A blueberry-enriched diet provides cellular protection against oxidative stress and reduces a kainate-induced learning impairment in rats.
- *Acute effects of MK801 on kainic acid-induced seizures in neonatal rats.
- *Aged garlic extract inhibits peroxynitrite-induced hemolysis.
- *Curcumin attenuates peroxynitrite-induced neurotoxicity in spiral ganglion neurons.
- *Hydrogen peroxide- and peroxynitrite-induced mitochondrial DNA damage and dysfunction in vascular endothelial and smooth muscle cells.

There are many more classes of drugs identified than are shown here, and they cover the full spectrum of drugs. The most highly pervasive drug categories include antineoplastic agents, anti-infective agents, anti-inflammatory agents, cardiovascular agents, central nervous system agents, immunologic factors, hematologic agents, and steroids/ hormones. Moderately pervasive drug categories include antihypertensive agents, gastrointestinal agents, lipid regulating agents, dermatologic agents, vaccines/ vaccination, anti-bone-loss agents, antidiabetic agents, and antirheumatic agents. Pervasive drug categories include anti-allergic agents, anti-hypotensive agents, antithyroid agents.

There are many specific drugs identified with very high frequencies. The main message here is that drugs across the board are not benign. Individually, drugs can contribute to causing serious disease. Drug combinations (with both drugs and non-drugs) may have the potential to exacerbate the adverse effects of individual drugs through synergistic effects.

A substantial number of adverse effects/ complications from surgical and other treatment procedures are identified. These include both acute and longer-term chronic effects. The most highly pervasive surgeries include transplantation, cardiovascular, orthopedic, gastrointestinal, kidney/ urologic, and brain/ neural. Moderately pervasive surgeries include dental/ oral/ nose/ ear, gynecologic, respiratory/ thorax, and liver/ spleen. Pervasive surgeries include ocular, breast, dermal/ tissue/ neck, thyroid, pancreas, and general procedures. As in the case of drugs, these absolute numbers of complications must be considered in light of the numbers of procedures performed.

Radiotherapy has an extremely large number of side-effects/complications.

2D. Diagnostic Agents/ Procedures

2D1. Contrast Media

(e.g., Iodine)

- *A case of cardiac arrest with ST elevation induced by contrast medium.
- *A case of contrast-induced encephalopathy using iodixanol.
- *A case of idiopathic colitis developed after barium enema.
- *Acute kidney injury with iodinated contrast.
- *Acute hyperglycemia and contrast-induced nephropathy in primary percutaneous coronary intervention.
- *Acute orbital edema causing reversible blindness after the administration of intravenous contrast agent in a patient with thyroid eye disease.
- *Anaphylactoid reactions to radiocontrast media.
- *Case of fatal toxic epidermal necrolysis due to cardiac catheterization dye.
- *Contrast-induced transient cortical blindness.

2D2. Radiation

2D2a. Ionizing

(e.g., X-Ray Computed Tomography (CT))

- *An association between cerebral aneurysm re-bleed and CT angiography--more than a coincidence?
- *Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians.
- *Cancer risks from diagnostic radiology.
- *CT scans in childhood: leukaemia, brain tumours.
- *Risk estimates for meningiomas and other late effects after diagnostic X-ray exposure of the skull.
- *Leukemia among medical diagnostic X-ray workers in China.
- *Theoretical increase of thyroid cancer induction from cervical spine multidetector computed tomography in pediatric trauma patients.

There is a very extensive literature on radiation doses from CT scans, the dose-disease translation, and ways to reduce the dosage and eliminate unnecessary scans. There are also many papers on the adverse effects of the contrast media used as part of the CT scan, but since the taxonomy contains a category for contrast media, they are not included here.

2D2b. Non-Ionizing

(e.g., Magnetic Resonance Imaging (MRI))

- *An unusual burn during routine magnetic resonance imaging.
- *Arteriovenous fistula complication following MRI.
- *Deleterious effects of MRI on chondrocytes.
- *Efficacy of diphenhydramine in the prevention of vertigo and nausea at 7 T MRI.
- *Genotoxic effects of 3 T magnetic resonance imaging in cultured human lymphocytes.
- *Hearing loss after noise exposure.
- *Iatrogenic hyperthermia during cardiac magnetic resonance imaging.
- *MRI magnetic field stimulates rotational sensors of the brain.
- *Spontaneous dissociation during functional MRI experiments.

There were many papers addressing the impact of MRI on implantable devices, many of these impacts being adverse, but only biological issues were used for these examples.

2D3. Invasive

(e.g., Biopsy; Cardiac Catheterization; Colonoscopy; Bronchoscopy; Digestive System Endoscopy)

- *A case of iatrogenic tension pneumoperitoneum following colonoscopy in a patient with cytomegalovirus colitis.
- *Acute appendicitis caused by colonoscopy.
- *Acute colonoscopy-induced splenic rupture presenting to the emergency department.
- *Chilaiditi syndrome precipitated by colonoscopy: a case report and review of the literature.
- *Colonoscopy-induced ischemic colitis in patients without risk factors.
- *Fatal dysnatraemia caused by elective colonoscopy.
- *Fatal massive air embolism following diagnostic colonoscopy.
- *Hepatic injury following colonoscopy.
- *Ileocolic intussusception precipitated by diagnostic colonoscopy: a case report.
- *Mechanical small bowel obstruction precipitated by colonoscopy.
- *Tako-tsubo cardiomyopathy following colonoscopy: insights on pathogenesis.
- *An unusual complication during bronchoscopy: hypotension, global ST segment elevation, and acute severe left ventricular systolic dysfunction.
- *Bilateral pneumothorax after bronchoscopy without biopsy--a rare complication: case presentation and literature review.
- *Bronchoscopic suctioning may cause lung collapse: a lung model and clinical evaluation.
- *Cardiogenic shock secondary to Tako-tsubo syndrome after debridement of malignant endobronchial obstruction.
- *Uvular necrosis as an unusual complication of bronchoscopy via the nasal approach.
- *Double balloon endoscopy associated pancreatitis: a description of six cases.
- *Esophageal perforation as a complication of esophagogastroduodenoscopy.
- *Intramural duodenal hematoma after upper gastrointestinal endoscopy.
- *A case report of cerebral air embolism after esophagogastroduodenoscopy: diagnosis and management in the emergency department.

There are many papers on problems induced by the bowel preparation solutions prior to colonoscopy. The focus of the examples is on the problems induced by the mechanical procedure itself.

2D4. Other

(e.g., Diagnostic Errors)

- *Can rt-PA be administered to the wrong patient? Two patients with somatoform disorder.
- *Delay and misdiagnosis in sub-massive and non-massive acute pulmonary embolism.
- *Effects of disease misclassification on exposure-disease association.
- *Fatal outcome of belated diagnosis of an acral lentiginous melanoma.
- *Gleason pattern 5 is frequently underdiagnosed on prostate needle-core biopsy.
- *Mistakes in diagnostics and treatment of soft tissue sarcomas.
- *Overdiagnosis and mistreatment of malaria among febrile patients at primary healthcare level in Afghanistan: observational study.
- *Traumatic pulmonary arteriovenous fistula may be misdiagnosed with residual shunt after patent foramen ovale closure.

The main diagnostic sources are radio-contrast agents, especially iodinated agents, and the invasive procedures. The general category of diagnostic errors has some causative problems, but the major focus tends to be on worse outcomes as a result of missed diagnoses. Ionizing radiation, especially for treatment but even for diagnostics, is also causative.

3. BIOTOXIC AGENTS

3A. Mycotoxins

(e.g., Aflatoxin)

- *A rapid screening method to test apoptotic synergisms of ochratoxin A with other nephrotoxic substances.
- *A time-series study of sick building syndrome: chronic, biotoxin-associated illness from exposure to water-damaged buildings.
- *A toxicogenomics approach to identify new plausible epigenetic mechanisms of ochratoxin a carcinogenicity in rat.
- *Airway toxicity of house dust and its fungal composition.

*Cognitive impairment associated with toxigenic fungal exposure": a critique and critical analysis.

*2-(allylthio)pyrazine inhibition of aflatoxin B1-induced hepatotoxicity in rats: inhibition of cytochrome P450 2B- and 3A2-mediated bioactivation.

*5-Methylcytosine in CpG sites and the reactivity of nearest neighboring guanines toward the carcinogen aflatoxin B1-8,9-epoxide.

*Aflatoxin and hepatitis B virus biomarkers: a paradigm for complex environmental exposures and cancer risk.

*Aflatoxin B1 exposure, hepatitis B virus infection, and hepatocellular carcinoma in Taiwan.

3B. Exotoxins

(e.g., Lipopolysaccharides; Envenomation; Histamine; Amyloid; Amyloid Beta; N-Methyl-D-Aspartate; Retinoic Acid; Botulinum Toxin; Catecholamine; Collagen; Arginine; Albumin; Testosterone; Androgen; Thrombin; 4-hydroxy-2-nonenal; Excitatory Amino Acid Agonists; Glutamic Acid; Arachidonic Acid; Ovalbumin)

For purposes of the present analysis, a substance was considered an exotoxin if it was administered externally during experiments. Thus, amyloid beta, an endogenous substance, could be viewed as an endotoxin when internal processes are being discussed, but also as an exotoxin when given in laboratory experiments.

*1,8-cineol attenuates LPS-induced acute pulmonary inflammation in mice.

*A comparison of lipopolysaccharide-induced hepatitis in ethanol-fed Wistar and Lewis rats.

*A mouse model of severe acute pancreatitis induced by caerulein plus lipopolysaccharide.

*2-Deoxy-D-glucose reverses the Indian red scorpion venom-induced cardiopulmonary abnormalities in anesthetized rats.

*A case of neurotoxicity following envenomation by the Sidewinder Rattlesnake, *Crotalus cerastes*.

*A model for venom-induced consumptive coagulopathy in snake bite.

*A case of histamine poisoning related to the consumption of Iwashi preserved herring.

*A comparison of sevoflurane with halothane, enflurane, and isoflurane on bronchoconstriction caused by histamine.

*Histamine-induced coronary artery spasm: the concept of allergic angina.

*3-Nitropropionic acid exacerbates N-methyl-D-aspartate toxicity in striatal culture by multiple mechanisms.

- *N-methyl-D-aspartate (NMDA)-induced seizures in developing rats.
- *NMDA- and beta-amyloid1-42-induced neurotoxicity is attenuated in serine racemase knock-out mice.
- *1 alpha-hydroxyvitamin D3 inhibits type II collagen-induced arthritis in rats.
- *Collagen-induced thrombosis in large vessels using native prothrombotic substrates.
- *Collagen: a potential factor involved in the pathogenesis of glaucoma.
- *Enteral glutamine supplementation impairs intestinal blood flow in rats.
- *A preliminary experimental study on the cardiac toxicity of glutamate and the role of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor in rats.
- *Glutamate-induced cell death in HT22 mouse hippocampal cells is attenuated by paxilline, a BK channel inhibitor.

3C. Bacteria/Fungi/Parasites

(e.g., *Escherichia coli*; ***Staphylococcus aureus***; *Streptococcus*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Staphylococcus epidermidis*; *Staphylococcus*; *Mycobacterium tuberculosis*; *Pseudomonas aeruginosa*; *Salmonella*; *Aspergillus*; *Clostridium*; *Chlamydia trachomatis*; *Mycoplasma*; *Helicobacter pylori*; *Candida albicans*; *Streptococcus pneumoniae*; *Bacillus Calmette-Guerin*; *Klebsiella*; *Klebsiella pneumoniae*; *Campylobacter*; *Schistosoma*; *Yersinia*; Parasite; Vibrio Cholerae/Cholera)

- *2 newborn infants with septicemia caused by multiresistant *Streptococcus mitis*.
- *A case of infective endocarditis in a farmer caused by *Streptococcus equinus*.
- *A case of meningitis caused by *Streptococcus pyogenes* in a previously healthy woman.
- **Streptococcus viridans*-induced crystalline keratopathy and fungal keratitis.
- *A case of community-onset meningitis caused by hospital methicillin-resistant *Staphylococcus aureus* successfully treated with linezolid and rifampicin.
- *Acute lymphadenitis with cellulitis caused by *Staphylococcus lugdunensis*.
- *Acute lung injury induced by Staphylococcal enterotoxin B: disruption of terminal vessels as a mechanism of induction of vascular leak.
- *Fatal meningitis due to *Staphylococcus cohnii*. Case report.
- *A case of endocarditis caused by *Clostridium* entering through the gastrointestinal system.
- *A review of mortality due to *Clostridium difficile* infection.

- *Acute aortic dissection caused by Clostridium septicum aortitis.
- *A case of fatal disseminated infection caused by Mycobacterium bovis BCG strain and the identification of the isolate by spoligotyping.
- *Acute granulomatous tubulointerstitial nephritis caused by intravesical BCG.
- *A case with hepatitis and interstitial pneumonitis caused by intravesical bacillus Calmette-Guerin (BCG) instillation.

3D. Viruses

(e.g., Human Immunodeficiency Virus; Cytomegalovirus; Herpes Viruses; Human Herpesvirus 4; Hepatitis Virus; Hepatitis B virus; Epstein Barr Virus; Influenza Viruses; Adenovirus; Papillomavirus; Hepacivirus; Retrovirus; Human Herpesvirus 6; Human Herpesvirus 8; Human Herpesvirus 1; Human T-lymphotropic virus 1; Papillomaviridae; Parvovirus; Varicella Zoster Virus; Human Herpesvirus 3; Human Herpesvirus 2)

- *A case of arthritis caused by cytomegalovirus after kidney transplantation.
- *Acute pericarditis caused by cytomegalovirus in a normal host.
- *CMV antigenemia following bone marrow transplantation: risk factors and outcomes.
- *Cytomegalovirus-induced gastrointestinal disease in previously healthy adults.
- *Acute retinal necrosis caused by herpes simplex virus type 2 in children: reactivation of an undiagnosed latent neonatal herpes infection.
- *Herpes simplex virus-induced cardiomyopathy successfully treated with acyclovir.
- *Herpes simplex virus-induced epithelial damage and susceptibility to human immunodeficiency virus type 1 infection in human cervical organ culture.
- *A case of acute myocarditis caused by pandemic (H1N1) 2009 influenza virus.
- *2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States.
- *Acute epiglottitis caused by Haemophilus influenzae type b in children: presentation of 21 cases.
- *A Case of Associated Laryngeal Paralysis Caused by Varicella Zoster Virus without Eruption.
- *A delayed life-threatening complication after uneventful varicella infection: transient complete heart block.
- *Acute meningitis caused by reactivation of the varicella-zoster virus without cutaneous lesions. Contribution to the serologic diagnosis.

Bacteria and viruses were dominant in this class. Bacteria are somewhat ubiquitous, so the flexibility of cause removal for this sub-category is much less than for the Lifestyle and Iatrogenic categories. Unlike the Iatrogenic drug category, where the disease causative nature of the drug depended on whether the drug was used as a treatment for a specific disease, the causative nature of the bacteria and viruses was unambiguous. Almost every Title containing a bacterium or virus described a disease or symptom caused by the bacterium or virus. Thousands of examples could have been shown!

3E. Other

(e.g., *Toxic Plants*)

- *A review of the hepatotoxic plant *Lantana camara*.
- *Aortoesophageal fistula--an unusual complication of esophagitis caused by *Dieffenbachia* ingestion.
- *Case of colchicine intoxication caused by tubers of *Gloriosa superba*.
- *Chewing of betel, areca and tobacco: perceptions and knowledge regarding their role in head and neck cancers in an urban squatter settlement in Pakistan.
- *Full thickness burn caused by exposure to giant hogweed: delayed presentation, histological features and surgical management.
- *Genotoxic damage in Maras powder consumers from Kahramanmaras province of Turkey.
- *Grayanotoxin poisoning from *Rhododendron simsii* in an infant.
- *Hypotension, bradycardia and syncope caused by honey poisoning.
- *Unilateral mydriasis due to Angel's trumpet.

4. OCCUPATIONAL/ENVIRONMENTAL EXPOSURES

4A. Chemicals/Materials

4A1. Industrial/Household Chemicals/Materials

4A1a. Hydrocarbons

(e.g., *Benzo(a)pyrene*; Naphthalenes; Polycyclic Aromatic Hydrocarbons; Toluene; 7 12-dimethylbenz(a)anthracene; Petroleum)

- *A CASE-CONTROL STUDY OF ASPHALT AND TAR EXPOSURE AND LUNG CANCER IN MINORITIES.
- *Environmental polycyclic aromatic hydrocarbon (PAH) exposure and DNA damage in Mexican children.

