Austin Environmental Sciences

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Review Article

Evidence for an Estrogen Disruptor Driven Meta-Epidemic Including Hygiene Hypothesis Related Potentiation and Beneficial Effects Related to the Obesity Paradox

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Received: February 07, 2022; **Accepted:** March 07, 2022; **Published:** March 14, 2022

Abstract

Evidence is presented for an estrogen disruptor related meta-epidemic with three overlapping waves. The first arose in the 1930s with animal intersexes, but few apparent human effects, and involved substances such as halogenated biphenyls and DDT. The second began around 1960 and continues today, with obvious ongoing human epidemics with diverse estrogenic effects, connections to hygiene hypothesis related immune disorders that explain epidemic timing, and health benefits related to strokes, heart attacks, and cognition where alternative medical explanations are insufficient. A single novel disruptor with dual estrogenic effects explains similar timing for adverse and beneficial changes. Dual effects could also account for the obesity paradox, where excess weight improves outcomes with other diseases, since the same agent that causes obesity could also ameliorate sequelae. Bisphenol A, a common constituent of plastics, is a likely candidate, with detectable levels in humans, including fetuses, estrogen disruption *in vitro*, and multiple links to epidemic findings. Production and use are historically consistent with early epidemic changes. Bisphenol S, a common replacement, is probably equally harmful. First and second waves exposures overlap, and a third wave involves chronic effects and interactions.

Keywords: Bisphenol A; Dementia; Epidemic; Estrogen; Estrogen disruptor; Hygiene hypothesis; Myocardial infarction; Obesity paradox; Stroke

Introduction

We are now facing a confusing array of epidemics: "Over the past 40 years we have seen a 57% increase in prostate cancer, 40% in breast cancer, 85% increase in hypospadias (penile defects), and a 50% reduction in sperm count. In addition, attention-deficit hyperactivity disorder has increased by 30%, autism spectrum disorders have doubled in the past 10 years, obesity has doubled in the past 30 years, and the number of US adults with diabetes has more than tripled since 1980. Clearly we must look to the environment as the primary cause of such increases and endocrine disruptors are likely to be a key factor in the surge of many diseases and disorders." [1].

As Auric Goldfinger noted, "Once is happenstance. Twice is coincidence. Three times is enemy action" [2]. With multiple overlapping epidemics (Table 1), concerns should be obvious.

Birnbaum implicated endocrine disruptors, which can mimic, block, or distort hormone effects through multiple mechanisms. One disruptor can affect several pathways, with different effects in different circumstances, even at seemingly negligible levels, and nonlinear dose response curves [1,3,4].

However, although other hormones may be involved, and ancillary factors can affect epidemic parameters [5], evidence supports a central role for estrogen disruption with three overlapping pandemic waves.

The first wave arose with the estrogen disruptors Dichlorodiphenyltrichloroethane (DDT) and biphenyl derivatives [3], effects on animal reproduction in the 1930s and 1940s [6], plus subtler human issues [7,8].

The second wave, which defines the current meta-epidemic, began around 1960 with prominent human changes commonly linked to estrogen effects. Evidence will be presented a role for estrogen disruptors in two other changes occurring at the same time: Hygiene hypothesis related immune findings, and a series of health benefits, with reductions in strokes, heart attacks and cognitive issues unexplained by medical advances. First and second wave exposures and effects overlap, with ongoing animal and human reproductive issues even after limitations on first wave pollutants.

Simultaneous multiple issues with related mechanisms suggest a single cause, with bisphenol A, an estrogen disruptor common in plastics, as a likely second wave candidate [5].

The third wave involves evolving chronic effects and interactions, as well as additional findings related to a changing environment.

General Issues- Disruptors and Epidemics

Besides the immune effects and benefits noted above, a consensus

Citation: Lubinsky M. Evidence for an Estrogen Disruptor Driven Meta-Epidemic Including Hygiene Hypothesis Related Potentiation and Beneficial Effects Related to the Obesity Paradox. Austin Environ Sci. 2022; 7(2): 1072.

statement noted three "strands of evidence that fuel concerns" [3].

