Where did Inflammatory Bowel Disease come from? What the history tells us about emerging therapies.
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Autoimmune Disease Incidence: Epidemic velocity since 1955

The Man Behind the Disease

Burrill Bernard Crohn (1884-1983)

- Went into medicine to help his father who suffered from severe indigestion.
- The first to formally describe the risk factors, symptoms, pathology, and progression of IBD in 1932.
- Identified the following risk factors: young age, female gender, Jewish heritage, lack of chronic infection, rich food, urbanization, and affluence.
Pop Quiz

Affluence, urban dwelling, household piped water and electricity, lack of chronic infection, country of birth, and household size are all risk factors for IBD that correlate with which hypothesis?

- A) Genetic/Ethnicity Hypothesis
- B) Inflammatory Foods Hypothesis
- C) Northern Latitude Hypothesis
- D) Infectious Microbe Hypothesis
- E) Hygiene Hypothesis

**ANSWER:**

- E) Hygiene Hypothesis
Hygiene Hypothesis

Glossary:

A collection of observations suggesting that exposure to infectious microbes prevents allergic & autoimmune disease. As a concept, it’s usually traced back to a 1980 paper by the epidemiologist David Strachan. He proposed that childhood infections prevented allergy. That view has since been supplanted, however. Now scientists think abundant early-life exposure to innocuous environmental microbes protects children from developing allergic and autoimmune disease. Arguing that the emphasis on “hygiene” is inaccurate, some have proposed variations on the theme, including the “old friends” hypothesis.
Childhood hygiene increases risk of IBD

Urban dwelling, household electricity, and piped water increase risk of IBD by 3 fold, 1.5 fold, and 2 fold; respectively.

### TABLE 4. Associations between IBD and childhood living conditions and hygiene

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.1</td>
<td>0.7–1.6</td>
</tr>
<tr>
<td>Age ≥40 years</td>
<td>1.2</td>
<td>0.8–1.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
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<tr>
<td>White (ref)</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Colored</td>
<td>0.3</td>
<td>0.1–0.8</td>
</tr>
<tr>
<td>Black</td>
<td>N/A</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>0.2–4.3</td>
</tr>
<tr>
<td>Born in South Africa</td>
<td>0.2</td>
<td>0.04–1.1</td>
</tr>
<tr>
<td>Married*</td>
<td>1.0</td>
<td>0.8–1.1</td>
</tr>
<tr>
<td>Tertiary education†</td>
<td>3.8</td>
<td>1.6–9.5</td>
</tr>
<tr>
<td>Parental education†</td>
<td>9.1</td>
<td>2.6–31.8</td>
</tr>
<tr>
<td>Smoker‡</td>
<td>0.4</td>
<td>0.3–0.7</td>
</tr>
<tr>
<td>Childhood living conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban dwelling</td>
<td>3.1</td>
<td>1.9–5.0</td>
</tr>
<tr>
<td>Shared housing</td>
<td>0.2</td>
<td>0.08–0.3</td>
</tr>
<tr>
<td>Farm living</td>
<td>0.5</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Household electricity</td>
<td>0.6</td>
<td>0.4–0.9</td>
</tr>
<tr>
<td>Household piped water</td>
<td>2.4</td>
<td>1.3–4.3</td>
</tr>
<tr>
<td>Childhood hygiene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw beef consumption</td>
<td>0.1</td>
<td>0.06–0.3</td>
</tr>
<tr>
<td>Raw pork consumption</td>
<td>1.3</td>
<td>0.4–3.8</td>
</tr>
<tr>
<td>Raw fish consumption</td>
<td>0.6</td>
<td>0.3–1.2</td>
</tr>
<tr>
<td>Raw vegetable consumption</td>
<td>0.3</td>
<td>0.1–0.6</td>
</tr>
<tr>
<td>Helminth infection</td>
<td>0.2</td>
<td>0.09–0.3</td>
</tr>
</tbody>
</table>

For the multivariate model, bold values are statistically significant which was defined as P < 0.05 (as stated in the methods).
N/A, not applicable.
Old Friends Hypothesis

Glossary:

A reframing and extension of the “hygiene” hypothesis that focuses on the co-evolution of humans with a plethora of immune regulatory organisms that have accompanied us since at least the Paleolithic Era. As a concept, it’s traced back to a 2004 paper by Graham Rook. The exposure to massive biodiversity and to organisms that taught our immune system to be tolerant has been lost following urbanization. Autoimmune diseases including multiple sclerosis, type 1 diabetes, and IBD, involve disrupted immunoregulatory circuits, likely reflecting reduced exposures to “old friend” organisms that the human immune system has evolved to be dependent upon.
Space Sickness
(Space Adaptation Syndrome)
Evolved Dependence

An organism that evolves in the presence of some factor over an extended period of time adapts to that factor and can no longer function properly without that factor.