- *Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons.
- *Carcinogenic potencies of polycyclic aromatic hydrocarbons for back-door neighbors of restaurants with cooking emissions.
- *7,12-dimethylbenzaanthracene-induced malignancies in a mouse model of menopause.
- *7,12-dimethylbenzaanthracene-induced 'early' squamous cell carcinoma in the Golden Syrian hamster: evaluation of an animal model and comparison with 'early' forms of human squamous cell carcinoma in the upper aero-digestive tract.
- *Obesity increases the incidence of 7,12-dimethylbenz(a)anthracene-induced mammary tumors in an ovariectomized Zucker rat model.
- *7,12-Dimethylbenz(a)anthracene-induced myelotoxicity differs in mice selected for high or low acute inflammatory response: relationship with aryl hydrocarbon receptor polymorphism.
- *Elevated cancer mortality in a German cohort of bitumen workers: extended follow-up through 2004.
- *CANCER INCIDENCE IN AN OCCUPATIONAL COHORT EXPOSED TO BITUMEN FUMES.
- *A common carcinogen benzo(a)pyrene causes neuronal death in mouse via microglial activation.
- *Cancer preventive potential of *Momordica charantia* L. against benzo(a)pyrene induced fore-stomach tumourigenesis in murine model system.
- *Capsaicin modulates pulmonary antioxidant defense system during benzo(a)pyrene-induced lung cancer in Swiss albino mice.
- *A mild progression type of naphthalene-induced cataract in brown-Norway rats.
- *Protective effect of *Coleus aromaticus* Benth (Lamiaceae) against naphthalene-induced hepatotoxicity.
- *Hemolysis from exposure to naphthalene mothballs.
- *Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction.
- *Developmental neurotoxicity after toluene inhalation exposure in rats.
- *Erythrospia following exposure to toluene.
- *A case-control study of leukemia among petroleum workers.
- *Cancer incidence of workers in the Swedish petroleum industry.

*Urinary bladder cancer and the petroleum industry: a quantitative review.

*Residential proximity to petroleum storage tanks and associated cancer risks: Double Kernel Density approach vs. zonal estimates.

*Polycyclic aromatic hydrocarbons in residential dust and risk of childhood acute lymphoblastic leukemia.

4A1b. Solvents

(e.g., Acetamides; Trichloroethylene; Methanol)

*Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites.

*OCCUPATIONAL TRICHLOROETHYLENE EXPOSURE AND KIDNEY CANCER RISK: A META-ANALYSIS.

*OCCUPATIONAL TRICHLOROETHYLENE EXPOSURE AND RISK OF LYMPHATIC AND HAEMATOPOIETIC CANCERS: A META-ANALYSIS.

*Preexistence of chronic tubular damage in cases of renal cell cancer after long and high exposure to trichloroethylene.

*A case of optic neuropathy after short-term linezolid use in a patient with acute lymphocytic leukemia.

*Acute oral poisoning due to chloracetanilide herbicides.

*First case of lacosamide-induced psychosis.

*A case of occupational hypersensitivity pneumonitis associated with trichloroethylene.

*EXPOSURE TO CHLORINATED SOLVENTS AND LUNG CANCER: RESULTS OF THE ICARE STUDY.

4A1c. Chemical Compounds

(Chlorine Compounds; Carbon Compounds; Carbon Monoxide; Carbon Dioxide; Sodium Compounds; Hydrogen Compounds; Hydrogen Peroxide; Hydrochloride Compounds; Silicon Compounds; Silica/Silicon Dioxide; Magnesium Compounds; Nitrogen Compounds; Nitrates/Nitrites; Manganese Compounds; Ethylene Compounds; Chromium Compounds; Sulfur Compounds; Sulfides)

*A case of hepatocellular carcinoma related with exposure to vinyl chloride monomers.

*A fatal case of hypermagnesemia caused by ingesting magnesium chloride as a folk remedy.

*Acute poisoning caused by chlorinated solvents.

***CARCINOGENIC HAZARD OF CHLOROFORM AND OTHER DRINKING WATER CHLORINATION BY-PRODUCTS.**

- *Cardiac arrhythmias induced by chloral hydrate in rhesus monkeys.
- *Neurotoxicity of allyl chloride in rats. Dose-effect relationship following long-term exposure.
- *A case of delayed post-anoxic encephalopathy after acute carbon monoxide poisoning.
- *A case of carbon monoxide poisoning presenting with supraventricular tachycardia.
- *Acute liver toxicity by carbon tetrachloride in HSP70 knock out mice.
- *Carbon tetrachloride-induced nephrotoxicity and protective effect of betaine in Sprague-Dawley rats.
- *Carbon dioxide-induced panic attacks and quantitative electroencephalogram in panic disorder patients.
- *Carbon dioxide-induced retinopathy in the neonatal rat.
- *Pulmonary embolism caused by CO₂.
- *Carcinogenic hazards from inhaled carbon black, titanium dioxide, and talc not containing asbestos or asbestiform fibers: recent evaluations by an IARC Monographs Working Group.
- *Nano-sized carbon black exposure exacerbates atherosclerosis in LDL-receptor knockout mice.
- *PNEUMOCONIOSIS IN CARBON BLACK WORKERS.**
- *Carbon disulfide exposure and neurotoxic sequelae among viscose rayon workers.
- *Cardiovascular disturbances in workers exposed to carbon disulfide.
- *A case of sodium bromate intoxication with cerebral lesion.
- *A severe case of interstitial nephritis caused by sodium valproate.
- *Adverse effects of sodium chloride on bone in the aging human population resulting from habitual consumption of typical American diets.
- *LUNG CANCER INCIDENCE AMONG NORWEGIAN SILICON CARBIDE INDUSTRY WORKERS: ASSOCIATIONS WITH PARTICULATE EXPOSURE FACTORS.**
- *Carcinogenic properties of silicon carbide whiskers.
- *A CD36 synthetic peptide inhibits silica-induced lung fibrosis in the mice.
- *Cancer mortality in women with probable exposure to silica: a death certificate study in 24 states of the U.S.

- *Association of indoor nitrogen dioxide exposure with respiratory symptoms in children with asthma.
- *Nitrogen dioxide is genotoxic in urban concentrations.
- *In vitro neurotoxic and DNA-damaging properties of nitrogen mustard.
- *Chromium-induced genotoxicity and interference in human lymphoblastoid cell (TK6) repair processes.
- *Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment.
- *Chromium (VI) induces insulin resistance in 3T3-L1 adipocytes through elevated reactive oxygen species generation.

This particular sub-category is very broad, and thousands of examples could have been generated, given the large numbers of these myriad chemical compounds in the literature. All the chemical types mentioned had copious adverse effects, especially compounds containing chlorine, nitrogen, chromium, and carbon.

4A1d. Other

(e.g., Chemical Water Pollutants; Arsenic; Dioxides; Asbestos; Phosphate; Selenium; Streptozotocin; Dioxin; Methyl Compounds; Ozone; Coal; Organophosphates; Polychlorinated Biphenyl/PCB; Hydrogen Sulfide; Sulfones; Coloring Agents; Mining; Bisphenol A; Xenobiotics; Tetrachlorodibenzodioxin; Endocrine Disruptors; Chemical Warfare Agents; Benzenesulfonates; Formaldehyde; Cosmetic Techniques; Ozone; Cosmetics; Fluorocarbons; Disinfectants; Nitrogen Dioxide; Polymers; Silicones; Carbon Tetrachloride; MPTP; Fluoride; Wood; Dextran Sodium Sulfate; Methylmercury; Phenol; Bromine; Arsenite; Tetradecanoylphorbol Acetate; Welding)

- *Abnormal development of motor neurons in perfluorooctane sulphonate exposed zebrafish embryos.
- *Acute and chronic toxicities of Irgarol alone and in combination with copper to the marine copepod *Tigriopus japonicus*.
- *A case of neuropathy mimicking Guillain-Barre syndrome after arsenic intoxication.
- *A case of scrotal superficial basal cell carcinoma caused by chronic arsenic exposure.
- *Asbestos-induced malignant pulmonary and pleural diseases.
- *Can features of phosphate toxicity appear in normophosphatemia?
- *Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin.
- *Dietary phosphate restriction ameliorates endothelial dysfunction in adenine-induced kidney disease rats.

- *Dioxin induces genomic instability in mouse embryonic fibroblasts.
- *Dioxin strongly immunotoxic.
- *Chloracne after exposure to dioxin.
- *Acute lung disease after exposure to fly ash.
- *Coal workers' pneumoconiosis with progressive massive fibrosis.
- *Carcinogenic effects of polychlorinated biphenyls (PCBs) and their derivatives, including carcinogenicity to the lung.
- *Polychlorinated Biphenyl (PCB) carcinogenicity with special emphasis on airborne PCBs.
- *Coal dust exposure and mortality from ischemic heart disease among a cohort of U.S. coal miners.
- *Lung cancer mortality is elevated in coal-mining areas of Appalachia.
- *Adverse effects of formaldehyde vapor on mouse sperm parameters and testicular tissue.
- *Bone marrow injury induced via oxidative stress in mice by inhalation exposure to formaldehyde.
- *1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in non-human primates is antagonized by pretreatment with nimodipine at the nigral, but not at the striatal level.
- *MPTP-induced duodenal ulcers in rat. Prevention by reuptake blockers for serotonin and norepinephrine, but not dopamine.
- *Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden.
- *Aluminum welding fume-induced pneumoconiosis.
- *Risk of lung cancer according to mild steel and stainless steel welding.

4A2. Agricultural Chemicals

(e.g., Pesticides; Herbicides; Insecticides; Triazines; Morpholines; Organophosphorus Compounds)

- *A case-control study on correlation of pesticide exposure with childhood acute leukemia.
- *Pesticide exposure and amyotrophic lateral sclerosis.
- *Pesticide exposure and risk for Parkinson's disease.
- *Acute fatal paraquat poisoning.

- *Paraquat- and rotenone-induced models of Parkinson's disease.
- *Paraquat-induced pulmonary fibrosis starts at an early stage of inflammation in rats.
- *Chlorpropham induces mitochondrial dysfunction in rat hepatocytes.
- *Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers.
- *Hepatotoxicity induced by sub-acute exposure of rats to 2,4-Dichlorophenoxyacetic acid based herbicide "Desormone loud".
- *Pesticide exposure and endocrine dysfunction in the cotton crop agricultural workers of southern Punjab, Pakistan.
- *DNA damage and cholinesterase activity in occupational workers exposed to pesticides.

The industrial, household, and agricultural chemicals are a major cause of disease. There were large numbers of chemicals identified, especially at lower frequencies. Many of these are ubiquitous in daily life, and eliminating exposure to them may be a challenge.

4A3. Materials

4A3a. Heavy metal

(e.g., Lead; Iron/Iron Overload; Zinc; Cadmium; Copper; Mercury; Lithium; Silver; Aluminum; Gold; Nickel; Titanium; Cobalt)

- *Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort.
- *Heavy metal poisoning: the effects of cadmium on the kidney.
- *Acute pulmonary toxicity and body distribution of inhaled metallic silver nanoparticles.
- *Potential health risks of heavy metals in cultivated topsoil and grain, including correlations with human primary liver, lung and gastric cancer, in Anhui province, Eastern China.
- *Roles of EGFR, PI3K, AKT, and mTOR in heavy metal-induced cancer.
- *Cancer mortality among female and male workers occupationally exposed to inorganic lead in the printing industry.
- *Acute cardiovascular toxic effects of copper in anesthetized rabbits.
- *Copper-induced immunotoxicity involves cell cycle arrest and cell death in the spleen and thymus.
- *Aluminum exposure and Alzheimer's disease.

- *Aluminum toxicity in patients with chronic renal failure.
- *Cardiac oxidative damage in mice following exposure to nanoparticulate titanium dioxide.
- *Asthma caused by hard metals: responsibility of titanium.
- *Acute exposure to cobalt induces transient methemoglobinuria in rats.
- *Cobalt chloride induces hepatotoxicity in adult rats and their suckling pups.
- *Carcinogenic nickel induces genes involved with hypoxic stress.
- *Carcinogenicity of nickel is the result of its binding to RNA and not to DNA.
- *LUNG CANCER RISK ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO NICKEL, CHROMIUM VI, AND CADMIUM IN TWO POPULATION-BASED CASE-CONTROL STUDIES IN MONTREAL.

4A3b. Particulates

(e.g., Dust; Air Pollutants; Occupational Air Pollutants; Traffic; Aerosols; Diesel Exhaust; Vehicle Emissions)

- *Ambient air pollution is associated with the increased incidence of breast cancer in US.
- *AMBIENT EXPOSURE TO CRITERIA AIR POLLUTANTS AND FEMALE LUNG CANCER IN TAIWAN.
- *AMBIENT EXPOSURE TO CRITERIA AIR POLLUTANTS AND RISK OF DEATH FROM BLADDER CANCER IN TAIWAN.
- *AIR POLLUTION FROM TRAFFIC AND CANCER INCIDENCE: A DANISH COHORT STUDY.
- *Accelerated silicosis in workers exposed to agate dust in Guangzhou, China.
- *Acute pulmonary alveolar proteinosis due to exposure to cotton dust.
- *Adenocarcinomas of the nose after exposure to wood dust.
- *Airborne occupational allergic contact dermatitis from coal dust.
- *Acquired dyschromatopsia among petrochemical industry workers exposed to benzene.
- *Acute respiratory health effects of air pollution on children with asthma in US inner cities.
- *Air pollution shortens life expectancy and health expectancy for older adults: the case of China.
- *Ambient air pollution alters heart rate regulation in aged mice.

4A3c. Nanotechnology

(e.g., Nanoparticles)

- *Acute inhalation toxicity of cerium oxide nanoparticles in rats.
- *Amorphous nanosilica induce endocytosis-dependent ROS generation and DNA damage in human keratinocytes.
- *An increase in mouse tumor growth by an in vivo immunomodulating effect of titanium dioxide nanoparticles.
- *Carcinogenicity of inhaled nanoparticles.
- *Cardiovascular effects of pulmonary exposure to titanium dioxide nanoparticles in ApoE knockout mice.
- *Nanoparticles and colloids as contributing factors in neurodegenerative disease.
- *Adverse effects of industrial multiwalled carbon nanotubes on human pulmonary cells.
- *Oxidative damage of single-walled carbon nanotubes in striatum and hippocampi of mice.
- *Teratogenicity of multi-wall carbon nanotube (MWCNT) in ICR mice.
- *Using carbon nanotubes to induce micronuclei and double strand breaks of the DNA in human cells.
- *Metallic nickel nanoparticles may exhibit higher carcinogenic potential than fine particles in JB6 cells.
- *Genotoxicity and carcinogenicity risk of carbon nanotubes.
- *Focal amplification of HOXD-harboring chromosome region is implicated in multiple-walled carbon nanotubes-induced carcinogenicity.
- *The carcinogenic potential of nanomaterials, their release from products and options for regulating them.

4B. Physical/Mechanical

4B1. Electromagnetic Radiation

4B1a. Ionizing

(e.g., Gamma Rays)

- *Repair of ionizing radiation-induced DNA damage and risk of second cancer in childhood cancer survivors.

- *Differential expression of cell adhesion molecules in an ionizing radiation-induced breast cancer model system.
- *Ionizing radiation-induced gamma-H2AX activity in whole blood culture and the risk of lung cancer.
- *Molecular characterisation of murine acute myeloid leukaemia induced by 56Fe ion and 137Cs gamma ray irradiation.
- *Gamma-ray-induced mutagen sensitivity and risk of sporadic breast cancer in young women: a case-control study.
- *Radiation-induced carcinogenesis: mechanistically based differences between gamma-rays and neutrons, and interactions with DMBA.
- *MicroRNA-21 is involved in ionizing radiation-promoted liver carcinogenesis.
- *Urinary bladder carcinogenesis induced by chronic exposure to persistent low-dose ionizing radiation after Chernobyl accident.
- *Risk factors for induction of breast cancer by X-rays and their implications for breast screening.
- *Enhanced risks of cancer from protracted exposures to X- or gamma-rays: a radiobiological model of radiation-induced breast cancer.

4B1b. *Non-Ionizing*

(e.g., *Electromagnetic Fields*; *Electromagnetic Fields Radiofrequency*)

- *RISKS OF CARCINOGENESIS FROM ELECTROMAGNETIC RADIATION OF MOBILE TELEPHONY DEVICES.
- *RESIDENCE NEAR POWER LINES AND MORTALITY FROM NEURODEGENERATIVE DISEASES: LONGITUDINAL STUDY OF THE SWISS POPULATION.
- *Disturbance of the immune system by electromagnetic fields-A potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment.
- *Potential health risks due to telecommunications radiofrequency radiation exposures in Lagos State Nigeria.
- *POOLED ANALYSIS OF CASE-CONTROL STUDIES ON MALIGNANT BRAIN TUMOURS AND THE USE OF MOBILE AND CORDLESS PHONES INCLUDING LIVING AND DECEASED SUBJECTS.
- *A population-based prospective cohort study of personal exposure to magnetic fields during pregnancy and the risk of miscarriage.
- *Exposure to magnetic fields and the risk of poor sperm quality.