- "The high incidence and the increasing trends of many endocrine-related disorders in humans."
- "Endocrine-related effects in wildlife populations." This includes abnormal sexual differentiation, infertility, and reduced sperm production in aquatic animals [9], reduced semen quality and increased cryptorchidism in dogs from 1988-2004 in one facility [10] and, mirroring human changes, increasing body weight over several decades in domestic dogs and cats, research colony primates and rodents, as well as feral rodents [11].
- "Chemicals with endocrine disrupting properties linked to disease outcomes in laboratory studies," with close to 800 known or suspected substances, with "the vast majority" in commerce untested.

Estrogen and Its Discontents

The four major types of estrogen have similar structures, and are all referred to as estrogen here. Women have relatively high levels, men low. Classic sexual effects [12] include low sperm counts, breast and prostate cancer, hypospadias, and intersexes [1,3,4], but other findings, such as obesity [13], certain birth defects [14,15] and immune related disorders [3] (Table 1) reflect less familiar properties.

For exposures, estrogen disruptors are common pollutants with human absorption, and include DDT and endosulfan, often banned insecticides, zeranol, a growth promoter for cattle, weed killers such as atrazine, industrial chemicals like phthalate esters, PCBs and PBBs (poly-chlorinated and -brominated biphenyls), and by-products such as dioxin, plus multiple others with poorly (if at all) understood effects, distributions, bio-availability, derivatives, and interactions [3]. Many are high volume products: In 2011, roughly 12 billion lbs. of bisphenol A were produced [16], with detectable levels in humans [17], including fetuses [18].

The First Wave

With biphenyl derivatives in the environment in the 1930s, and DDT the next decade [6], human findings primarily reflected high dose local contamination; although laboratory studies show subtler changes [8], and DDT has long term, reproductive issues [7].

However, animals showed typical estrogen effects. For the common cricket frog in Illinois, intersexes began increasing around 1930, peaked by 1960, and then decreased with DDT declines and early pollution limits. But, despite major environmental improvements after 1980, reproduction continued to be impaired [6].

Current ongoing decreases of insects and amphibians have multiple causes, including estrogen disruption related factors including first wave chemicals [19,9] still detectable in animals and humans, overlapping with later contaminants (below)

The Second Wave

"New" human epidemics with three likely estrogen disruptor links began around 1960: 1. Direct estrogen related effects; 2. Subsidiary contributions to allergies and infections; and, 3. Health benefits. Determining timing can be tricky, since early changes may be subtle, and latencies between exposures and effects may extend over decades, e.g., prenatal bisphenol A affects adult sperm counts [20].

Table 1: Epidemics from 1960 on. (Partial list. References in text).

Prostate cancer	Breast cancer	Uterine cancer
Hypospadias	Septo-optic dysplasia	Gastroschisis
Food allergies	Asthma	Low sperm count
Obesity	Autism spectrum	Attention-deficit disorder
Kawaski disease	Reye syndrome	Diabetes type 2
Childhood eczema	Diabetes type 1	Bullous pemphigoid
Inflammatory bowel disease	Celiac disease	Myasthenia gravis
Atrial fibrillation	Animal intersexes	-

For direct estrogen effects, gastroschisis, a prenatal vascular disruption of the abdominal wall, is a particularly helpful marker, since it is obvious at birth, hard to misdiagnose, and typically referred to tertiary surgical centers. Risks reflect maternal estrogen effects on coagulation. The disorder was first described in 1953 with 7 cases, and stayed rare until increases began in Great Britain, Scandinavia, and the U.S. in the early 1960s, correlating with early uses of bisphenol A [5]. Increases continue, with 4,713 cases in 15 American states from 1995 to 2005 [21], while rates rose about 9% a year between 2009 and 2013 in another study [22]!

Septo-optic dysplasia/optic nerve hypoplasia, another prenatal vascular disruption that variably affects the optic nerve, has a similar epidemiology, but diagnostic issues make it harder to track. Still, while exceedingly rare before 1960, prevalence quadrupled in Sweden between 1980 and 1999 [23], where it was the most common cause of infant blindness by 1997 [24]. Recently, Manitoba showed roughly 800% increases from 1996 to 2015 [25].