4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632706/
The incidence of Crohn disease has risen dramatically. This strongly suggests that a change in the environment has increased the risk of developing Crohn disease. Data from [72–85].

Mice genetically engineered to get IBD do not get IBD when raised in sterile conditions; whereas these same mice do get IBD when raised with a normal microbiome or with a microbiome free of bacteria associated with IBD.

6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752651/
Greater than 2 courses increases risk of CD by 94%, risk of UC by 65%, in pediatric populations.

7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074626/
Variable results for UC remission (0-68%) and improvement in symptoms (20-92%). Small sample sizes, high variability in effectiveness.

For CD, very few studies and the jury is still out. Preliminary evidence suggests possibly effective for improvement in symptoms (0-63%) and remission (0-56%). Very small sample sizes, mostly pediatric populations, high variability in effectiveness.
Getting reacquainted with “old friends”…
Getting reacquainted with old friends…

- Joel Weinstock, Gastroenterologist

- In the mid-1990s he correlated the absence of intestinal worms – helminths – with the incidence of IBD in the US and then around the world.

- Wherever helminth prevalence fell below about 10 percent, IBD skyrocketed upwards.

- A better predictor than genes, hygiene in childhood, and childhood antibiotic exposure.
Missing “Old Friends”

Decline of Hookworm prevalence in the Southern United States

92.12% drop
71.21% drop

10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2024663/
11. http://www.ajtmh.org/content/journals/10.4269/ajtmh.1940.s1-20.493
Immunology of IBD & Helminths

Th1

- Prokaryote (Bacterial) Infections
- Autoimmune Disease

Th2

- Eukaryote (Parasite) Infections
- Allergic Disease
The worm returns...

Response (UCDAI decrease of at least 4 points)

Remission (UCDAI score of 0-1)

The worm returns…

Response (CDAI decrease of at least 100 points)
Remission (CDAI score < 150 points)

Average CDAI dropped 177.1 points
The worm returns…

18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856386/
Ongoing research

• At this time, there are two recently completed studies to evaluate the use of the **pig whipworm** in UC (2016, 2015) and two in CD (2015, 2013).

• Assuming this works, introducing benign intestinal worms could prove an easy and cost-effective way to treat IBD.

• Additionally, there are studies underway to evaluate the use of **hookworm** to treat multiple sclerosis, celiac disease, asthma, and seasonal allergies; whereas the **pig whipworm** is being evaluated to treat multiple sclerosis, autism, peanut allergy, and psoriasis.
Arguments against a therapeutic role for “old friends”

- **IBD is a disease with many diverse presentations**, and onset of the disease likely reflects a multitude of causative/contributory factors that need to be addressed therapeutically.

- **Many other changes have occurred with modernization**, some of which are known to shift immune response towards autoimmunity. Ex: diet composition, sleep reduction, sedentary lifestyle, psychological stress, pollution, vitamin D insufficiency.

- **IBD incidence continues to increase in countries decades after loss of helminths**, This may be due to a loss of generational epigenetic patterning (loss of maternal helminth colonization can influence infant immunity) that increases incidence over several generations.

- **The developmental window of the immune system may close early and permanently in some individuals.** The immune system has a period of plasticity early in life as it gets set up and this is when helminth exposure historically occurred in our evolutionary past. It is unclear how malleable the immune system is later in life and the degree to which helminths acquired later in life can shape long-established immune system architecture.

- **Safety of helminth use in IBD patients on immunosuppressive drugs is a concern** b/c of potential pathogenicity. Most helminths are biologically unable to multiply in their host and therefore no alteration in host immunity would permit an increase in helminth population. To date, no helminth pathogenicity has been reported in IBD patients treated therapeutically. Another concern is that immunosuppressive drugs may blunt or negate the immunoregulatory effect of helminths.

- **Helminthic therapy is not ready for primetime.** While the hypothesis appears sound and there’s some clinical evidence to support a therapeutic role for helminths, this therapy is still in its infancy and there will undoubtedly be future challenges and complications to consider. The studies are few, the study populations are small, and the therapeutic effect varies depending on the specific species of helminth being used.
Can understanding the worm produce the pill?

- Glycoprotein ES-62 from the filarial nematode *Acanthocheilonema viteae* protects against developing rheumatoid arthritis in mice.

- An artificial drug version of ES-62 mirrors the efficacy of natural ES-62 in protecting against rheumatoid arthritis, and does so by the same IL-17 inhibiting mechanism of action.

- In mice, investigation of several worm ES compounds (rTsP53, Av17, AcES) in the treatment of IBD is ongoing.

15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123613/
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