- *Maternal exposure to magnetic fields during pregnancy in relation to the risk of asthma in offspring.
- *Acceleration of the development of benzopyrene-induced skin-cancer in mice by microwave-radiation.
- *Low-frequency electromagnetic-radiation enhances the induction of rat mammary-tumors by nitrosomethyl urea.
- *Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers.
- *Electromagnetic fields enhance chemically-induced hyperploidy in mammalian oocytes.
- *Exposure to a 50 Hz electromagnetic field induces activation of the Epstein-Barr virus genome in latently infected human lymphoid cells.
- *New data for proving the presence of significant effects of electromagnetic exposure (to autoimmune changes in rats).
- *A possible association between fetal/neonatal exposure to radiofrequency electromagnetic radiation and the increased incidence of autism spectrum disorders (ASD).
- *Autism-relevant social abnormalities in mice exposed perinatally to extremely low frequency electromagnetic fields.
- *Autism and EMF? Plausibility of a pathophysiological link - Part I.
- *Combined exposure of ELF magnetic fields and X-rays increased mutant yields compared with X-rays alone in pTN89 plasmids.
- *Microwave-radiation enhances the teratogenic effect of cytosine-arabinoside in mice.

4B1b1. Non-Visible

(e.g., Ultraviolet Rays; Ultraviolet B)

- *3-Aminobenzamide can act as a cocarcinogen for ultraviolet light-induced carcinogenesis in mouse skin.
- *A possible link between neural tube defects and ultraviolet light exposure.
- *A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma.
- *Action spectrum and recovery for in vitro UV-induced cataract using whole lenses.
- *Animal model of ultraviolet-radiation-induced recurrent herpes simplex virus infection.

*ASSOCIATION BETWEEN INCIDENCE OF NON-HODGKIN'S LYMPHOMA AND SOLAR ULTRAVIOLET RADIATION IN ENGLAND AND WALES.

*Does exposure to UV radiation induce a shift to a Th-2-like immune reaction?

*Facial nerve neuritis secondary to ultraviolet radiation.

*Ultraviolet irradiation induced brain oedema in rats. A microgravimetric study.

4B1b2. Visible

(e.g., Sunlight/Light; Laser)

*17beta-Estradiol Ameliorates Light-Induced Retinal Damage in Sprague-Dawley Rats by Reducing Oxidative Stress.

*ARE SOME MELANOMAS CAUSED BY ARTIFICIAL LIGHT?

*A case of linear immunoglobulin A bullous dermatosis in a patient exposed to sun and an analgesic.

*A case of tetany due to exposure to the sun

*A fatal case of sun exposure in a multiple sclerosis patient.

*Acute neuropathy after exposure to sun in a patient treated with St John's Wort.

*Allergic hypersensitivity skin reactions following sun exposure.

*Association between light exposure during the night and myopia in children.

*Blue light has a dark side. Light at night is bad for your health, and exposure to blue light emitted by electronics and energy-efficient lightbulbs may be especially so.

*Chronic exposure to dim light at night suppresses immune responses in Siberian hamsters.

*Circadian desynchrony and metabolic dysfunction; did light pollution make us fat?

*Clinical evidence for light-induced thermal damage in cortical cataracts.

*Dark nights reverse metabolic disruption caused by dim light at night.

*Fatal air embolism as a complication of laser-induced hyperthermia.

*A laser-induced mouse model of chronic ocular hypertension to characterize visual defects.

*Acute effects of anti-inflammatory drugs on neodymium:yttrium aluminum garnet laser-induced uveitis in dogs.

- *Anti-angiogenic effects of non-peptide integrin $\alpha v \beta 3$ specific antagonist on laser-induced choroidal neovascularization in mice.
- *Aqueous humor dynamics in monkeys with laser-induced glaucoma.
- *Argon laser-induced retinal herniation.
- *CO₂ and Nd:YAG laser-induced pulmonary parenchymal lung injury in a rabbit model.
- *Cortical microcirculation in a new model of focal laser-induced secondary brain damage.
- *Cutaneous lupus erythematosus following laser-induced thermal injury.

4B2. Sound

(e.g., Noise; Ultrasound)

- *0098 Occupational deafness due to co-exposure to noise and ototoxic agents.
- *0274 Occupational noise exposure and the prevalence of hyperglycemia.
- *Noise-induced perilymph fistula.
- *Noise-induced duodenal lesions: a light and electron microscopy study of the lesions of the rat duodenal mucosa exposed to low frequency noise.
- *Music: a new cause of primary spontaneous pneumothorax.
- *Myocardial fibrosis in rats exposed to low frequency noise.
- *Low frequency noise and stress: bronchitis and cortisol in children exposed chronically to traffic noise and exhaust fumes.
- *Cardiac arrhythmia and injury induced in rats by burst and pulsed mode ultrasound with a gas body contrast agent.
- *Cardiopulmonary function in rats with lung hemorrhage induced by pulsed ultrasound exposure.
- *Changes in mouse behavior induced by fetal exposure to diagnostic ultrasound.
- *Changes in Na and K ions in mouse liver following in vivo exposure to ultrasound.
- *Comparison of mouse and rabbit lung damage exposure to 30 kHz ultrasound.
- *Damage to cultured corneal endothelium caused by ultrasound during phacoemulsification.
- *Diagnostic ultrasound activation of contrast agent gas bodies induces capillary rupture in mice.
- *Hemolysis in vivo from exposure to pulsed ultrasound.

4B3. *Temperature; Heat/Cold*

(e.g., *Cold; Burn; Hypothermia; Hot Temperature; Cold Temperature*)

- *³¹P-magnetic resonance spectroscopic study on the effect of glycerol on cold-induced brain edema.
- *5-Hydroxytryptamine 1A receptors inhibit cold-induced sympathetically mediated cutaneous vasoconstriction in rabbits.
- *A breathing filter exchanging heat and moisture prevents asthma induced by cold air.
- *Acute estrogen administration can reverse cold-induced coronary Raynaud's phenomenon in systemic sclerosis.
- *Acute myocardial infarction induced by alternating exposure to heat in a sauna and rapid cooling in cold water.
- *Acute rhabdomyolysis due to prolonged exposure to the cold.
- *Angiotensinogen gene knockout delays and attenuates cold-induced hypertension.
- *Cold air-induced rhinitis.
- *Cold exposure exacerbates the development of diabetic polyneuropathy in the rat.
- *Cold-induced hyperthyroidism produces oxidative damage in rat tissues and increases susceptibility to oxidants.
- *0401 Repeated pre and post-shift urinalyses show kidney dysfunction among Costa Rican sugarcane cutters exposed to heat stress.
- *A possible role of NF-kappaB and HSP72 in skeletal muscle hypertrophy induced by heat stress in rats.
- *A single, mild, transient scrotal heat stress causes hypoxia and oxidative stress in mouse testes, which induces germ cell death.
- *Chronic heat stress weakened the innate immunity and increased the virulence of highly pathogenic avian influenza virus H5N1 in mice.
- *Heat-induced liver injury in old rats is associated with exaggerated oxidative stress and altered transcription factor activation.
- *Heat-induced squamous cell carcinoma of the lower extremities in a wildlands firefighter.
- *Mapping an X-linked locus that influences heat-induced febrile seizures in mice.
- *Placental glucose transport in heat-induced fetal growth retardation.

4B4. Force/ Pressure/ Physical Trauma

(e.g., Hypoxia; Hyperbaric Oxygen; Traumatic Brain Injury; Spinal Cord Injury; Vibration)

*Hypoxia-induced metastasis of human melanoma cells: involvement of vascular endothelial growth factor-mediated angiogenesis.

*150-kDa oxygen-regulated protein (ORP150) suppresses hypoxia-induced apoptotic cell death.

*15-Lipoxygenase promotes chronic hypoxia-induced pulmonary artery inflammation via positive interaction with nuclear factor-kappaB.

*Hypoxia-induced dysfunction in developing rat neocortex.

*A model for predicting central nervous system oxygen toxicity from hyperbaric oxygen exposures in humans.

*Acute respiratory distress syndrome after prolonged hyperbaric oxygen therapy: a case of pulmonary oxygen toxicity?.

*Brain blood flow modulates the neurotoxic action of hyperbaric oxygen via neuronal and endothelial nitric oxide.

*Central nervous system oxygen toxicity during routine hyperbaric oxygen therapy.

*Exogenously administered and endogenously produced melatonin reduce hyperbaric oxygen-induced oxidative stress in rat lung.

*Enhancement of glucose toxicity by hyperbaric oxygen exposure in diabetic rats.

*Focal status epilepticus induced by hyperbaric oxygen therapy.

*Genotoxicity of hyperbaric oxygen.

*A p1 aneurysm and diabetes insipidus caused by traumatic brain injury.

*A population-based study of risk of epilepsy after hospitalization for traumatic brain injury.

*A tension pneumocephalus caused by severe traumatic brain injury.

*Agrin expression during synaptogenesis induced by traumatic brain injury.

*Astereopsis caused by traumatic brain injury.

*0068 Occupational exposure to hand-transmitted vibration and risk of Dupuytren's contracture.

*A follow up study of vascular disorders in vibration-exposed forestry workers.

*Adverse effects of whole-body vibration on gastric motility.

- *Back disorders and health problems among subway train operators exposed to whole-body vibration.
- *Back pain and exposure to whole body vibration in helicopter pilots.
- *Vibration-induced nystagmus - A sign of unilateral vestibular deficit.
- *Vibration-induced carpal-tunnel syndrome.
- *Vibration-induced hearing loss: mechanical and physiological aspects.
- *Vibration-induced pulmonary disease: transformation of the bronchial mucosal epithelium and endothelium.

4C. Other

(e.g., Pets)

- *18 cases of asthma induced by hamster or guinea-pig bred as pets.
- *Asthma caused by a pet bat.
- *Dermatophytes transmitted by pets and cattle.
- *Ocular and subcutaneous dirofilariasis in a Sri Lankan infant: an environmental hazard caused by dogs and mosquitoes.
- *The danger of contracting salmonellosis from exotic pets.
- *Control of injuries caused by dogs: a public health perspective.
- *Outbreak of urban rabies transmitted by dogs in Santa Marta, northern Colombia.
- *Bite-related and septic syndromes caused by cats and dogs.
- *Zoonotic sporothricosis transmitted by cats in Rio de Janeiro, Brazil. A case report.
- *Zoonotic parasitosis transmitted by dogs in the Chaco Salteno, Argentina.
- *Cutaneous zoonoses transmitted by dogs and cats.
- *A study on wounds caused by cats as basic materials of cat scratch disease.
- *Dog and cat bite-associated infections in children.
- *Zoonoses transmitted by mouse and rat maintained as laboratory or pet animals.

The particles and different forms of radiation emitted to the environment are broadly-based, and in many cases have become part of the average lifestyle. Avoiding exposure to these

emissions (e.g., electromagnetic fields, vehicle exhausts, noise, metals in agriculture, etc) would require a major change in lifestyle (and probably location) for most people.

The 'Other' category was an amalgam of traumatic injuries due to pets and various diseases transmitted by pets (or animals in general). It could also have been placed in the appropriate Biotoxin sub-categories.

5. **PSYCHOSOCIAL/SOCIOECONOMIC**

5A. **Psychological**

(e.g., **Psychological Stress**; **Abuse**; **Child Abuse**; **Spouse Abuse**; **Combat**; **Fear**; **War**; **Work Schedule Tolerance**)

- *A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults.
- *Cardiovascular disease caused by earthquake-induced stress: psychological stress and cardiovascular disease.
- *Chronic psychological stress induces vascular inflammation in rabbits.
- *Psychological stress induces chemoresistance in breast cancer by upregulating mdr1.
- *Abuse and violence during home care work as predictor of worker depression.
- *Association of maternal exposure to childhood abuse with elevated risk for autism in offspring.
- *Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study.
- *Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study.
- *Clinical management of bladder dysfunction caused by sexual abuse.
- *Epileptic seizures induced by sexual abuse. Pathogenic and pathoplastic factors.
- *Migraine headaches induced by sexual abuse.
- *Adverse childhood experiences, posttraumatic stress disorder symptoms, and emotional intelligence in partner aggression.
- *Association between domestic violence and miscarriage: a population-based cross-sectional study among women of childbearing ages, Sivas, Turkey.
- *Association of various reproductive rights, domestic violence and marital rape with depression among Pakistani women.

There were large numbers of papers focused on variants of abuse, including child abuse, sexual abuse, and partner abuse. Most titles were insufficiently descriptive of health consequences of abuse.

5B. *Sociological*

(e.g., *Educational Status*)

*Cardiovascular risk factors in relation to educational level in 36 000 men and women in The Netherlands.

*Educational inequalities in the co-occurrence of mental health and substance use problems, and its adult socio-economic consequences: a longitudinal study of young adults in a community sample.

*Education and race-ethnicity differences in the lifetime risk of alcohol dependence.

*Education and the risk of Alzheimer's disease: findings from the study of dementia in Swedish twins.

*Education, occupation, noise exposure history and the 10-yr cumulative incidence of hearing impairment in older adults.

*Education, socioeconomic and lifestyle factors, and risk of coronary heart disease: the PRIME Study.

*Educational inequalities associated with health-related behaviours in the adult population of Singapore.

*Educational level and obstructive lung disease given smoking habits and occupational airborne exposure: a Norwegian community study.

*Effect of socioeconomic status on mortality after bacteremia in working-age patients. A Danish population-based cohort study.

*Health literacy is associated with healthy eating index scores and sugar-sweetened beverage intake: findings from the rural Lower Mississippi Delta.

*Low educational performance is associated with drunk driving: a 31-year follow-up of the northern Finland 1966 birth cohort.

*Maternal education is an independent determinant of cariogenic feeding practices in the first year of life.

*Maternal educational level and risk of gestational hypertension: the Generation R Study.

5C. *Economic*

(e.g., *Socioeconomic Factors*; *Socioeconomic Status*; *Poverty*)

- *Addictive diseases and poverty.
- *Assessment of interrelationship between poverty and blindness in Maiduguri, Nigeria.
- *Association between poverty and malaria in randomly selected families in Dar es Salaam.
- *Associations of educational attainment, occupation and community poverty with knee osteoarthritis in the Johnston County (North Carolina) osteoarthritis project.
- *Associations of neighborhood concentrated poverty, neighborhood racial/ethnic composition, and indoor allergen exposures: a cross-sectional analysis of los angeles households, 2006-2008.
- *Associations of subsite-specific colorectal cancer incidence rates and stage of disease at diagnosis with county-level poverty, by race and sex.
- *Cancer and poverty: breaking the cycle.
- *Cervical cancer, a disease of poverty: mortality differences between urban and rural areas in Mexico.
- *Diseases of poverty with high mortality in infants and children: malaria, measles, lower respiratory infections, and diarrheal illnesses.

Stress in all its variants was a major causative factor. Psychological stress in all its components was deleterious, and the sociological and economic types seemed to play less of a direct role.

6. GENETICS (Categories Only)

6A. Polymorphism/ Genotypes/ Haplotypes

6B. Mutations

6C. Linkages

6D. Risk alleles

6E. Genotoxicity

6F. Familial

6G. Congenital

Chapter 9

UNDER-REPORTING OF ADVERSE EVENTS

The previous chapters (1-8) focus on identifying and displaying the pervasive foundational causes of disease. The primary message these chapters convey is the foundational causes that can be extracted from the published literature are voluminous, and cover a wide swath. Their secondary message, which may be of equal importance, is there may be a large number of foundational causes that, for myriad reasons, have either not entered the published literature or have entered in distorted form.

The present chapter provides the reasoning and 'evidence' to support the latter assertions. It initially presents myriad reasons for foundational causes being absent from, or distorted in, the published literature, and follows the conceptual arguments with specific examples. The costs (and other consequences) of these omissions and distortions, both in human terms and financially, can be significant, as shown by one example in section [9C5](#).

Structurally, this chapter contains six sections. [9A](#), Technical Reasons for Under-Reporting of Adverse Events, focuses on technical/ text mining issues limiting the identification of foundational causes in the biomedical literature. [9B](#), Policy Implications of Under-Reporting of Adverse Events, focuses on (mainly) non-technical issues limiting foundational causes from entering the literature. [9C](#), Illustrative Examples of Under-Reporting of Adverse Events, provides some examples of how the research literature becomes deliberately deficient and distorted. [9D](#), Clinical Trials Implications of Under-Reporting of Adverse Events, shows deficiencies in clinical trials outcomes due to

- 1) insufficient attention devoted to identifying foundational causes experienced by the trial participants,
- 2) data deficiencies, and
- 3) oversight deficiencies.

[9E](#), Epilog, provides final thoughts on this chapter and its importance.