Other disorders support similar timing. In particular, U.S. obesity, systematically studied since 1960, showed slow increases up to 1980 followed by more rapid rises. Overall, from 1962-64 to 2007-08, age adjusted adult prevalence for obesity and extreme obesity from 13.4% to 34.3%, and 0.9% to 6.0%, respectively [26]; together, almost a 280% rise. There is considerable evidence for environmental "obesogens" [27] (including bisphenol A [28]) with estrogen effects and higher frequencies in industrialized countries [29].

While "estrogens play critical roles in a number of brain functions, including cognition, learning and memory, neurodevelopment, and adult neuroplasticity" [30], neuropsychiatric disorders are particularly difficult to evaluate, with often common findings, heterogeneity, and variable diagnostic criteria and ascertainment [31].

Still, increases here are apparent with autism spectrum disorders, which went from under 4/1000 in the late 1980s to 14.5/1000 in 2012, with major changes unlikely before 1960 [32]. For mechanisms, mTOR, a regulatory protein affecting neuronal pruning, may be implicated [33], with a role for estrogen stimulated mTOR-mediated protein synthesis [34] and bisphenol A specifically activates mTor [34].

Recently discovered links between autism and maternal DDT [35] are puzzling, since DDT levels have decreased since 1970 or so [6], while autism rates keep rising. Here, a combination of factors may be involved, with DDT in a subsidiary role as first and second wave exposures overlap.

Similarly, estrogen disruptors can lower sperm counts [36].

Table 2: Increasing immune related disorders since 1960.

Kawaski disease	Reye syndrome	Asthma
Food allergies	Childhood eczema	Inflammatory bowel disease
Bullous pemphigoid	Celiac disease	Myasthenia gravis
Acute Flaccid Myelitis	Diabetes type 1	-

Despite some controversy [37], a meta-analysis starting with 1973 showed ongoing declines [38] that may have started as early as the 1940s [39]. One model indicated an abrupt change in the mid 1960s [40], suggesting a superimposed second wave effect.

However, despite such exceptions, all three types of findings- direct estrogen effects, subsidiary immune changes, and benefits- typically show similar likely beginnings after 1960.

Immunology

Immune related issues (Table 2) began in the 1960s, ranging from rare disorders such as bullous pemphigoid [41] to common allergies like asthma [42] and even "new" infections: Kawasaki disease, an autoimmune vasculitis, probably an innate susceptibility triggered by an infection, first came to modern medical attention in Japan in 1961, with multiple cases reported in 1967 [43], although classic coronary artery aneurysms were seen as early as 1871 [44]. Similarly, Reye syndrome, an acute encephalopathy with fatty degeneration of the liver, was reported in 1929, but ongoing epidemics were first noted in 1963 and 1964 [45]. A recent "new" epidemic of acute flaccid myelitis [46] is also worrisome.

A widely accepted hygiene hypothesis saw reduced early infections and antigen exposures with sanitary improvements sensitizing the immune system, increasing hay fever, asthma, and eczema after 1960 [42]. This now covers a broad range of allergic and autoimmune disorders [47] with similar timing, such as inflammatory bowel disease in North America [48], while others, such as bullous pemphigoid, appear to have begun later [41].

An earlier cited change for multiple sclerosis [49] is "highly questionable" [50]. Type 1 childhood diabetes is a slight exception, with increases starting in the 1950s [51]. Type 2 diabetes is harder to assess- early data is sparse and, until the mid-1950s, diagnosis was often through glycosuria, with poor sensitivity and specificity [52].

While autoimmune and allergic issues have been linked to endocrine disruptors [3], sensitization is more commonly cited, with evidence from animal and laboratory studies, epidemiology, and even therapeutic interventions [47] unaccounted for by disruptors. The two mechanisms are rarely considered together- a 10/15/2018 PubMed search for "hygiene hypothesis" AND "endocrine disruptor" gave only one paper, which simply cited both as alternatives [53]. However, linking both together can explain important timing issues.