The first two types of limitations need to be considered especially when estimating the discrepancy between

- 1) foundational causes extracted from the published literature and
- 2) the full spectrum of foundational causes operating to produce the global disease burden.

9A. Technical Reasons for Under-Reporting of Adverse Events

The actual numbers of direct foundational causes identified in this book may be substantial under-representations of the total direct foundational causes that exist globally, for many operational reasons. Several key reasons for these under-representations are discussed in the following sections:

- 1) Absence from Database;
- 2) Text Mining Limitations;
- 3) Foundational Cause Differences among Diseases;
- 4) Indirect Foundational Causes;
- 5) Ease of Identifying Foundational Causes; and
- 6) Under-Representation of Foundational Causes.

9A1. Absence from Database

A foundational 'cause' for a disease will enter the Medline database only after it has been researched, a connection has been shown between the foundational cause and disease, and the foundational cause evidence has been published in the appropriate venue for Medline (neglecting articles with negative foundational 'cause' results). Thus, if a potential foundational 'cause' for a disease has not been researched, or its relevant data has not been entered into a tracking database, or has not been published in the appropriate venue, it won't show up in our studies as a foundational 'cause'.

The importance of a well-designed tracking database cannot be over-emphasized. It has been estimated that, in some cases, the poor reporting characteristic of passive surveillance databases could **under-represent potential causes by one or two orders of magnitude!**

(<http://www.whale.to/vaccines/ploy1.html>)

Additionally, as [6B](#) (the Background section on 'causes of multiple diseases') implies, there is a vast body of literature describing the under-reporting of adverse events. The under-reporting means that some foundational causes will not appear at all in the literature, and other foundational causes will be linked to only a sub-set of the actual number of diseases impacted.

9A2. Text Mining Limitations

The present text mining approach makes extensive use of both MeSH and text linking terms. Even if evidence of foundational cause has been published and is accessible in Medline, it may not show up as a foundational 'cause' in the approach used in this book (especially at the lower frequencies of occurrence), if it is not associated with the relevant linking terms that allow foundational 'causes' to be extracted algorithmically. The 'dot product' components of the queries, which intersect external lists of potential foundational causes with the full lists of MeSH

or text terms in the present source databases, are designed to circumvent this linking term limitation, to some extent.

Many articles have no MeSH terms assigned. The foundational 'causes' in these articles will not show up in either of our MeSH-derived databases. If the appropriate MeSH Qualifiers have not been assigned in the articles that do contain MeSH terms, the foundational 'causes' will not be identified through the extraction process in the MeSH Qualifiers-derived database. Similarly, if the Titles do not contain the appropriate linking terms, the foundational 'causes' will not be identified in the Titles text-derived database by the linking term component of the query. Neither the CRN database nor the (relatively) unambiguous MeSH Headings-derived database had linking terms. In both cases, only the highest frequency terms were inspected visually for evaluation of causality, and lower frequency terms were accessed through the 'dot product' extraction process mentioned above.

9A3. Foundational Cause Differences among Diseases

There seem to be some diseases and symptoms that include a wider spectrum of foundational causes. It may be there are more foundational causes of these diseases and symptoms, or that more research effort has been devoted to examining a wider range of foundational causes. Thus, the results can only show which items have been reported (and appropriately assigned) to be foundational causes of diseases and symptoms; the results cannot rule out that diseases without those items listed as foundational causes are in fact not caused (at least in part) by those items. **Given the linkages among the immune, neural, endocrine, circulatory, etc systems, one would expect some ripple-down effect from a foundational cause that impacted any one of these systems to the other systems, and therefore expect that an identified foundational cause of one disease would have impacts of different degrees on many diseases.**

9A4. Indirect Foundational Causes

One potential sub-set of unlisted or unidentified foundational causes constitutes what I have termed indirect foundational causes. In other words, these indirect foundational causes of a disease may be potential direct foundational causes of the disease that have not yet been identified through research. If this is true, having a systematic approach to identifying potential direct foundational causes of disease **would open up vast areas for future biomedical research.** This book presents such a systematic approach.

9A5. Ease of Identifying Foundational Causes

Some types of foundational causes may be under-represented in relation to more numerous foundational causes that are easier to research and identify. For example, the shorter the time elapsed between the foundational cause and the disease, the easier it is to make the connection. The stronger the effect of the foundational cause on the disease, the easier it is to extract the connection from the data. The more a foundational cause acts in a stand-alone mode, with less need for synergy with other foundational causes, the easier it is to connect the foundational cause with the disease(s). Conversely, the more a foundational cause acts in

synergy with myriad other causes, the more difficult it is to identify the contribution of any specific foundational cause to the disease.

Additionally, the less controlled the experiments for determining foundational cause, the more ambiguity and uncertainty in the data, and the less strong conclusions can be made about whether a foundational cause has been identified. Some foundational causes are more amenable to quantification, like known chemical or radiation or carcinogen exposures. Others are far more difficult to quantify, such as psychological or socioeconomic foundational causes, and therefore more difficult to connect to disease(s) with any degree of certainty. Finally, the more expensive the research required to identify a foundational cause, the fewer data that will be available to conclusively confirm that a foundational cause exists.

9A6. Under-Representation of Foundational Causes

Truly, in the detailed pervasive foundational causes data presented in [Chapter 8](#), *the absence of evidence is not evidence of absence*. All the foundational cause number bands presented should be viewed as threshold values, with the real number bands larger, and, in some cases, much larger. Given that some of the number bands of foundational causes are quite large despite the aforementioned obstacles, the extreme pervasiveness of these foundational causes must be inferred.

9B. Policy Implications of Under-Reporting of Adverse Events

9B1. Overview

This section provides more detail about under-reporting of adverse events and the larger issues of deficiencies and distortions in the premier biomedical published literature. This topic is sufficiently serious that any results and conclusions derived from analyses of the biomedical literature have to be placed within the context of the credibility of that literature. The following analysis in the present section is an evolution and expansion from two sources: a Letter to the Editor of JASIST [126], and a plenary presentation to a Forensic Science Research Evaluation Workshop on 26-27 May 2015, held in Washington, DC.

The larger issue is policy implications of an inadequate literature, where 'inadequacy' covers distortions, deficiencies, and any other weaknesses that drive a wedge between a fully credible literature and the partially credible literature that exists today. The analytic approach presented in this chapter consists of four sequential steps:

- 1) identify the characteristics of a literature adequate to support policy,
- 2) show how each of these characteristics gets degraded to an inadequate literature,
- 3) identify incentives for an inadequate literature, and
- 4) show policy implications of an inadequate literature.

The fifth step is not addressed, namely, identify amelioration strategies.

9B2. Inadequate Literature

9B2a. Characteristics of an Adequate Literature

Characteristics of an *adequate* literature for policy purposes include:

- 1) all critical research problems necessary for credible policy are addressed/ funded;
- 2) all research performed is credible and high quality;
- 3) all research findings are submitted for publication;
- 4) all high quality research submissions are published;
- 5) all published articles are available to the general public;
- 6) all accessible articles are easily retrieved.

Each of the above characteristics will now be examined, and those factors that degrade each characteristic to one representing an inadequate literature will be enunciated.

9B2b. Critical Research not Funded

Some critical research problems are not addressed/ funded, for myriad reasons:

- 1) the funds available to the sponsor organization are insufficient to cover all critical research areas;
- 2) the process for setting funding priorities within the sponsor organization is poor;
- 3) there are external pressures effectively limiting what topics can be funded, including
 - 3a) industry pressure to suppress topics that may have commercial sensitivity, and/ or
 - 3b) government pressure to suppress topics that may have political sensitivity.

The pressures may operate intra-organizationally or inter-organizationally.

9B2c. Research not Submitted for Publication

Some research findings are not submitted for publication, for myriad reasons:

- 1) the topic may have national security classification, or classification for other reasons;
- 2) the topic may be organizationally proprietary;
- 3) the organization or individual performing the research may have little or no publishing tradition, and have equally little motivation to publish;
- 4) there are costs associated with submissions for publication, both in time and money, which some organizations may not be willing to spend.

Most disturbing is the potentially deliberate suppression of research findings. This may result from:

- 1) negative findings, which many organizations/ journals/ researchers are reluctant to publish;
- 2) adverse events, which many industrial organizations in the biomedical community and, as will be shown, even some governmental organizations in the biomedical community, are reluctant to publish;
- 3) commercial sensitivity, which includes items 1) and 2) above, as well as other factors, all of which industry would rather not be published;
- 4) political sensitivity, which includes items 1) and 2) above, as well as other factors, all of which government would rather not be published; and,
- 5) unethical research, whose performers would rather not be published, and whose quality may be relatively low due to lack of research oversight and lack of reproducibility.

9B2d. Poor Research Published; Good Research not Published

Some research that enters the literature may be of low quality, due to:

- 1) poor peer review (where the peer review process and/ or the peer reviewers are of low quality) or no peer review;
- 2) contribution to the journal Editor's pre-determined agenda.

Some high quality research may not get published due to:

- 1) poor peer review or biased peer review;
- 2) non-contribution to the journal Editor's pre-determined agenda.

Additionally, some high quality research may not get published because the journal Editor does not view it as having the potential to increase the journal's Impact Factor. In recent years, the Impact Factor (one measure of a journal's papers' citability) has become an important objective. On many journal Web pages, the first item mentioned is the most recent Impact Factor.

While there are many determinants of a paper's citability [127], a key driver is the sheer number of researchers working in the topical field of the paper. All other things being equal, more researchers addressing a particular topic translates into more people potentially available to cite any paper on that particular topic. And, the number of researchers working on a particular topic is driven mainly by the funding available for that topic, which in turn is supplied primarily by the government and secondarily by industry. Thus, in the end, the Impact Factor and the citations are strongly influenced by the limited choice of sponsored topics of interest to government and industry.

In the biomedical community, as I showed in a citation analysis of a major medical journal [128] (but which applies to other medical journals as well), high-tech products garner the lion's share of citations. This includes high-tech drugs (large high-tech drug clinical trials receive, on average, the highest citations), high-tech surgery, high-tech diagnostics, high-tech therapy, etc. While high-tech products may have strong useful applicability to treating wounds and injuries, and for diagnosing wounds, injuries, and disease, it is less clear that they have equally strong applicability to the prevention and reversal of chronic disease. So, while high Impact Factor may be valuable for improving a journal's reputation, readership, and, especially, sponsorship, the value of high citations as a marker for identifying concepts that will aid in the prevention and reversal of chronic diseases is less than clear.

9B2e. Manufactured Research

Finally, some/ much research that enters the published literature may be deliberately distorted or skewed; I call such research "manufactured research". The purpose of this manufactured research is to both

- 1) counter publications showing adverse effects from specific products and
- 2) sow confusion among the public and decision-makers, not allowing the consensus required for policy.

The book *Merchants of Doubt* describes this research manufacturing process quite well [129]. A few illustrative examples of some of the more egregious misrepresentations of science mentioned above, especially suppressed and manufactured research, will be presented in the [next section](#).

9B2f. Published Research not Easily Accessible

Even for the good research that finally gets published, it may not be easily accessible to the public and the decision-makers. There are myriad reasons for this. The research may have been published in relatively obscure media, such as

- 1) a foreign language journal not in one of the major indexing databases, or
- 2) an obscure English language journal not contained in one of these major databases.

The research may have been published in a good journal, and it is behind a high paywall. For example, if a person does not have access to the Science Citation Index (SCI) through some home institution, the cost for accessing any non-open access full-text article is usually high, and if one needs to access many of these articles, the cost could be prohibitive. But, the SCI is only one example among many. The ethics of taxpayers supporting most of the basic research behind these paywalls, and being prohibited financially from accessing it, is the subject for a separate analysis.

Finally, even though the database is available to the analyst, the desired information may still be inaccessible due to poor search engines/ algorithms. This is an area in which I have worked for decades, and improving such algorithms has been a central feature of my research. Improved search algorithms are the bases of the text mining advances in both the present book and the preceding paper identifying foundational causes and treatments for chronic kidney disease [12].

9B2g. Incentives for Inadequate Literature

One reason for the existence of an inadequate literature is that there are many incentives for an inadequate literature.

For Industry, there are financial advantages (at least in the short-term) for concealing the adverse effects of their products and services.

For Government, the incentives are myriad. The Federal agencies are run by political appointees, who are sensitive to the interests of the political parties that appointed them. In many cases, it is in the career interests of these appointees to support corporate or individual large donor interests. At the lower levels in these Federal agencies, it is in the career interests of the managers and staff to support upper level management interests for advancement. For both upper and lower level bureaucrats, supporting corporate and large donor interests will also lay the groundwork for future industry employment.

For journal Editors, there are strong incentives to support corporate interests as well. Many journals are sponsored by professional societies or supported in part by advertising. In

turn, the professional societies tend to be supported strongly by industry. Sponsors and advertisers are not interested in articles adverse to industrial products.

For research performers, there exist incentives to contribute to inadequate literature as well. In the modern world of research, grants and publications are important for researcher advancement. Grants allow purchase of cutting-edge equipment, hiring of graduate students and post-docs, travel to conferences, etc. To have a continuous influx of grants, it is important to satisfy the interests of potential sponsors. This may exclude the possibility of working on critical questions/ issues whose answers are not desired by these potential sponsors. Moreover, it is important to satisfy existing sponsors in order to maintain the grants, which could lead to suppression and distortion of critical findings.

Further, in order to get published, it is necessary to satisfy journal Editors, which may involve not including results antithetical to the interests of the journal (and its sponsors or advertisers). Finally, if academic or industrial research performers want to lay the groundwork for future industry employment and/ or consultancies, it would not be in their best interests to publish findings antithetical to the interests of industry.

The latter issue of laying the groundwork for future employment should not be underestimated. When evaluating people to serve on research advisory panels, whether for peer review of future research investment strategy, peer review of proposals, peer review of programs, or journal manuscript peer reviews, the affiliations and relevant financial ties of prospective panelists are usually requested and stated, to identify and avoid potential conflicts-of-interest. However, stated affiliations can be very limiting and potentially misleading. Most important is to understand the reviewer's 'intent'. If the reviewer has no stated conflict-of-interest affiliations, but has plans to obtain grants or employment from some entity being involved with the review, then the outcome would be essentially pre-determined before the review. Stated affiliations, while useful, are only a part of the picture of conflicts.

In this section, I have identified the incentives (for an inadequate literature) for four classes: Industry, Government, Journal Editors, Research Performers. There are individuals who span multiple classes. For example, a person who works in government may also be a research performer and a journal Editor. The incentive (for an inadequate literature) associated with e.g. their government function may 'spill over' to their journal Editor and research performer roles. So, even though the journal may not have industry or government financial support as a source of potential bias, the potential biases arising from the government or research performer affiliations of the Editor could (in theory) influence the journal Editor role.

9B3. Policy Implications of Inadequate Literature

There are myriad important drivers of policy. The published literature, technical or otherwise, is only one of the drivers, and as will be shown, may not be the most important driver in many cases. For present purposes, the policymaker is assumed to be a government employee, whose organization at the highest level is headed by a political appointee(s), and who is therefore influenced by major political determinants: campaign donors and the electorate. For the

following discussion, then, the three critical drivers of policy considered will be technical literature, interests of political donors, and interests of the electorate.

Four options that relate policy to technical literature will now be examined briefly.

Option 1: The topical area is non-sensitive commercially or politically (e.g., weather satellite research). There is little incentive for much 'manufactured research'. Donors and voters would agree with policy dictated by adequate literature; donors and voters agree with policy dictated by inadequate literature; policy reflects literature.

Option 2: The topical area is non-sensitive commercially or politically (e.g., age of universe research). There is little incentive for much 'manufactured research'. Donors and voters would be indifferent to policy dictated by adequate literature; donors and voters would be indifferent to policy dictated by inadequate literature; policy reflects literature.

Option 3: The topical area is sensitive commercially and/ or politically (e.g., climate change amelioration; EMF health impacts [130]). There is incentive for much 'manufactured research', and my own studies have confirmed this. In this case, donors and voters would ***disagree*** with policy dictated by adequate literature. The donors are driven by profit, and the voters are addicted to the specific technology in this case (e.g., fossil fuels, wireless communications). Thus, donors and voters agree with policy dictated by inadequate literature.

In the case of e.g. EMF health impacts, the policy on EMF exposures that would be required by an objective reading of the credible technical literature (severe restrictions on the use of wireless communications, etc) would not be acceptable to the vast majority of donors and voters. And, in the case of e.g. climate change amelioration, the policy on CO2 emissions from fossil fuels that would be required by an objective reading of the credible technical literature (extremely severe restrictions on the use of fossil fuels for energy generation starting today, etc) would not be acceptable to the vast majority of donors and voters. Thus, the policy in practice reflects the interests of the donors and voters, not the dictates of an adequate technical literature.