First, a lack of immune epidemics with earlier advamces: From 1870 or so, diphtheria, pertussis and respiratory tuberculosis deaths steadily dropped [54], and U.S. infectious disease deaths fell 8.2% per year from 1937 to 1952, then 2.3% per year until 1980 [55]. Peak ages for paralytic polio, which reflect the initial infection, went from under a year in 1900 to 5 to 9 years in 1950, when roughly a third of all cases were over 15 years old [56]. Hookworm and tapeworm infections in the American South also radically decreased during the first half of the 20th century [57].

Second, ongoing immune epidemic increases despite diminishing room for hygienic improvements, e.g., in 1975, with vaccinations, mumps and measles were only about a tenth as frequent as ten years before [49].

In other words, hygiene related sensitization had few effects when there should have been many, and a surfeit when decreases would be expected.

However, timing is understandable if a second factor drove changes after 1960, and estrogen disruption is likely. Estrogen modifies maternal responses to an immunologically foreign conceptus [58,59], and receptors are present on most immune cells [60]. Specifics include:

Regulatory T cells (Treg), suppressor CD4+ T cell subsets, and their products, especially IL-10 and TGF-β, that are central to self-tolerance [4], with at least two estrogen suppression pathways [61], while estrogen can also stimulate Treg cell IL-10 and TGF- β1 expression *in vitro* [62].

T helper cell subsets Th1 and Th2 interactions are important immune regulators, and estrogen suppresses TH1 and potentiates TH2 [63]. For Th17, more recently implicated, estrogen also has a role in maintenance and regulation [64].

Estrogen receptor α appears necessary for Toll-like receptor signaling modulation [65] as it recognizes "conserved pathogenic or microbial molecules" [66]. Similarly, dendritic cells, which process and present antigens to T cells, also respond to estrogen [67].

Finally, the gut microbial biome, another source of immune modification, interacts with sex hormones and gut flora related to immune responses in animal models [68].

Both pro- and anti- inflammatory estrogenic properties involve multiple interactions, so that "a uniform concept as to the action of estrogens cannot be found for all inflammatory diseases due to the enormous variable responses of immune and repair systems" [69]. Still, links are real, e.g., bisphenol A affects T cell subsets, B cell functions, dendritic cells and macrophages [70].

In short, estrogen disruptors can affect the immune system in varied ways, making sensitization interactions feasible, so that disruptor increases starting around 1960 would explain the observed temporal patterns.

Epidemics with Benefits

The final group of second wave estrogenic changes involves health benefits, which should not be surprising, since positive estrogen effects are apparent as different hormone levels in men and pre- and post-menopausal women affect cardiac, stroke, and cognitive issues.

Premenopausal women have less cardiovascular disease than men, with postmenopausal increases and protection mediated through estrogen receptors [71]. Lower rates and later onsets of stroke and neurodegenerative diseases in women correlate with estrogen levels, and decrease or end with natural or surgical menopause. Estrogen receptors are involved "through a complex array of genomic and non-genomic signaling, antioxidation and mitochondrial effects," and

aging related signaling issues affect ischemic injury [72], all supported by laboratory and animal studies [73]. Cognition also reflects estrogen levels [74], and surgical menopause increased cognitive decline and dementia rates, while early postmenopausal estrogen replacement is neuroprotective [75].

With these effects, estrogen disruptors are compatible with improvements in several areas:

Myocardial infarction (MI)

After steady rises in industrialized countries, incidence and severity progressively declined. Acute electrocardiogram based rates roughly halved from 1960 to 1999, with more than a 60% decline in coronary disease mortality. Changes varied geographically, but, for the U.S. As a whole, seem to have begun in the early 1960s [76].

Stroke

After some decline starting in 1925 [77], U.S. stroke mortality largely stabilized until moderate declines in the 1960s that greatly increased in the next two decades before becoming moderate again. By 2008, age-adjusted annual stroke death rates were less than a quarter of the 1931-1960 norm (40.6 *vs.* 175.0 per 100,000). From 1987 to 2011, one cohort showed a 24% overall decline in first-time strokes in each of the last two decades, mostly in older than 65 year-olds, and a 20% overall decrease per decade in stroke deaths, mostly in the younger group [78].

Neurocognition

Age related deterioration and dementia rates are lessening. In a French study of cognitively normal cohorts in their 70s and 80s, people in their 80s in 2008 performed as well as those in their 70s in 1991 [79]. In over 70 year-olds from 1993 to 2002, cognitive impairment and dementia fell almost 30%, from 12.2% to 8.7%. Similarly, with a 1978 baseline, new dementias in 60 year-olds declined by 22% in the late 1980s, 38% in the late 1990s, and 44% in the late 2000s.

Lending further support to beneficial estrogen links, while other immune disorders increased after 1960 [47], rheumatoid arthritis, where the hormone is protective [80], decreased [81].

Estrogen disruptor benefits and harm have different impacts on different groups, as with rising immune and psychological disorders in children versus cardiac, stroke, and cognitive improvements in adults. However, adult benefits are counterbalanced by increases in chronic diseases, especially obesity and diabetes (Appendix 1).

Medical explanations are a major alternative to estrogen disruptor benefits. However, there is considerable evidence that these are inadequate, and those additional factors, often second wave related, should actually have exaggerated negative outcomes. As a bit of a side issue, this is reviewed separately in Appendix 1.

A Paradox

Non-medical factors are also supported by the obesity paradox, where excess weight improves outcomes with specific diseases. So, adult diabetic mortality decreased as body mass index rose [82,83], and overweight and obese status lowered cardiovascular [82] and stroke mortality [84] and bettered long term survival [85]. This also occurred with heart failure [86], and for ischemic heart disease and hypertension, a Norwegian group found lower mortality with overweight patients, and even lowers with obesity [87]. This can be both long and short term, e.g., despite associated metabolic abnormalities with obesity, lower mortality after acute MIs persisted over a 7-year follow-up [88]. And obesity reduced hospital mortality with acute surgery for severe soft tissue infections [89]. There were also better outcomes with oral anticoagulant treatment for atrial fibrillation [90], even though obesity also supports progression to persistence, and associates with risk factors "such as hypertension, diabetes mellitus, sleep apnoea, dyslipidaemia, and increased pericardial fat with unique adipose tissue infiltration from the epicardial adiposity together with increased interstitial fibrosis contributing to atrial conduction abnormalities and increased AF propensity," with an almost 30% rise in fibrillation per 5-unit body mass index increments [91].

Since estrogen disruptors can have multiple effects, the obesity paradox makes sense if the same exogenous obesogen [27] also protects against harmful sequelae. The interplay between beneficial and adverse effects may produce variable outcomes as parameters change, explaining J shaped curves with benefits from some excess weight followed by a worsening with higher degrees of obesity, as with early hip surgery complications [92].

With these findings, the obesity paradox is, in fact, part of a broader contradiction, as dramatic increases in risk factors are accompanied by marked improvements in related outcomes, including the study cited above where severity fell as risks per MI patient rose [93]. This also occurs without diseases: In a large study of adults 70 to 75 from 1996 followed for up to 10 years, mortality risk with r overweight was 13% less than for normal [94].

Still, this ultimately means a health deficit from rising disorders despite improvements. So, for diabetes, from 1990 to 2010, heart and diabetic crisis mortality declined by over 60%, strokes and leg amputations by about 50%, and end stage renal failure by about 30% [95].

However, diabetes prevalence went from 0.91% in 1960 to 2.97% for 1991-93 [51] and reached 13.6% in a 1999-2006 national survey, with 80.3% overweight (body mass index ≥ 25) and 49.1% obese. Normal weight diabetic prevalence was 8%, overweight 15%, and 23%, 33%, and 43% for obesity classes 1, 2, and 3 [96], so most of the increased diabetes probably reflected an almost three-fold rise in obesity that more than outweighed (so to speak) any benefits. From 1995-2010, the relative median increase in age-adjusted prevalence of diagnosed diabetes was 82.2%, plus about 40% undiagnosed; total 2005-06 crude prevalence for ≥20 years of age was 12.9% [97].