Option 4: The topical area is sensitive commercially and/ or politically (e.g., exposures/ treatments that cause disease [12]). There is incentive for much 'manufactured research' in this case, and my own studies have confirmed this. In this case, donors would disagree with policy dictated by an adequate literature, whereas the voters would ***agree*** with policy dictated by adequate literature. The donors are driven by profit, whereas the voters are driven by the benefits of technology in this specific case. ***Unlike the previous option, the voters are not addicted to the technology, since its application may be unpleasant in many cases.***

The donors still agree with policy dictated by inadequate literature, whereas the voters agree with policy dictated by inadequate literature, ***only because they believe it is adequate.*** This means that some literatures may be highly manufactured to maintain voter support. The policy reflects donors, not adequate technical literature.

In conclusion, the published technical literature is inadequate for myriad reasons, and the degree of inadequacy is unknown and may be unknowable. The fraction of inadequacy due to

deliberate misinformation is unknown, but may be large for topical areas with commercial or political sensitivity.

9C. Illustrative Examples of Under-Reporting of Adverse Events

9C1. Industry

There are literally thousands of industrial products, processes, practices, and services that could be contributing factors to myriad diseases in isolation or in combination, as the results in this book have shown. It would be to the financial advantage of the responsible industries if the adverse effects resulting from these products, processes, practices, and services were concealed from the public and policymakers.

Myriad studies have been reported/ published showing how the science has been distorted by skewed literature, skewed panels, skewed media, etc. Unfortunately, such evidence of skewing and distortion is extremely difficult to obtain. Miscreants take great pains to conceal such wrong-doing, and many exposures of such activities are eventually revealed by whistle-blowers or through lawsuits. Because whistle-blowing tends typically to result in professional and financial suicide, only a very few are willing to risk the repercussions. Thus, most of the science distortions remain hidden from public view.

Further, because of potential media involvement in science distortion and concealment (as will be shown in some of the examples in the present section), public disclosure of these misdeeds may not necessarily occur in the mainstream media outlets or the most prestigious science and technical journals. As the reader will see, a few of the references I use are Web page URLs. While these types of references are frowned upon in mainstream journal publications, unfortunately (in some of the more egregious examples), these Web sites are the only media sources sufficiently courageous to challenge the distorted (or expose the concealed) messages promulgated by government and industry.

Two examples of distorted science/ literature will be presented: tobacco smoking and asbestos. Much of the incriminating evidence in both cases resulted from 'discovery' (in the legal sense) from lawsuits.

The extent of distorted science/ literature related to all industrial products and services is completely unknown at this point. It could range from

- 1) the modest number of industries already reported in the literature to have contributed to distorted science to
- 2) the thousands of industries behind the thousands of potential contributing factors reported in this book.

9C1a. Tobacco Smoking

Distortion of science by the tobacco industry has probably had the most extensive reporting and analysis. Due to the 'discovery' required by the numerous lawsuits filed against the tobacco industry, there has resulted a treasure-trove of internal documents made available for people to analyze. Many researchers have published analyses based on disclosure of these internal corporate documents.

Lisa Bero has written numerous articles on the distortion of science by the tobacco industry. The following two excerpts [131] are a representative brief summary of how the science was distorted.

"A report prepared by the Roper Organization for the Tobacco Institute in 1978 noted that the industry's best strategy for countering public concern about passive smoking was to fund and disseminate scientific research that countered research produced by other sources"

"Strategies that the tobacco industry uses to stimulate controversy about tobacco involve manipulating research at multiple stages. The tobacco industry, through its funding mechanisms, has attempted to control the research agenda and types of questions asked about tobacco.

The industry's lawyers and executives have been involved in the design and conduct of industry-supported research as well as the suppression of research that has not been favorable to the industry."

9C1b. Asbestos

Inhalation of asbestos fibers can lead to inflammation and scarring of the lungs. This could increase the risk of lung cancer and mesothelioma, and possibly other cancers as well. Many lawsuits have been filed by potential victims for compensation.

Legal 'discovery' similar to that obtained in the tobacco lawsuits was obtained from lawsuits against asbestos manufacturers. David Egilman has been one of the more prolific authors on distortion of science by the asbestos and related corporate community. An excerpt from a recent paper [132] states:

"MetLife established itself as an authority in public and industrial health in the early part of the twentieth century, gaining the trust of the public and government. They were able to use this trust and authority to avoid financial loss, including the firing of sick workers, and avoid legal liability by organizing a network of experts to testify on their behalf in silica- and asbestos-related damage suits. They further manipulated the results of scientific findings from major research institutions, delaying important knowledge about the asbestos-cancer relationship."

9C2. Government

Because of the close and 'revolving-door' relationships between many government agencies and industry, some of the incentives to distort and conceal science become applicable to government as well. Additionally, some technologies become critically important for government to conduct operations, and science can become distorted or concealed if the government places higher priority on continuance of the operations than on e.g. safety aspects.

In this section, three brief examples of potential government distortion of science are presented: [EPA](#), [CDC](#), and [FDA](#).

9C2a. EPA

In 1993, EPA generated a sludge rule that allows biosolids, or treated sewage sludge, to be used for different types of lands (farms, forests, playgrounds, parks, etc) [133]. These biosolids contain very toxic ingredients, in high concentrations, and have the potential for causing myriad types of damage. Dr. David Lewis, a whistle-blower and ex-EPA senior researcher, exposed how EPA, in coordination with other Federal Agencies, research institutions, and advisory groups, suppressed public knowledge of these potential adverse effects for years [134].

He initially did this exposure through published research articles. Later testimony and depositions before Congress, before Department of Labor hearings, and during lawsuits revealed (under oath) the detailed participation of EPA officials and others in the science distortions. Dr. Lewis was forced to retire and, in 2014, published a book (recounting his experiences) entitled *Science for Sale* [134]. Lewis:

- 1) implied that EPA-sponsored research had to support EPA policy;
- 2) implied that there was selective funding of scientists who supported EPA's sludge rule;
- 3) showed myriad ways the science was distorted to present biosludge as safe;
- 4) showed collusion among EPA and other Agencies.

The book is unique in its portrayal of collusion among the diverse groups mentioned in its sub-title: "*How the US Government Uses Powerful Corporations and Leading Universities to Support Government Policies, Silence Top Scientists, Jeopardize Our Health, and Protect Corporate Profits*". The biosludge example presented here, the example of the MMR vaccine in the next section, and the example of EMF adverse effects from my detailed study [130] provide strong evidence that what we have operating (in these commercially and politically sensitive issues) is a **Government-Industrial-Media-Complex** that monopolizes the discourse and exerts strong influence on what the public knows and believes about these topics.

Dr. Lewis has only scratched the surface of the research required to show the full extent of adverse impacts of biosludge. The application of biosludge does not occur in a vacuum. There are various pesticides, herbicides, and other potentially harmful chemicals applied to many of these biosludge-covered lands, depending on usage. Location in polluted water and polluted air areas adds other layers of pollution and uncertainty. There could be many types of pollutants operating synergistically with the biosludge to enhance damage; decoupling the influence of the biosludge would be a complex process. One would have to identify the relevant windows in parameter space in which adverse events occurred, and an enormous number of tests would have to be performed to identify these windows, since the multi-causal problem is combinatorial in nature. We found this to be the case in our EMF health impacts study [130], and it would be conceptually similar for biosludge.

Additionally, there could be adverse impacts on human beings (from these combinations of foundational causes that include biosludge as one contributing factor) that do not show up for years, or decades. For example, latency periods for many cancers are on the order of decades.

As another example, latency periods for serious diseases following relatively innocuous food poisoning may be years or decades [135].

From first principles, why should we expect less from biosludge? Health studies of many disease causative factors are done for a relatively short period compared to a human being's lifetime. Long-term studies on short-lived animals might or might not be relevant for humans. Long-term studies (of many potential foundational causes) on humans remain to be done, and biosludge is no exception.

9C2b. CDC

9C2b1. CDC senior researcher allegations

On 27 August 2014, the following excerpted statement by Dr. William Thompson (a CDC Senior Researcher) appeared on the Web site of Morgan Verkamp, LLC, a legal organization representing Dr. Thompson [136].

*"I regret that my coauthors and I omitted statistically significant information in our 2004 article published in the journal Pediatrics. **The omitted data suggested that African American males who received the MMR vaccine before age 36 months were at increased risk for autism.** Decisions were made regarding which findings to report after the data were collected, and I believe that the final study protocol was not followed....."*

*My concern has been the **decision to omit relevant findings in a particular study for a particular sub- group for a particular vaccine.** There have always been recognized risks for vaccination and I believe it is the responsibility of the CDC to properly convey the risks associated with receipt of those vaccines.*

I have had many discussions with Dr. Brian Hooker over the last 10 months regarding studies the CDC has carried out regarding vaccines and neurodevelopmental outcomes including autism spectrum disorders. I share his belief that CDC decision-making and analyses should be transparent. I was not, however, aware that he was recording any of our conversations, nor was I given any choice regarding whether my name would be made public or my voice would be put on the Internet....."

I will not be answering further questions at this time. I am providing information to Congressman William Posey, and of course will continue to cooperate with Congress. I have also offered to assist with reanalysis of the study data or development of further studies. For the time being, however, I am focused on my job and my family."

Dr. Hooker had approximately thirty phone conversations with Dr. Thompson, the last four of which were recorded by Dr. Hooker without Dr. Thompson's knowledge or approval. Excerpts from some of these recorded conversations have been placed on the Web.

Not only were the African-American children who received the MMR vaccine at substantially greater risk for autism (as alleged by Dr. Thompson), but, according to Dr. Hooker,

Dr. Thompson mentioned that children of all races were shown to have an increased risk of **'Isolated Autism'**

(young children, regardless of race, who had

- 1) received the MMR vaccine on schedule, as recommended by the CDC, and
- 2) had no other factors sometimes observed to accompany autism, such as cerebral palsy, mental retardation, and birth defects.).

The MMR vaccine-autism study to which Dr. Thompson referred had been performed shortly after the turn of the new millennium, and the stated results (no link between MMR vaccine and autism) had been published in the journal *Pediatrics* in 2004 [137]. As of 1 August 2015, the article has not been retracted by *Pediatrics*, despite the serious allegations of intentional omission of critical data by one of its co-authors.

Thus, according to Dr. Thompson's allegations of 27 August 2014 (which have yet to be made (under oath) in an adversary proceeding such as a Court of Law or a Congressional Hearing), CDC had known for at least a decade that these two groups of children were at increased risk for autism from the MMR vaccine, and did not disclose this information to the public. Internal CDC memos released (again, which have yet to be presented in some type of adversary proceedings) also showed the highest levels of CDC management had been informed of these problems with the MMR vaccine since the early 21st century (<http://www.marketwatch.com/story/cdc-epidemiologist-whistleblower-confirms-new-review-showing-vaccine-autism-link-2014-09-11>).

According to Dr. Thompson's statement above, thousands of documents have been turned over to Congress. Dr. Thompson has been awarded immunity to testify before Congress, but, as of this writing (almost one year after Dr. Thompson's statement), Congress has not yet scheduled a Hearing.

However, on 29 July 2015, as this book was about to go to press, the Congressman to whom Dr. Thompson provided the documents, Rep. William Posey (R-FL), made a five minute speech on the Floor of the House (<https://www.youtube.com/watch?v=qxr-cv-JuI8>). He stated, in part (quoting from Dr. Thompson's own words):

"At the Sept 5th meeting we discussed in detail how to code race for both the sample and the birth certificate sample. At the bottom of table 7, it also shows that for the non-birth certificate sample, the **adjusted race effect statistical significance was huge**.

'All the authors and I met and decided sometime between August and September 2002, not to report any race effects from the paper. **Sometime soon after the meeting, we decided to exclude reporting any race effects. The co-authors scheduled a meeting to destroy documents related to the study. The remaining four co-authors all met and brought a big garbage can into the meeting room, and reviewed and went through all the hardcopy documents that we had thought we should discard, and put them into a huge garbage can.** However, because I assumed it was illegal and would violate both FOIA and DOJ requests, I kept hardcopies of all

documents in my office, and I retain all associated computer files. ***I believe we intentionally withheld controversial findings from the final draft of the Pediatrics paper.***"

Because of the gravity of this revelation, and the added credibility of Dr. Thompson's allegations provided by a Congressman's endorsement on the Floor of the House, I decided to add an estimate of the human and financial costs that might result from this alleged withholding of critical information. Section [9C5](#) addresses the potential consequences of this information having been withheld intentionally (assuming Dr. Thompson's allegations are validated).

9C2c. FDA

Charles Seife is a journalism Professor at New York University. He performed a study whose objectives were "to identify published clinical trials in which an FDA inspection found significant evidence of objectionable conditions or practices, to describe violations, and to determine whether the violations are mentioned in the peer-reviewed literature." [138]. He examined "publicly available documents, dated from January 1, 1998, to September 30, 2013, describing FDA inspections of clinical trial sites in which significant evidence of objectionable conditions or practices was found." He found that "only 3 of the 78 publications (4%) that resulted from trials in which the FDA found significant violations mentioned the objectionable conditions or practices found during the inspection. No corrections, retractions, expressions of concern, or other comments acknowledging the key issues identified by the inspection were subsequently published." He concluded that "when the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct." He provided additional perspective in a Slate magazine article [139].

In an interview with Truthout magazine [140], Dr. Ronald Kavanagh, a former drug reviewer for the FDA in the Center for Drug Evaluation and Research, describes some FDA safety shortcuts. His comments complement the findings of Dr. Seife above, and both sets of comments reflect both

- 1) good research not reaching the open literature and
- 2) distorted findings being published.

9C3. Journals

This section will present one example of alleged journal bias on publishing adverse effects. As the reader will see, obtaining data to support allegations of bias is extremely difficult in this case, and validating allegations would be even more difficult.

Dr. Lous Slesin has been publishing a newsletter addressing myriad issues related to microwave radiation, and it is aptly entitled 'Microwave News' (MN). I came across this newsletter during the course of our EMF health impacts study [130], and found the MN articles were quite accurate in the areas where they overlapped our study.

In 2006, MN published an article entitled “Radiation Research” and The Cult of Negative Results [141]. It was a unique study with major contributions from Dr. Henry Lai, a leading researcher in the technical area of the article. The study's focus was essentially to ascertain how reflective of the microwave-induced genotoxicity publications in the larger technical literature were those published in the journal Radiation Research on this topic.

In short, MN found that:

- 1) [In the larger technical literature on microwave-induced genotoxicity] "There is just about an even split between effect and no-effect papers";
- 2) "A clear —and disconcerting— pattern emerges: 32 of the 35 studies that were paid for by the mobile phone industry and the U.S. Air Force show no effect. They make up more than 75% of all the negative studies. You don't need to be a statistician to infer that money, more often than not, secures the desired scientific result";
- 3) "A similar loss of balance occurs when you look at only the papers published in Radiation Research.....Over the last 16 years, only one positive paper on microwave genotoxicity has appeared in Radiation Research. During the same time, the journal has published 21 negative genotox papers. (Australia's Pam Sykes, the lead author of the lone positive paper, was denied money for a follow-up and soon moved on to other research areas.)....80% of the negative papers (17 out of 21) published in Radiation Research were paid for by either industry or the U.S. Air Force." [141].

At this point, the statements in MN are only *allegations*. There could be journal bias, or the best papers submitted to the journal happen to be the ones showing the absence of an impact of microwaves on genotoxicity. How could this issue be resolved?

One could (in theory) obtain the original peer reviews of all the manuscripts submitted to the journal on this topic, and re-evaluate them for bias. Unfortunately, we would then have the issue of determining the biases of the second group of reviewers. This cannot be determined easily. Information on organizational and financial conflicts-of-interest might be available as suggestive of potential bias, but such information is incomplete and perhaps the tip of the iceberg. The real metric is 'intent' of the reviewers; how does one measure 'intent'? If a reviewer has a clean 'paper trail' in terms of potential conflicts, but hopes to apply for industry funding, consultation, or employment in the future, would that not affect his actions relative to a technology of interest to a company?

Additionally, even for reviewers who are unbiased, there is not always complete agreement. Scientists can sometimes have very differing opinions on the value of the same concept. Proving deliberate bias for a journal is extremely difficult, and may border on the impossible in practice.

I would, however, recommend that the reader access the MN article and read it carefully. It is one of the very few of this genre that one will see in print, and covers a wide range of issues

related to potential bias. How well this particular example reflects all, or any, other technical/ biomedical journals is unknown.

9C4. Researchers

One example will be provided. In 2010, a book titled *Merchants of Doubt* [129] was published. This well-documented landmark publication examined myriad high-sensitivity technical issues, including smoking, climate change, acid rain, ozone hole, and DDT. It showed how disinformation was promoted using well-known scientists and front organizations. The disinformation was promoted through think tanks, government panels, and all types of media including the research literature. The biosludge example presented in section 9C2a can be viewed as one example of how this disinformation is promoted/ disseminated. The purpose of this disinformation is to spread confusion and promote doubt, thereby delaying any policy for action due to the (manufactured) absence of a consensus.

9C5. Consequences of Under-Reporting of Adverse Events

Consequences of under-reporting or distorted reporting of adverse events could include:

- 1) the numbers of people who become afflicted as a result of insufficient knowledge or distorted knowledge produced by the under-reporting;
- 2) the numbers of people who die prematurely;
- 3) the financial costs borne by the afflicted and/ or by society, etc.

If the under-reporting is deliberate, and it becomes known to the public that it is deliberate, then a serious additional consequence could be potential loss of credibility of the under-reporting organization in the eyes of the public. If the under-reporting organization is a government Agency, the potential loss of credibility could be disastrous!

For some of the examples presented in section 9C, the numerical estimates of potential damage may be quite large, but are rarely, if ever, provided. And, even for advertised compensations awarded, the actual costs may not be reflected in any settlements.

9C5a. Magnitude of impact of alleged CDC intentional withholding of critical information

9C5a1. Domestic Impact

I will end section 9C with some estimated economic and health consequences of one of the lesser-known examples outlined [previously](#): CDC intentional withholding of critical information (alleged by Dr. William Thompson, CDC) in order to not inform the public about sub-groups who have higher risk for autism from the MMR vaccine. The assumption here is that Dr. Thompson's allegations [136] about CDC's intentional withholding of the adverse effects of the MMR vaccine relative to autism will be validated. This section on estimated economic and health consequences of the CDC's alleged actions is relatively long and detailed compared to any of the other examples in 9C, and the estimated costs are extremely high.

The alleged intentional withholding of the link between the MMR vaccine and autism (the link being found in the very early 21st century by the CDC's study) resulted in many children (from specific sub-groups) being placed at higher risk for autism. These children could have minimized this risk (had their parents been informed of the potential increased risk) through either alternative vaccinations, modified vaccination schedules, or no vaccinations. Thus, there were potentially more children who suffered from autism as a result of the alleged intentional withholding of this critical information, and there were resulting health and economic consequences that accompanied the additional potential cases of autism.

The potential economic cost resulting from this alleged intentional withholding of critical information is the product of the number of children afflicted times the cost per victim. Given that:

- 1) Dr. Thompson has not released the documentation supporting his specific findings to the general public (but only to Congress, and perhaps other selected individuals),
- 2) Congress has not held Hearings on Dr. Thompson's allegations yet, and none have been scheduled,
- 3) there have been essentially no investigations into Dr. Thompson's allegations reported by the mainstream news media,

then, obtaining primary source estimates of the number of children placed at higher risk for autism because of the alleged CDC intentional withholding of critical information becomes extremely difficult. I am left with selecting the most credible secondary sources for these estimations, and will mention two secondary sources.

On 25 June 2015, Robert F. Kennedy, Jr published an Open Letter on Eurweb [142] stating: "Based upon all the population data and CDC's most recent autism incidence estimates, at least 100,000 African-American male children could have been spared debilitating neurological injury if the CDC scientists had told the truth when the increased risk was first known to them in 2001."

Kennedy has:

- 1) been studying the problem of adverse vaccine impacts for years,
- 2) access to credible experts on this topic,
- 3) discussed Dr. Thompson's revelations with Congressional staffers who have seen the documentation Dr. Thompson gave to Congress,
- 4) recently published a book (with two M.D.s) on the adverse effects of Thimerosal in vaccines, and
- 5) co-authored an upcoming book on the alleged CDC misconduct addressed here (Vaccine Whistleblower: Exposing Autism Research Fraud at the CDC)

(<http://www.ageofautism.com/2015/08/new-book-from-skyhorse-publishing-vaccine-whistleblower-exposing-autism-research-fraud-at-the-cdc.html#comments>).

Another secondary source is a Web site author [143]. The principal of this site has computed the number of African-American children placed at higher risk of autism, based on her interpretation of the increased risk numbers that Dr. Thompson presented on his lawyer's site. The principal has presented all the computational details of her estimate on the referenced site, and she arrives at (in her estimation) a conservative estimate of 250,000 African-American children at increased risk due to the CDC's alleged intentional withholding of critical information.

Kennedy has not provided the computations used to generate the 100,000 African-American injured children estimate, so the two sets of computations cannot be compared. The discrepancy between the estimate in [143] and that of Kennedy may be due to the differing interpretation of the increased risk suggested by Dr. Thompson. For purposes of my analysis, I will take the *far more conservative* estimate of Kennedy.

I start with an estimate of 100,000 African-American children who developed autism (between 2001 and 2015) due to the CDC's alleged intentional withholding of its findings of increased risk starting about 2001. The human costs are more than mere statistics. The 100,000 are innocent human beings who, in many cases, could have become great artists, engineers, doctors, lawyers, etc, and who were robbed of these opportunities because critical information was allegedly withheld by the CDC.

The next question is: what are the economic costs associated with these 100,000 additional cases of autism? There are at least three main components of potential cost:

- 1) the cost of care for an autistic person;
- 2) the cost of medication and other medical treatments and services for an autistic person;
- 3) the wages lost over a lifetime by an autistic person.

A 2014 study [144] estimates a *lifetime* cost for a person (in the USA) with autism on the order of \$1.4 to 2.4M (depending on the level of seriousness of the disease). However, as stated in the body of the full-text of [144] (but not in the Abstract), these numbers are *discounted present values*, using a discount rate of 3.5%. For each age group examined (0-5; 6-17; >=18), the authors assume a *mean annual cost for each age group, held constant over the age group period*. So, for example, for adults with intellectual disability in the USA, the authors assume an annual mean cost of ~\$88K per year, constant for ~50 years.

I have two major problems with the results:

- 1) the numbers used for the cost streams are low;

2) use of a discount rate of 3.5% for computing present value, in parallel with the assumption of living accommodation and medical costs constant over decades, is neither realistic nor consistent internally.

For problem 1), one of the cost stream components in [144] is 'productivity loss', which is essentially lost wages from having autism and being unable to work the same way as a person without autism. From Table 4 [144], the 'productivity loss' for an adult 'individual with ASD', with Intellectual Disability, from the USA, is \$10,718 per year. This number is slightly over \$5.00 per hour for full-time employment, or about 2/3 of the USA minimum wage! For a severely disabled person, who would reflect the upper end of the lifetime autism cost range (estimated at ~\$2.4M in [144]), it would seem more realistic to use the median USA wage (of ~\$28K per year) as the 'productivity loss'. That is more than double the 'productivity loss' stream used in [144] to estimate costs! Some of the other cost stream components used are underestimated as well.

For problem 2), given the increases in healthcare and assisted-living costs over the past few decades, one would expect to see projected healthcare and assisted-living accommodation costs rising far faster than 3.5% per year. For example, a study published recently (in Health Affairs by economists in the Office of the Actuary at the Centers for Medicare and Medicaid Services) projected healthcare costs to rise an average of 5.8% over the next decade [145]. Further, the potential of rapidly increasing health insurance premiums could portend even substantially higher growth in health care costs [146].

A 2015 study [147] on autism costs effectively cancels out growth rates and discount rates by assuming a discount rate of zero (no discounting): "Because both the burden and GDP grow over time, we do not apply discount rates. We assume a societal perspective."

Assuming healthcare and assisted-living accommodation costs to be inflating at the discount rate is more realistic for autism cost projections than the approach used in [144], although still very optimistic. If we sum an undiscounted cost stream to arrive at total lifetime costs, using the annual costs stated in [144], the total (very optimistic) undiscounted lifetime costs for the high end in the USA are ~\$6M. Given the unrealistically low numbers the authors also use for annual 'productivity loss' et al, the *real* lifetime costs (at the high end, for the USA) are at least triple those presented by the authors. For purposes of the present cost estimates, I will use a much more *conservative* estimate of twice the [144] authors' published numbers, with a mean of about \$4M lifetime cost per capita for all USA autism afflicted. As I will show in the next paragraph, both the \$4M conservative lifetime cost per capita and the \$2M extremely conservative lifetime cost per capita (based on the numbers in [144]) result in *astronomical* total costs.

For 100,000 African-American children in the USA over the period 2001-2015, using the approximate mean lifetime cost per capita of \$4M from the above computations yields a total *lifetime* cost for the sub-group of roughly \$400B! Using the approximate mean lifetime cost per capita of \$2M based on the numbers in [144] would have yielded a total *lifetime* cost for the sub-group of roughly \$200B. Either cost figure is astronomical, especially when the narrowness of the afflicted group is considered. Even if we followed [147] and used an undiscounted cost

stream for the computations, we would have obtained total lifetime costs approaching \$500B. The overall conclusions are essentially the same irrespective of which of these cost streams we assume; for purposes of further computation, the conservative assumption of \$4M lifetime cost per capita will be used.

That \$400B total lifetime cost estimate *neglects* the other sub-group identified at risk in the CDC study, children of all races who developed **Isolated Autism** from the MMR vaccine (according to Dr. Thompson's revelations to Dr. Hooker). This latter sub-group would be about seven or eight times as large as the African-American sub-group, since it includes *all races*, and the economic costs could be numerically larger than the African-American sub-group, depending on the level of increased risk for **Isolated Autism**.

As a side note, the NVICP (National Vaccine Injury Compensation Program), which is a special Court set up to compensate the vaccine injured, has paid out approximately \$3.2B since 1988 for injuries *from all vaccines*. Approximately 9% of all compensated claims were for the MMR vaccine, *for all groups*, so the **total** MMR compensation would be somewhat less (perhaps substantially less) than \$1B since 1988. Compare that with the ~\$400B cost estimate above for African-American children for the 2001-2015 time period for the USA for the MMR vaccine only. That's a **small fraction of one percent** of the total costs being compensated for this one group over one period. Other sub-groups potentially injured from the MMR vaccine, such as children with Isolated Autism, are not included in the \$400B estimate!

So, if the lifetime autism cost for this one afflicted sub-group is ~\$400B over its lifetime, and the Trust Fund compensation has been on the order of one-tenth of one percent of the lifetime autism cost (or less), then on the order of 99.9% (or more) of the total lifetime autism costs are being borne by sources other than the Trust Fund. Who are these sources? The main sources would appear to be the afflicted (and their families) and the taxpayers, through their support of myriad social services.

Thus, 99.9+% of the ~\$400B total lifetime autism costs is the effective subsidy provided (for this one narrow sub-group only) by the 1986 Act and confirmed by the 2011 Supreme Court decision!

9C5a2. Global Impact

The ~\$400B total lifetime autism costs above are for **one parameter (timing of vaccination) for one sub-group for one vaccine for one disease for one time period in one country**. What would the numbers look like if the impacts were integrated over this narrow sub-group globally?

There are over 1.1B people living in Africa. Assume 1B are similar racially to the US African-Americans, with respect to their response to the MMR vaccine. There are roughly 40M African-Americans, about thirty percent of the total African diaspora globally. The fraction in each region that gets the MMR vaccine is roughly the same. So, taking Kennedy's conservative estimate of 100,000 cases of MMR vaccine-induced autism for African-Americans (over the fourteen years that the CDC was allegedly aware of this increased risk), and multiplying *conservatively* by about twenty-five, we have a total of about 2.5M cases of autism induced in Africans (or people of African descent) globally over fourteen years. That's about 180,000 cases of autism globally per year from that potential single MMR vaccine impact on one disease on one sub-group on one parameter!

The dollars globally won't scale up from the African-American costs because Africa has a far lower standard of living than the USA, as do some of the other locations of the African

diaspora. But, even if the African (and its diaspora) component scales up with 1/10 the unit costs of the African-American costs, overall the total (avoidable) *lifetime* costs since about 2001 are on the order of almost \$1.4T!

However, while limiting the costs to the period 2001-2015 may be valid for the specific CDC omission alleged by Dr. Thompson, these are not the only additional costs for the African-American sub-group from the MMR vaccine if a longer time perspective is taken. The MMR vaccine was licensed in the USA in 1971. Assuming the sensitivity of the afflicted sub-groups to the MMR vaccine has remained approximately constant for the past forty years, then had the MMR vaccine been monitored sufficiently pre- and especially post-licensing, and the actual test results provided openly to the public, we should have known conservatively about the racial disparity (and other affected sub-groups, such as **Isolated Autism**) by ~1980 (or before). Thus, the African-American and global sub-group estimates should not start in 2001, but rather ~1980.

It is difficult to extrapolate the 2001-2015 estimates back to 1980, in order to obtain specific cost damages. The vaccination rates from 1980-2000 might have been less (especially in the less developed countries), and the synergies resulting from other toxic substance ingestions or exposures combined with the MMR vaccine could have been very different (given the rapid introduction of new potentially toxic technologies in the past few decades, and the large ramp-up of vaccines to the recommended schedule). The only conclusion at this point is that the \$400B estimated lifetime costs for African-Americans alone, and \$1.4T estimated lifetime costs for Africans and those of African heritage world-wide, are a floor for the actual costs of this one narrow impact of the MMR vaccine (assuming Dr. Thompson's allegations are validated), and possibly a very low floor.

9C5a3. Other Sub-Groups Affected

The above numbers would be augmented by the cases of **Isolated Autism** for all races, which must be scaled up from the USA total population to the global population (roughly a factor of twenty). I have not seen any numerical estimates for **Isolated Autism** increased risk resulting from the MMR vaccine domestically or globally, and Dr. Thompson provided no numbers publically on the level of increased risk. I therefore cannot make an economic estimate of the additional costs due to **Isolated Autism**, but, as stated previously, they could be large because of the size of the all-races pool compared to that of the African-American pool.

Dr. Thompson's statement *does not exclude other impacts from the MMR vaccine* on increased risk of autism or any other disease as well. All we know is that he *admitted to knowledge* of two sub-groups at increased risk for autism for one parameter (timing of vaccination) on his lawyer's Web site and to Dr. Hooker. There could be other affected sub-groups beyond those of which he *admitted to knowledge*.

More generally, if Dr. Thompson's allegations are validated (implying *involvement of multiple levels of the CDC organization*), it would then be reasonable to ask:

what other CDC studies of any type were either deliberately not funded or conducted (or, if conducted, manipulated) to downplay or suppress the adverse effects of other vaccines or other pharmaceutical substances?

APPENDIX TO 9C5a

9C5a-A1. Pediatrics 2004 study deficiencies

9C5a-A1a. Baseline

The CDC study is a case-control study [137], with the main goal of identifying any effects of timing of the MMR vaccination on autism occurrence in the total group and selected sub-groups. That study did not provide baseline information on autism incidence resulting from the MMR vaccine.

To generate baseline information, CDC would have had to

- 1) design and implement a study comparing an MMR-vaccinated group with an unvaccinated group, and
- 2) ascertain the level of autism (and other diseases) caused in toto by the MMR vaccine. Conceivably, that could have been equal to, or much greater than, any marginal timing effect that was reported in the actual study performed.

Reviewers of this book raised the ethical issue of conducting an experiment with a placebo (unvaccinated cohort) where an alternative treatment is available. The ethical issue of denying available treatment for a non-vaccinated cohort of participants in a clinical trial could be readily avoided by using children

- 1) who had not been vaccinated in the past by design, or
- 2) whose parents choose not to have them vaccinated today and when the study is conducted.

Finding a credible non-vaccinated cohort is a non-issue today, when many non-vaccinated children are available. Given the recent flurry of activity by governments to mandate vaccinations and remove most exemptions, this cohort of non-vaccinated children will probably shrink considerably with the passage of time, and it will become much more difficult to assess the safety of vaccines as a result. **It is rather paradoxical that a major resource required for ascertaining the safety of vaccines (an unvaccinated cohort) is being rapidly eliminated by the forced introduction and implementation of vaccines whose safety has not yet been established!**

9C5a-A1b. Synergy and Long-Term

According to the National Vaccine Information Center, there are 69 doses of 16 vaccines on the present recommended vaccination schedule. According to other organizations' estimates, there are hundreds of vaccines in the pipeline awaiting licensing and subsequent addition to the schedule. Any specific ***combinations of vaccines*** proposed could not be assumed to be safe based on ***isolated vaccine results*** (due to potential synergistic effects), and would have to be ***tested in the combination(s) recommended***. That was our finding from the EMF health effects study [130] as well, where combinations of substances could have adverse effects not seen when using the individual substances.

For the 69 doses of the 16 vaccines recommended in the present vaccination schedule, what safety studies have been performed examining the synergistic effects of these 69 doses of vaccine over the recommended sequencing and timing intervals, including the effects of myriad other toxins to which the child is exposed over this time period? What long-term human health effects studies have been performed with the current mix of vaccines and myriad other toxins, given that the vaccine combinations on the recommended schedule have expanded rapidly over the past few years, and ***the combinations*** are essentially new?