A Third Wave

As the second wave persists, chronic issues arise. Ongoing pollution or body storage can cause prolonged exposures, e.g., even after being banned for decades, DDT persists in human tissues [98]. There also can be prenatal links to later issues, including excess weight and metabolic disturbances [99], and some findings, such as obesity, predispose to others. Extended exposures could weaken endocrine and immune responses, increasing vulnerabilities to other effects, including climate change related stress.

And here, the diabetes/obesity data brings us to a third wave of estrogen disruptor issues, as chronic issues and long term interactions emerge. So, for a start, most, but not all, type 2 diabetes today is

weight associated (above), indicating weight independent and weight dependent risks related to estrogen disruption! The two effects are probably synergistic, rather than simply additive.

Another possibility is a 1999-2015 0.7% per year rise in uterine cancer [100], where most risk factors are estrogen related. Obesity increases estrogen exposures here [101], so that a direct estrogen disruption effect on cancer may be interacting with an excess body weight effect also associated with disruption.

One final long-term concern involves evidence that environmental chemicals can have epigenetic effects that are transferred across generations [102]

Bisphenol A (BPA) Redux

Contemporaneous second wave estrogenic epidemics, hygiene hypothesis related disorders, and health benefits, suggest a new estrogen disruptor around 1960 with ongoing rises in exposures. And here, the evidence for bisphenol A as a likely candidate is worth reviewing.

Overall, a specific second wave cause should show estrogen disruptor effects, human uptake, and epidemic disorder links with initial exposures being around 1960, with subsequent increases. Geographically, the epidemiology of gastroschisis indicates initial exposures starting in the U.S. and North-east Europe and then spreading to other industrialized countries [5].

And here, BPA interacts with estrogen receptors α and β, estrogen-related receptor γ, membrane-bound estrogen receptor, G-protein-coupled estrogen receptor 1, as well as aryl hydrocarbon receptor, thyroid hormone receptor, and androgen receptor [17].

For links to epidemic issues, "animal and human research has associated BPA with many health problems including infertility, weight gain, behavioral changes, early-onset puberty, prostate and mammary gland cancers, cardiovascular effects, and diabetes" [103], plus connections with immune and autoimmune diseases [104] and cancer in general through different mechanisms [105,106].

Human BPA exposures and levels [17], include fetuses [18].

For early distribution, and later increases, "BPA was first made commercially in 1957 in the U.S. and 1958 in Europe to produce epoxy resin and polycarbonate plastic, both of which can directly or indirectly lead to human uptake of BPA. In Europe, polycarbonate was initially used in electrical insulators, but by 1963 it was "widely used for kitchenware and camping utensils," with a "wide variety of products," including food containers such as milk jugs, added the next year. I have not found documentation for the U.S., but a similar course is likely... Production rose steadily, making it probably the highest volume synthetic estrogen disruptor. World-wide, it reached 2.8 million metric tons in 2002, with an estimated 5.5 million metric tons (about 12 billion pounds) in 2011" Lubinsky [5]. (With permission of the author). Global consumption for 2015 was an estimated 7.7 million metric tons, with expectations of 10.6 million metric tons in 2022 [107].

Also supporting BPA effects are papillary thyroid cancer increases from 3.4 to 12.5 per 100,000 from 1975 to 2009 [108] consistent with BPA thyroid hormone disruptor effects. The authors also note that women have higher rates, and a far greater relative increase than men. Estrogen receptors are involved as well, with direct estrogenic BPA effects for this disorder [109], and possible "crosstalk" between the two [110].

Other BPA non-estrogen disruptors may also contribute elsewhere, e.g., aryl hydrocarbon issues [17] might supplement immune system effects [111].

Finally, other factors fail to fit the data [5].

A replacement for BPA, bisphenol S, is probably equally harmful [112].

What Has Posterity Done for Me?