Two typical examples of safety/ efficacy studies of vaccine combinations reported in the peer-reviewed literature are the following (Titles presented):

1. *Concomitant use of the 3-dose oral pentavalent rotavirus vaccine with a 3-dose primary vaccination course of a diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-Haemophilus influenzae type b vaccine: immunogenicity and reactogenicity.*

2. *Immunogenicity and safety of measles-mumps-rubella, varicella and Haemophilus influenzae type b vaccines administered concurrently with a fourth dose of heptavalent pneumococcal conjugate vaccine compared with the vaccines administered without heptavalent pneumococcal conjugate vaccine.*

The CDC recommendations include the dose for each vaccination, and the timing/ sequencing of the vaccinations. The combinations listed above do not constitute the full recommended vaccine spectrum, either in number of vaccines or timing. I have not found published safety studies that include the full recommended vaccination ***pattern***.

In the above two efficacy and 'safety' studies, antibody levels are measured after a short period of time, which gives some measure of vaccine efficacy. Side-effects over this short period are documented as well, and (in most of these combination studies I have seen reported in the literature) are judged to be 'well-tolerated'. Long-term effects are typically not measured (but sometimes they are; see below).

During the data acquisition phase (of the overall present pervasive foundational causes study), I observed reports of adverse impacts from myriad foundational causes ***spanning the full time spectrum from seconds to decades***. We know that e.g. some cancers can have latency periods on the order of three-five decades, and other serious diseases can have decadal latency periods as well. ***Why would one expect deliberate stimulation of relatively immature immune systems with multiple toxins not to have some long-term consequences as well?***

In fact, there has been a modest amount of ***reported*** research examining long-term adverse impacts of immunization. The following research article ***Titles*** reflect a small sampling of this ***reported*** research, and provide some indication of the findings:

**Public should be told that vaccines may have long term adverse effects*

**The timing of immunization affects the development of diabetes in rodents*

**Subacute meningoencephalitis in a subset of patients with AD after A beta 42 immunization*

**Vaccination Safety Update: Long Term Side Effects Due to Vaccination And Pharmacovigilance*

**Epidemiology of autoimmune reactions induced by vaccination*

**Autoimmune diseases and vaccinations*

**Autoimmunity, environmental exposure and vaccination: is there a link?*

**Systemic immunotoxicity reactions induced by adjuvanted vaccines*

**The spectrum of post-vaccination inflammatory CNS demyelinating syndromes*

**Long-term epidemiologic longitudinal study on the effect of vaccines on public inoculation*

These studies either demonstrate *long-term impacts resulting from vaccines*, or, in some cases, conclude that *long-term effects cannot be ruled out*. How much would the economic costs (of adverse impacts from the MMR vaccine alone) be increased if long-term effects of the MMR vaccine were studied objectively?

9C5a-A2. CDC and Vaccine Manufacturer Structural Disincentives

There are some structural disincentives for the vaccine production, distribution, and regulation/ safety monitoring infrastructure whose removal would improve the situation dramatically. These disincentives include CDC structural deficiencies and vaccine manufacturer incentive deficiencies.

9C5a-A2a. Structural Deficiencies

CDC has at least two major roles relative to vaccines. First, it co-manages VAERS (vaccine adverse events reporting system) with FDA. VAERS is a *passive* monitoring system, and, like all similar systems, suffers from *substantial* under-reporting of adverse events. I have seen different estimates on the degree of under-reporting, and all are in the single digit percentage range. In other words, **the actual numbers of adverse reactions to vaccines are one to two orders of magnitude higher than those reported in VAERS!**

Second, the CDC distributes vaccines through the Vaccines for Children Program and Section 317 Program. The latter two programs are presently on the order of four billion dollars per year combined.

Thus, we have a serious conflict when the CDC has responsibility for both

- 1) distributing a significant amount of vaccines and
- 2) monitoring the safety of these vaccines.

Its incentives for distribution could, in theory, over-ride or compromise its incentives for insuring safety of vaccines. Placing the safety monitoring in an organization separate from the

distribution organization would go a long way toward eliminating the conflict and correcting this problem.

9C5a-A2b. Incentive Deficiencies

In 1986, Congress passed the National Childhood Vaccine Injury Act, which *effectively* removed liability from the vaccine manufacturers (and people who administer the vaccines) for defects or injury (as upheld by the Supreme Court in 2011). Shortly thereafter, a National Vaccine Injury Compensation Program was established, whose main purpose is to offer compensation to those injured by vaccines. It is funded by the Vaccine Injury Compensation Trust Fund. In turn, the Trust Fund is funded by a \$0.75 excise tax on each *dose* of a vaccine targeted toward a specific disease.

This has created a distorted set of incentives for the vaccine manufacturers, and a source of serious problems for the public. The manufacturers can maximize profits by having as many new vaccines as can be licensed added to the recommended vaccination schedule.

The FDA licenses and regulates new vaccines, and the CDC monitors health effects and safety after vaccination. If Dr. Thompson's allegations are correct, the system has some serious monitoring problems. Repealing the 1986 Act so that vaccines are treated the same as drugs from a legal perspective would help to remove this strong disincentive.

9C5a-A3. Recommendations

I have made no recommendations on any of the examples in this chapter. However, I find the gap between

1) the potential enormity of the MMR vaccine injury problem and

2) the information about the potential seriousness of the problem released to the public

so large that I believe it is incumbent on me to make recommendations based on the findings presented here. The problem of MMR vaccine adverse impacts is ongoing, and awareness among the public has been heightened by Congressman Posey's recent speech.

I have spent years managing (and conducting peer reviews of) major projects and programs (and publishing some of those peer review experiences [154]). Based on those myriad experiences, I offer the following recommendations for providing better information on vaccines to the public.

RECOMMENDATIONS

1. **Damage Control:** The initial release of Dr. Thompson's allegations on 27 August 2014 resulted in a major credibility problem for the CDC. The allegations implied:

- a) collusion at myriad vertical levels of the CDC management to
- b) intentionally withhold information from the public that
- c) would have shown a link between the MMR vaccine and autism for selected sub-groups.

The impact of the allegations was contained for about a year because of:

- a) the effective information blackout by the mainstream media and
- b) the lack of Congressional Hearings.

However, Congressman Posey's comments of 29 July 2015 (on the Floor of the House) raised awareness of the CDC credibility problem substantially. I have noticed a major difference in the types of comments on this issue posted on the Web since his speech. Some of those posters who initially defended the CDC against Dr. Thompson's allegations have become far more muted in their defense. There needs to be some real damage control in the near future.

First, the copious documents provided to Congress by Dr. Thompson should be released to the American public without delay. These documents were funded by the taxpaying public, they do not involve national security, and their presence on the Web would help eliminate the rampant confusion and speculation concerning their specific content.

Second, the Department of Health and Human Services (HHS) Office of the Inspector General (OIG) (or other independent organization) needs to conduct a thorough investigation of Dr. Thompson's allegations. Surprisingly, given the gravity of this issue and Dr. Thompson's allegations, I have seen no mention of any OIG investigation of this issue either in the mainstream media or in the alternative media. *My inquiry to the OIG produced a non-committal response.* If an investigation is ever done, the OIG investigatory team needs to include external participants with independence on the vaccine safety issue.

Third, there need to be Congressional Hearings on this issue to bring the facts out in the open, and attempt to resolve the validity of Dr. Thompson's allegations. Further delay will only heighten the public's concerns about broad-scale information suppression by the CDC.

2. **Moratorium:** Dr. Thompson's allegations have raised questions not only about the safety of the MMR vaccine, but about the credibility of CDC safety studies for all other vaccines. Presently, there are vaccine mandates in most states as a requirement for school attendance, and there are laws in some states removing most of the exemptions from these mandates. If Dr. Thompson's allegations are correct, we presently have the State effectively imposing myriad

diseases upon children through these mandates. Until vaccines have been shown to be safe, the following precautionary steps are recommended.

First, declare a moratorium on

- 1) all vaccine mandates and on
- 2) the implementation of laws restricting exemptions.

Second, create a situation similar to that existing for cigarettes. Warnings would be included with each vaccine package, such as e.g. information concerning the potential of increased risk for autism among certain sub-groups from use of MMR vaccine. If parents choose to have their children vaccinated, they would still have that option, but children could attend school if their parents chose not to exercise the vaccination option.

3. *New Study*: There needs to be a credible study examining the safety of vaccines as administered in recommended combination, sequence, and timing. **The public has no assurance that any of the vaccine studies conducted to date (or sponsored) by the CDC had any more objectivity or credibility than that inferred from Dr. Thompson's allegations on the MMR vaccine study.**

First, the proposed study should be conducted by an organization independent of the CDC. It should include an advisory board whose views on vaccines cover the full range of the vaccine advocacy/ non-advocacy spectrum. There would be substantial benefits if international members were included, independent of the vaccine manufacturers or government regulatory agencies.

Second, it should be designed to identify disease incidence rates, as well as other important outputs. This would require including a large cohort of unvaccinated children as well as vaccinated. The ethical issue of denying available treatment for a cohort of participants in a clinical trial could be avoided by

- a) using children who had not been vaccinated in the past by design, or
- b) using children whose parents choose not to have them vaccinated today and when the study is conducted.

Third, it should include a very broad regional representation, as well as ethnic, racial, etc. The MMR vaccine study was limited to the Atlanta Metro area, and could have included problems peculiar to that region only. Hypothetically, if e.g. Vitamin D deficiency exacerbated the adverse effects of MMR vaccines (as it seems to do for multiple sclerosis and other diseases), then we would expect that children living in higher latitudes would be at greater risk to adverse effects from MMR vaccine. Representative sampling would minimize such potential distortions.

Fourth, it should have large statistical power, which will allow identification of important sub-group problems. This means a large number of participants in both the vaccinated and unvaccinated groups.

Fifth, it should include long-term effects as well as short-term. This may require aggressive proactive gathering of vaccination data from people vaccinated years or decades ago, and not have sole reliance on the results from passive surveillance databases. This type of approach will of necessity be relatively expensive, but given the potential (multi) trillion-dollar costs estimated in section 9C5 for possible damages from one vaccine for one parameter for one group over one period, even a relatively expensive large credible study will have an extremely high benefit/ cost ratio.

Sixth, it should include examination of effects of combinations of vaccines, not only individual vaccines, as well as effects of the timing and sequencing patterns of these vaccines. In our EMF study [130], we found that sequencing of members of combinations could make a difference in whether or not a disease occurred.

Seventh, a parallel study should be commissioned to examine the benefits of vaccinations, such that credible benefit/ cost studies can then be performed. I have seen studies that showed disease incidence rate trends plummeting before vaccines for the specific disease were introduced (due to improvements in nutrition, hygiene, etc), and the low present incidence rates for some of these diseases could have resulted from extrapolation of the pre-vaccination incidence rate trends. In other words, the rapid reduction of the specific diseases examined could have been coincidental with the introduction of the vaccines, not a result of the introduction of the vaccines.

The benefits study should include an oversight committee composed of representatives from all parts of the vaccine advocacy/ non-advocacy spectrum, as well as performers representing the full vaccine advocacy spectrum, and have the flexibility of including both majority and minority opinions.

4. **Monitoring:** Part of the vaccine safety uncertainty problem has been due to weak monitoring of vaccine adverse events. The VAERS system is a passive surveillance system, and may be under-reporting adverse vaccine events by at least an order of magnitude.

First, the monitoring efforts need to be increased in parallel with all the other actions recommended, and an active surveillance system needs to be implemented.

Second, an oversight committee for the monitoring system needs to be established, composed of people representing all regions of the vaccine advocacy spectrum.

5. **Infrastructure:** The CDC has a serious conflict in having responsibility for both

- 1) distributing a significant amount of vaccines and
- 2) monitoring the safety of these vaccines.

Its incentives for distribution might, at least in theory, over-ride or compromise its incentives for insuring safety of vaccines.

First, the CDC vaccine safety monitoring function should be placed in an organization separate

from the organization responsible for the vaccine distribution function.

6. **Legislative:** The National Childhood Vaccine Injury Act of 1986 *effectively* removed liability from the manufacturers (and people who administer the vaccines) for defects or injury from vaccines (as upheld by the Supreme Court in 2011). This has created a distorted set of incentives for the vaccine manufacturers, and a source of serious problems for the public. The manufacturers can maximize profits by having as many new vaccines as can be licensed added to the recommended vaccination schedule. The argument for this Act was that the vaccine manufacturers would stop developing and producing vaccines unless they could obtain an effective liability waiver.

First, the 1986 Act should be repealed, so that vaccines are treated the same as drugs from a legal perspective. Repeal would remove this strong disincentive.

Second, the National Vaccine Injury Compensation Program and its associated Court (with no jury) should be eliminated, and replaced by the same jury trial structure applicable to drug injuries.

Third, if the cost-benefit vaccine study proposed above shows a net benefit for vaccines, the government should consider alternative options for developing and manufacturing vaccines, under the constraint that the manufacturer (whether private or public) would be held legally liable for vaccine injuries. If the private sector is unwilling to develop and produce vaccines under these conditions, then the government should consider taking over the development, production, and distribution of vaccines as an option.

7. **Final Comments:** The recommendations above are only a partial set. Much more could be presented, and should be promulgated by an independent commissioned group for correcting these extremely serious problems. As I have shown for one very narrow example, the damage done already by alleged intentional withholding of critical information by the CDC could be in the trillions of dollars globally over the lifetime of those afflicted so far. Integrated over all vaccines, for all parameters, for all sub-groups, for all countries, for all time periods since vaccine introduction, this could amount to many trillions of dollars in damage, to say nothing of the unnecessary human suffering involved. Every day these modifications to the present administration of vaccines are delayed, billions of dollars in unnecessary costs from vaccine damage are potentially being added, as well as thousands of children condemned to suffer unnecessarily.

9D. Clinical Trials Implications of Under-Reporting of Adverse Events

9D1. Inadequacy of Foundational Cause Accounting

Clinical trials are very important for determining the efficacy of treatments for disease. While much effort and attention are expended on insuring a credible statistical structure for the trials, and some co-morbidity of the test subjects is taken into account, much less attention is typically placed on the potential foundational causes of disease being experienced/ pursued by the test subjects. Why is this important? I will demonstrate its perceived importance through examination of one interesting data point.

Dr. Terri Wahls is on the medical faculty of the University of Iowa. She developed Multiple Sclerosis (MS) and eventually became non-ambulatory. Her book [148] describing her experiences shows pictures of her giving classroom lectures from a wheelchair.

At that point, she decided to research the biomedical literature to ascertain whether MS could be reversed. Based on her research, she concluded that a major contributing factor to her MS was poor diet. She speculated that the MS could be halted/ eliminated using mainly a dietary improvement approach, and the motor control damage from the MS could be reversed using a technique called Neuromuscular Electrical Stimulation (NMES). Heretofore, NMES had only been used for athletes' rehabilitation from injury.

Dr. Wahls eventually integrated nutritional enhancement with NMES. Her experience was that she used NMES and made very slow progress, then improved her diet and made rapid progress. This comports with the LRDI holistic medical hypothesis: *removal of cause is a necessary, but not sufficient, condition for restorative treatment to be effective*. This appears to be exactly what happened in Dr. Wahls' case; the cause (poor diet) was removed and the restorative treatment (NMES) became effective.

If one separates the sequence of events necessary for healing into

- 1) disease cause removal,
- 2) disease symptom removal, and
- 3) disease damage removal,

explanation becomes somewhat easier. Dr. Wahls eliminated the major cause of her MS (poor diet), and the symptoms associated with MS disappeared (pain, fatigue, etc). However, the damage from MS (gait and motor control problems) remained, to some extent. To reverse that damage, she had two major options. She could let nature take its course and reverse the symptoms of the damage. This alone might work, but natural biological processes can take a long time for healing. For faster results, she could use some external form of treatment to accelerate healing. She chose NMES, and, in combination with improved nutrition, was able to accelerate healing.

Now comes one of the more critical insights from this book. Assume we rate the quality of diets from one to a hundred, where one is the lowest. Assume further that Dr. Wahls had an average American diet before she contracted MS; her diet pre-2000 (before being diagnosed with MS) was perhaps a 40. Then, she was diagnosed with MS, started to deteriorate, and changed to a Paleolithic diet in 2003 (there are various incarnations of the so-called Paleo diet, but they consist mainly of fish, grass-fed pasture raised meats, vegetables, fruit, roots, and nuts, and exclude grains, legumes, dairy products, salt, refined sugar, and processed oils). Assuming she followed it strictly, I would rate it about 95, based on our past LRDI (mainly dietary) findings for different diseases.

Then, in 2007, she started NMES. Her progress, if any, was minimal. When she switched to her present strict diet, which a pro-Paleo advocate might rate at 99, the NMES results increased dramatically.