With multiple changes and contributions, complex interactions, variable exposures and susceptibilities, and diagnostic and ascertainment issues, errors are inevitable. Also, with varying effects with different levels of exposures [113], findings may change over time. Still, the overall picture is clear, with ongoing changes related to estrogen disruption supported by multiple lines of evidence.

While individual scientists and groups such as the Endocrine Society have spoken out, comprehensive approaches are needed [3] as epidemics continue unabated.

However, our environmental record is mixed. Successes, as with DDT, involved considerable opposition, and even personal attacks [114], while economic and political interests continue to fight against acknowledging threats, and denigrate science (and scientists), with the climate change "debate" as just one disheartening example as the present response seems to be.

Conclusions

- Estrogen disruptors are responsible for three overlapping waves of epidemics.
- The first wave arose in the 1930s with animal intersexes, but few overt human effects, and involved known pollutants, especially PCBs and DDT.
- The second wave began around 1960, and continues today, characterized by:

a) Obvious human epidemics with estrogenic effects in addition to "standard" feminization;

b) Connections to hygiene hypothesis related immune disorders, including "new" infectious disorders.

c) Health benefits with strokes, heart attacks, and cognition are unequally distributed in the population.

- There are insufficient standard medical explanations for benefits (Appendix 1).
- Origins are uncertain, but abrupt onsets suggest a single novel disruptor.
- A single agent with dual estrogenic effects explains similar adverse and beneficial changes timing.
- Dual effects also explain the obesity paradox, since the same agent that causes obesity could also ameliorate its consequences.

- One likely candidate is bisphenol A, a common constituent of plastics. Bisphenol A:

a) Is produced in high volumes, and is a common pollutant.

b) Causes multiple endocrine disruptions in the laboratory;

c) Is epidemiologically linked to multiple epidemic findings, with both long and short term effects;

d) Is detectable in humans, including fetuses;

e) Early production and uses are consistent in time and space with initial epidemic changes.

- Current bisphenol a replacement involves bisphenol S, which is probably equally harmful.

- A third wave involves chronic second wave effects and interactions.

- Exposures from the first and second waves can overlap.

- Changing levels of exposures over time can alter findings and epidemiological parameters.

Appendix 1: Problematic Medical Benefits

Health improvements are typically explained medically. For cardiovascular benefits, "reductions in cigarette smoking, better control of serum lipid levels, more effective recognition and treatment of diabetes and hypertension, and more aggressive public health approaches to nutritional and other life style factors. The widespread use of aspirin or other medications has undoubtedly facilitated these trends as well" [115]. Or, for strokes, that "control of hypertension, hyperlipidemia, and tobacco, contributed most greatly to the mortality decline with a lesser but still substantial contribution of improved acute stroke care" [116]. Improvements in cognition and dementia are similarly justified [117, 118].

But there are problems here.

In two British populations, a few major risk factor changes covered roughly half of MI declines, with the rest unexplained. Other studies noted similar gaps [119,120], while less than half of stroke decreases reflected standard cardiovascular risk factors [121].

For interventions, recent studies show adverse instead of positive effects on morbidity and mortality from long term low dose aspirin [122-124], while lipid changes in one study were similar for adults taking and not taking lipid-lowering drugs [125].

Similarly, over 20 years, coronary heart disease and stroke deaths decreased by more than 50% in smokers and nonsmokers [126], even though the total relative risk of death for current smokers rose from 1971 to 2006 [127]. For 1982 compared to 1959, "smokers consumed more cigarettes per day, on average; women in 1982 began smoking earlier, smoked longer, and reported inhaling cigarette smoke more deeply... The potential benefits of reduced tar... appear to be overwhelmed by adverse changes in smoking practices and perhaps by other unidentified factors. Although smoking cessation clearly reduces the risk of CHD (Coronary Heart Disease) and stroke, much of the temporal decline in CHD and stroke mortality from CPS-I to CPS-II appeared to reflect factors other than smoking cessation because similar reductions were seen among current cigarette smokers and lifelong never-smokers" [128].