If she had received the NMES when her diet was 40, there probably would have been zero gain, since the poor diet was continually destroying the myelin sheath (the electrically insulating layer around the axon of a neuron whose degradation is a characteristic of MS). Even receiving the NMES when her diet was ~95 didn't do very much. It was only when her diet approached near-pristine status (from a pro-Paleo perspective) that real change occurred. So, if someone were to run clinical trials of the efficacy of NMES on many MS patients, the spectrum of responses they would see would be a **mirror of the quality of the diet (or, more generally, the degree of cause removal from whatever source), and tell relatively little about the efficacy of NMES.**

This means that if we see clinical trial results of a new 'treatment' performed on a number of patients who have the average American diet, and the test results don't show much improvement, **it may tell nothing about the quality of the treatment, irrespective of the randomized double-blindedness of the trials!** If all the test subjects were like Dr. Wahls pre-Paleo, with a ~40 level diet, and they had received NMES, **we probably would conclude that NMES does not work for MS.** The more accurate conclusion might be that it doesn't work for people with MS **when the dominant cause(s) is still being experienced;** in fact, **why would one expect it to work under those conditions?**

But, that's the reality of many medical 'treatments' today. The foundational cause is not addressed, 'treatments' are administered, and there is a wide range of responses. **The so-called 'incurable' diseases, like MS, are never 'cured' because the true foundational causes are never removed!**

9D2. Inadequacy of Data

In November 2004, Dr. David Graham (Associate Director for Science, Office of Drug Safety, Center for Drug Evaluation and Research, Department of Health and Human Services, Food and Drug Administration-FDA), a safety researcher, testified before Congress about potential hazards of numerous drugs, including Accutane, Arava, Bextra, Crestor and Meridia. His main testimony, however, addressed adverse effects of Vioxx, an arthritis/ pain drug. His testimony, and the hearing, can be seen in full at the following link, and for those who have not

seen this testimony, I highly recommend it (<http://www.c-span.org/video/?184513-1/vioxx-medication-withdrawal>).

From the above Hearing's transcript, Dr. Graham testified, in part: "Prior to approval of Vioxx, a study was performed by Merck named 090. This study found nearly a 7-fold increase in heart attack risk with low dose Vioxx. The labeling at approval said nothing about heart attack risks. In November 2000, another Merck clinical trial named VIGOR found a 5-fold increase in heart attack risk with high-dose Vioxx.....In 2002, a large epidemiologic study reported a 2-fold increase in heart attack risk with high-dose Vioxx.....In March of 2004, another epidemiologic study reported that both high-dose and low-dose Vioxx increased the risk of heart attacks compared to Vioxx's leading competitor, Celebrex. Our study, first reported in late August of this year found that Vioxx increased the risk of heart attack and sudden death by 3.7 fold for high-dose and 1.5 fold for low-dose, compared to Celebrex. A study report describing this work was put on the FDA website on election day. Among many things, this report estimated that nearly 28,000 excess cases of heart attack or sudden cardiac death were caused by Vioxx. I emphasize to the Committee that this is an extremely conservative estimate. FDA always claims that randomized clinical trials provide the best data. If you apply the risk-levels seen in the 2 Merck trials, VIGOR and APPROVe, you obtain a more realistic and likely range of estimates for the number of excess cases in the US. This estimate **ranges from 88,000 to 139,000 Americans. Of these, 30-40% probably died.** For the survivors, their lives were changed forever. It's important to note that this range does not depend at all on the data from our Kaiser-FDA study. Indeed, Dr. Eric Topol at the Cleveland Clinic recently estimated up to 160,000 cases of heart attacks and strokes due to Vioxx, in an article published in the New England Journal of Medicine."

How many of these injuries and premature deaths could have been avoided? The answer depends on when the FDA first 'knew' about potential adverse events, and what is meant by 'knew'. Merck documents show possibility of adverse cardiovascular events in the late 1990s, as Dr. Graham's comments about 090 implied. But, as Dr. Graham's testimony again shows, even when the FDA knew of these problems a few years later, it did not take action to withdraw the drug from the market. Merck voluntarily withdrew the drug in Fall 2004.

The two medical experts who testified before Congress along with Dr. Graham believed that:

- 1) larger tests should have been performed
- 2) more representative of the potential user population
- 3) for a longer period of time.

All three witnesses questioned the need for priority/ accelerated approval that FDA gave to Vioxx.

In 2009, a retrospective study of what was known about Vioxx (rofecoxib) at various points in time concluded [149]: "Cumulative pooled analysis of all randomized, placebo-

controlled trials demonstrates a **trend toward increased cardiovascular risk associated with rofecoxib compared with placebo as early as December 2000**, the comparison reaching a P value of .05 by June 2001, nearly 3(1/2) years before the manufacturer's voluntary market withdrawal." Had more extensive pre-licensing open testing been required, the problems with Vioxx might have surfaced before the license was granted. Why are trials not conducted independently of the sponsor, and why are all internal test results not required to be made available to the public?

The Vioxx example is somewhat different conceptually from the others presented in this chapter. In the Vioxx case, the literature was 'inadequate' at the time of decision-making because the regulators did not wait for adequate data to be generated. In some sense, this criticism may be valid for most drugs, chemicals, and other potentially harmful substances being considered for approval.

Latency times for serious diseases can be on the order of decades from initial exposure, a time scale incongruous with data available for many/ most substances waiting for approval. For extremely serious diseases, the risk of drugs tested for relatively short periods (relative to potential decadal human latency periods) may be acceptable, but for most non-emergency applications, accepting such risk is difficult to rationalize.

9D3. Clinical Trials Off-Shored to Developing Countries

9D3a. Ethical Concerns

In the past few decades, there has been a steady increase in the off-shoring of clinical trials to developing countries. Costs for these trials are cheaper than in the developed countries, many patients are 'treatment-naive' (having had less medical care and drugs than people in the developed countries), there is a plethora of sick people readily available, oversight tends to be less strict, and ethical standards may be relaxed.

For example, placebos (rather than an *available* alternative treatment) may be used in a control group to show a greater advantage for the drug being tested than if an alternative treatment were used in the control group. Typically, in the developed nations, it would be viewed as unethical if a placebo were to be used on sick people if an alternative treatment to the drug being tested were available. In some/ many cases, the poor and sick will be used as the 'guinea pigs', but will not be able to afford the expensive drugs that will eventually be used by the affluent developed nations.

Some of these questionable clinical trials have been documented (to some extent) over the past decade or two (e.g., [150-151]), and both of these references tell a similar story. Reference [151] (SOMO briefing paper on ethics in clinical trials) contains the following in its summary: "the paper aims to illustrate problems in the ethical conduct of clinical trials. It does not provide an analysis of clinical trials in general or of the scale of ethical violations. Indeed, **the scale of the problem is unknown, because it cannot be estimated how many unethical clinical trials escape public attention and therefore remain unnoticed.**"

This reference states further: "the nature of ethical concerns appears to be rather diverse.....The lack of voluntary, informed participation and adequately informed consent are probably the most common problems. Cases of trials that did not undergo adequate ethical review or failed to report serious adverse events indicate flaws in the regulation of clinical trials. Tests with experimental drugs of which the safety for testing in humans had not yet been fully established may be among the most alarming examples." These should be viewed as a sample of the myriad ethical concerns/ violations. Also, in this study, there were a few clinical trials from developed nations described.

9D3b. Accuracy of Trial Findings

There is a question about accuracy of reporting on these third-world clinical trials. I have shown some of the problems with displaying all the relevant data in USA clinical trials, where there tends to be substantial oversight and reasonable transparency. In the third-world clinical trials, the transparency situation is quite different. As [151] states about such transparency: "Furthermore, despite recent initiatives to increase transparency about drug trials, the design of most studies is still not publicly available.....Therefore this principle was also not used as a selection criterion for the overview of unethical clinical trials in this paper. The lack of transparency does limit the amount of information available on the studies described below, because in most cases it appears the study design is indeed not publicly available."

References [150-151] were generated from secondary sources and/ or talking to principals in the study. I would suspect that all the major participants in clinical trials in third-world countries would be very reluctant to reveal negative information to outsiders, such as the authors of the above two studies. These authors were neither sponsors nor regulators.

9D3c. Clinical Trial Sample Representation of Drug User Community

There is another issue with third-world clinical trials related to how well the trials represent the eventual user community. In section 9D1, I showed how the outcome of a treatment clinical trial could be strongly dependent on the spectrum of co-morbidities present in the trial population. One could re-word that statement such that the outcome of a clinical trial could vary depending on the genetic makeup, the dietary practices, other cultural practices that include foundational causes, exposures unique to a given location, etc. Thus, if a drug is tested in a foreign country very different from the USA, one could question the relevance of these test results to USA citizens.

As reference [152] states, when describing the results of a mainly overseas-tested cardiovascular drug: "But it certainly did nothing to dispel concerns that *trials conducted overseas may be sloppier or that genetic, cultural, and environmental differences from Americans mean the data are of questionable relevance to U.S. patients.*"

9E. Epilog

This chapter has presented myriad conceptual reasons for, and many illustrative examples of, under-reporting of adverse events and negative findings in the biomedical literature. Obviously, the only evidentiary conclusions that can be drawn relate to the credibility of the specific examples presented. How much can these conclusions be generalized? In other words, how much of the published biomedical literature can we trust, if any? And, how do we recognize which part of the published literature is credible?

I have presented some examples of whistle-blowers who were willing to risk their careers, their finances, and, in some cases, perhaps their lives, to present their cases to the media. I have shown some examples of testimony before the Congress of the United States. Yet, in spite of myriad media coverage and dramatic Congressional testimony, very little has been done to improve the situation. The recent examples presented in this chapter are testimony to this inaction.

Chapter 9 has emphasized the 'dark side' of research and medicine, and the role that a distorted literature has played in this process. I want to end this chapter on a more hopeful and positive note. The following boxed comments provide a glimpse of what can be done in the here-and-now to reverse chronic disease, in selected cases.

REVERSING CHRONIC DISEASE

The main focus of this book is identifying the full spectrum of foundational causes of disease, in order to implement the holistic medical principle that 'removal of cause is a necessary, but not sufficient, condition for restorative treatment to be effective'. Presently, the full spectrum of foundational causes for any chronic disease have not been identified to anywhere near the extent they have been identified in

- 1) reference [12],
- 2) this book, or
- 3) ongoing studies we are conducting on other serious diseases.

Therefore, the testing and proof-of-principle demonstration of the *full* holistic medical principle above on preventing and reversing chronic disease has not been possible.

However, there are examples where chronic disease reversal has occurred when some major foundational causes have been identified and removed. These examples do not include large numbers of participants, since these types of non-traditional approaches to disease reversal do not attract large amounts of government or industry sponsorship. I will summarize two recent examples briefly.

The first example is Dr. Wahls' reversal of advanced multiple sclerosis [148], summarized in 9D1. She used a combination of strict diet and NMES treatment to

- 1) halt the disease and
- 2) reverse the damage from the disease.

This was a good example of how cause removal allowed restorative treatment to be effective, as predicted by the holistic medical principle above.

The second example involves reversal of Alzheimer's Disease, amnesic mild cognitive impairment, or subjective cognitive impairment [153]. Dr. Dale Bredesen, a researcher at the Mary S. Easton Center for Alzheimer's Disease Research, Department of Neurology, University of California, Los Angeles, has developed a therapeutic regimen using a total systems approach to 'treat' the three related diseases listed above.

Nine of the first ten patients who utilized this program/ regimen "displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD. Six of the patients had had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Improvements have been sustained, and at this time [mid-2014] the longest patient follow-up is two and one-half years from initial treatment,

with sustained and marked improvement.....The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes." [153]

Dr. Bredesen used a combination of

- 1) foundational cause removal,
- 2) substitution of healthful practices for the harmful foundational causes, and
- 3) supplementation based on biomarker deficiencies

to achieve these results. This combination included dietary improvement, exercise and sleep enhancement, stress removal, etc.

The therapeutic regime for each patient was presented in [153]. Unfortunately, it was not possible for the reader to decouple the effects of cause removal from supplementation to identify which was dominant in the healing process. In other words, could the same results, or even better, have been obtained with cause removal alone? As I have pointed out previously in this book, an identified deficiency of e.g. a vitamin or mineral could be due to

- 1) insufficient intake of the relevant vitamin or mineral, or
- 2) a dysfunctional metabolic process that results in the deficiency of the vitamin or mineral.

Thus, adding supplements may or may not contribute to eliminating the underlying foundational causes of the deficiencies.

I have a number of other specific problems with [153], including selection of the sample, size of the sample, etc. However, the central point is that Dr. Bredesen appears to have reversed (to some extent) selected cases of Alzheimer's Disease and Cognitive Impairment, which from my perspective is a major accomplishment that overshadows any perceived deficiencies in approach. Further research in this area could pinpoint the role of cause removal and supplementation addition in the healing process, and could overcome any criticisms one could have on the approach.

Based on the CKD study [12], the results of the larger study presented in this book, and other analyses I have performed, I would estimate the number of foundational causes for Alzheimer's Disease to be on the same order of magnitude as the number of foundational causes for CKD (~800 direct foundational causes, plus many more indirect). Follow-on research to Dr. Bredesen's approach should include the full panoply of these foundational causes as candidates for elimination. It could very well be possible to reverse even the more advanced supposedly intractable cases of Alzheimer's Disease that Dr. Bredesen's limited approach could not, if the full panoply of these foundational causes were considered for elimination. And, the approach outlined in this book would be potentially applicable to any chronic disease, not limited to Alzheimer's Disease or CKD.

The final point is that we may not have to wait for decades in the hope that 'cures' for

Alzheimer's Disease or other chronic diseases will someday be achieved. **For selected/ many/ most people, such 'cures' may potentially be here and now, waiting to be demonstrated in large trials!** As in the case of Dr. Wahls, these potential 'cures' are not simple 'magic bullets'. They involve personal motivation, discipline, and hard work. In many cases, they involve rejecting lifelong habits and traditions, and addictions to harmful substances and behaviors. **For those who are willing to make these sacrifices, potential disease reversal may be within their grasp!**

Chapter 10

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The Handbook of Research Impact Assessment

<http://www.dtic.mil/dtic/tr/fulltext/u2/a296021.pdf>

Science and Technology Peer Review: Advanced Technology Development Program Review

<http://www.dtic.mil/docs/citations/ADA418830>

GLOSSARY OF TERMS

Pubmed MeSH tree

Pubmed is a search engine for the Medline database, generated by the national Library of Medicine, National Institutes of Health. Medline is a bibliographic database mainly covering biomedical articles. MeSH (Medical Subject Headings) is a controlled vocabulary (essentially keywords organized into a taxonomy) for indexing the Pubmed articles. The MeSH tree is the structure defining the taxonomy.

MeSH Qualifiers

Words added to MeSH Heading terms that narrow the scope of the term. If Mercury is a MeSH Heading term, and the Qualifier of interest is 'adverse effects', then the full MeSH term becomes mercury/adverse effects. There are 83 MeSH Qualifiers in the 2015 edition of Pubmed.

MeSH Headings No Explode

If MeSH Headings are entered into a Pubmed search, they will retrieve not only records containing the exact MeSH Heading specified, but also records containing any other MeSH Headings listed below the MeSH Heading entered (into the query) in the MeSH tree. MeSH Heading No Explode means that only records containing the exact MeSH Heading entered into the search query will be retrieved.

Text Mining

Extraction of useful information from large volumes of text

Hierarchical Taxonomy

A classification scheme different nested levels of detail

Passive Surveillance

Obtaining data from voluntary reports of patients or healthcare providers

Latent Variables

Variables that are not measured directly, but are hidden. They can be inferred from variables measured directly.

EPA

United States Environmental Protection Agency, whose mission is to protect human health and the environment

(<http://www2.epa.gov/aboutepa/our-mission-and-what-we-do>)

CDC

Centers for Disease Control and Prevention, the USA's "leading public health agency", whose mission is to protect America from health, safety and security threats, both foreign and in the U.S.

(<http://www.cdc.gov/about/facts/cdcfastfacts/cdcfacts.html>)

FDA

US Food and Drug Administration, a Federal Agency responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed[5] and veterinary products.

(https://en.wikipedia.org/wiki/Food_and_Drug_Administration)

(<http://www.fda.gov/AboutFDA/WhatWeDo/default.htm>)

ABOUT THE AUTHOR

Ronald Neil Kostoff received a Ph. D. in Aerospace and Mechanical Sciences from Princeton University in 1967. He has worked for Bell Laboratories, Department of Energy, Office of Naval Research, and MITRE Corp. He has published over 200 peer-reviewed articles, served as Guest Editor of four journal Special Issues since 1994 (Evaluation Review [Feb 94], Scientometrics [July 96], Journal of Technology Transfer [Fall 97]; Technological Forecasting and Social Change [Feb 08]), obtained two text mining system patents, and presently is a Research Affiliate at Georgia Institute of Technology. He has published on numerous medical topics in the peer-reviewed literature, including:

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