Life-style changes are also questionable: Carbohydrate and absolute fat intake in U.S. adults rose from 1971 to 2000 [129]. In 2000, for ages 18 to 74 years, only 3% of people combined nonsmoking, healthy weight, adequate fruit and vegetable intake, and regular physical activity [130]. From 1994 to 2007, the last two showed little change, with a 4-6% healthy life style frequency varying by region [131].

Other findings seem implausible. In one population, as MIs decreased from 1999 to 2008, risk factors per MI patient rose: diabetes, peripheral arterial disease, and chronic lung disease increased, dyslipidemia went from 46% to 80%, and hypertension from 45% to 76%- understandable if, as interventions succeeded, patients with poor compliance, adverse socioeconomic factors, etc., made up a larger part of a now smaller at risk cohort. However, instead of increasing, severity fell as MIs with more severe objective ST-segment elevation dropped from 47.0% to 22.9% [93].

In fact, rising risk factors should have worsened outcomes across the board. For U.S. adults:

- Obesity increased from 1960 on (above), raising risks for cognitive decline and dementia [132], all cause mortality [133], type 2 diabetes, dyslipidemia, metabolic syndrome [134], atrial fibrillation [91], stroke, heart disease, and other morbidities [135].

- Diabetes predisposes to cardiovascular disease, stroke, hypertension, dementia, cognitive decline, and other problems [136,137]. Prevalence rose from 0.91% in 1960 to 2.97% for 1991-93 [51]. From 1995–2010, the relative median increase in age-adjusted diagnosed diabetes was 82.2%, plus about 40% undiagnosed; total 2005–06 crude prevalence for ≥20 years of age was 12.9% [97], and reached 13.6% in a 1999–2006 national survey, with 80.3% overweight (body mass index ≥ 25) and 49.1% obese. Normal weight diabetic prevalence was 8%, then 15% for overweight, and 23%, 33%, and 43% for obesity classes 1, 2, and 3 [138], so most of the diabetes increase probably reflected a roughly three-fold rise in obesity from the 1960s on [26] that more than outweighed (so to speak) any benefits.

- Prediabetes affected, an estimated 35% of U.S. adults 20 years or older (50% for 65 years or older) by 2005-08 [138]. In one study, rates for healthy women went from 15.5% for 2001-02 to 28.8% for 2009-10 [140]. In another, for ≥18 years, for 1999-2002 to 2007-10, from 29.2% to 36.2% [141]. Cardiovascular risk factors- hypertension, cholesterol, triglycerides, and obesity- may increase up to 30 years here before diabetes is diagnosed [97], and hemoglobin A1c levels of 6.0% to <6.5% (the threshold for diagnosing diabetes) gave an 85% higher risk for coronary heart disease than 5.0% to <5.5% [142].

- Atrial fibrillation is associated with impaired cognition, dementia, chronic heart failure, mortality, and greater severity and a 5 fold increase in strokes [143]. Risks increase with age, and were <1% under 60 versus ≈10% in 80 to 84 year-olds in 2011 [144]. Age-adjusted estimates for the 1960s, 1970s, and 1980s were 5%, 8%, and 12% for men, and 4%, 6%, and 8% for women [145], plus an age and sex adjusted 12.6% increase over 21 years by 2000 [146]. With these

findings, a rough doubling from the 1960s through the 1980s should translate into at least an 8% rise in strokes.

- Low vitamin D is associated with autoimmunity, diabetes, cognitive dysfunction, dyslipidemia, hypertension, increased mortality [147], and progression from prediabetes to diabetes [148]. Cardiovascular effects are directly related [149,150] and, for dementia of all sorts, moderate deficiency gave a 53% increased risk, and severe, 122% [151]. From 1988-94 to 2001-04, mean serum levels dropped from 30 to 24 ng/mL levels <10 rose from 2% to 6%, and adequate levels ≥ 30 fell from 45% to 23% [152]. A meta-analysis found a 15% rate of severe deficiency (<10 ng/mL) with each 10 ng/mL decline associated with a 16% rise in all-cause mortality risk [153].

Other rising risks have been suggested, such as dietary fructose [132,154], but just the five above should significantly counter any medical advantages.

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