What you will leave with

• A toolbox with safe, effective, practical interventions to help change lives and increase satisfaction in your clinical practice
• The ability to get to the root cause of symptoms which have not been helped (often even by a specialist opinion)
• A refresher on useful physiology, biochemistry and immunology
• An understanding of how systems relate to symptoms
• Basic familiarity with lifestyle and preventive medicine principles
• The benefit of reducing prescribing and referrals
• Something useful to implement from Monday morning on both patients and yourself
Lifestyle medicine is a branch of evidence-based medicine in which comprehensive lifestyle changes (including nutrition, physical activity, stress management, social support and environmental exposures) are used to prevent, treat and reverse the progression of chronic diseases by addressing their underlying causes. Lifestyle medicine interventions include health risk assessment screening, health behavior change counseling and clinical application of lifestyle modifications. Lifestyle medicine is often prescribed in conjunction with pharmacotherapy and other forms of therapy.

Lifestyle medicine is an inter-disciplinary field of internal medicine, psychosocial and neurosciences, public and environmental health, and biology. Key LM principles include prevention strategies that address lifestyle habits, the underlying biological causes (also more distant causes such as urban design initiatives to make cities and neighborhoods more social and conducive to healthier lifestyles), and the pathophysiology common to LRDs (e.g. low-grade systemic inflammation, dysregulated stress axis, metabolic dysfunctions etc.). As such, LM is an adjunct form of treatment that helps to bridge the best aspects of public health and conventional clinical medicine.

Challenges of the 2022 NHS

1. An increase in the volume and complexity of health and social care needs, as more people live longer with long-term and often multiple conditions
2. The move to deliver more complex care in the community, as a means of both bringing it closer to patients and their families and reducing costs
6. The challenge of promoting healthy lifestyles and behaviours, while engaging patients and communities in supporting their own care and participating in shared decision-making

These long-term trends mean that expert generalist care is needed more now than at any time since the foundation of the NHS – and this requirement will become greater still over the next decade. Only a healthcare professional with highly developed generalist skills is able to apply his or her medical expertise to the growing range of long-term conditions; to incorporate this knowledge into ‘whole-person’ understanding of the patient and their family; to manage risk safely; and to share complex decisions with patients and carers, while adopting an integrated approach to their care.
We have known for many years now that patients have multiple conditions. We know too that these patients constitute most of the work and the cost of the health system: people with more than one condition account for about three quarters of the cost of healthcare. It is these slow but remorseless changes in epidemiology that have the biggest impact on health systems, which universally have failed to adapt fast enough.

We continue to have health systems based on disease, hospitals, doctors, drugs, and reactive, episodic care when we need the opposite. Medical education is based on a model of diagnose, treat, cure when the model is dead, and medical evidence and guidelines are built largely from randomised trials that excluded patients with multiple conditions.

We preach health, prevention, and primary whole person care but continue to head in the opposite direction.

Richard Smith

Doctors and patients heading in opposite directions


In the past 100 or so years, there have been two fundamental paradigm changes in medicine. One occurred in 1910, with the Flexner Report, which argued that medicine and healthcare should be science-driven, as should medical education,” said Hood. “The second occurred with the entree of systems thinking into medicine, and that’s led to the concepts of systems medicine, which is a global holistic approach to disease.”

“The second occurred with the entree of systems thinking into medicine, and that’s led to the concepts of systems medicine, which is a global holistic approach to disease,” Hood said. “The second occurred with the entree of systems thinking into medicine, and that’s led to the concepts of systems medicine, which is a global holistic approach to disease,“

Mike Millard

Legendary scientist Leroy Hood sees big changes ahead for 21st Century healthcare

Healthcare IT news
04/2018

http://www.pulsetoday.co.uk/views/letters/gps-need-start-prescribing-lifestyle-medicine/20032339.article
http://www.telegraph.co.uk/health-fitness/body/we-need-a-healthy-dose-of-lifestyle-medicine/
http://www.pulsetoday.co.uk/clinical/more-clinical-areas/diabetes/lifestyle-medicine-could-revolutionise-patient-care/20035520.article
A team from the Academy of Medical Sciences in the UK says this is a growing problem and a huge potential burden on the NHS and other health services. “Clusters” of diseases are becoming more common, they say, such as type 2 diabetes, high blood pressure, osteoarthritis, depression and chronic obstructive pulmonary disease of the lungs.

Specialised hospital doctors treat each of these conditions individually. Patients may have one problem treated and then have to wait months to see a different specialist for another condition.

The experts are calling for a greater role for the GP, who can look at the whole person, but needs more time than a 10 minute consultation.

Sarah Boseley

Patients with multiple conditions not getting best possible care, say experts

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Medical and Lifestyle approaches working together

- Disease oriented
- Specialised
- Same treatments/protocols
- Based on symptoms
- Early detection of disease

- Health oriented
- Looks at root causes
- Can be individualised
- Based on systems
- Preventive approach

Not just ‘Diet and Exercise’

Drivers of symptoms
- Food - nutrients (macro/micro)
- Movement – the right type
- Relaxation / mindset
- Sleep
- Environment
- Genetics

Systems Involved
- Gut / microbiome
- Immune system
- Endocrine system
- Nervous system
- Cardiovascular system
- Musculoskeletal system

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- Nervous system
- Cardiovascular system
- Musculoskeletal system
Two Huge Target Areas

Non-communicable symptoms (e.g. headache, weight gain, tiredness, joint pains, heartburn) → Chronic diseases (NCD)

The Current Situation - NCDs

- Non-communicable diseases (NCDs) kill 41 million people each year, equivalent to 71% of all deaths globally.
- Each year, 13 million people die from a NCD between the ages of 30 and 69 years; over 83% of these "premature" deaths occur in low and middle income countries.
- Cardiovascular diseases account for most NCD deaths, or 17.9 million people annually, followed by cancers (8.8 million), respiratory diseases (3.9 million), and diabetes (1.6 million).
- These 4 groups of diseases account for over 80% of all premature NCD deaths.
- Tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets all increase the risk of dying from an NCD.

The Current Situation - NCDs

- Detection, screening and treatment of NCDs, as well as palliative care, are key components of the response to NCDs.
- Non-communicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behaviour factors.
- The main types of NCDs are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma) and diabetes.
- NCDs disproportionately affect people in low and middle income countries where more than three quarters of global NCD deaths – 32 million – occur.
**Future projections – the scientific narrative**

1. **Autoimmunity**

   Frequencies of the autoimmune diseases increased significantly in the West and North when compared to East and South, respectively.

   **Conclusions:** Despite multiple reports on autoimmune disease frequencies, long-term longitudinal follow-ups are scarce. Incidences and prevalence have increased significantly over the last 30 years. Rheumatic, endocrinological, and gastrointestinal autoimmune diseases in Israel, Neth, and USA increased the most. These data strongly point to a stronger influence of environmental factors as opposed to genetic factors on autoimmune disease development.


2. **Type 2 Diabetes**


3. **Allergies**

   Conclusion: Evidence suggests a combination of strategies, including natural childbirth, breast feeding, increased social exposure through sport, other outdoor activities, less time spent indoors, diet and appropriate antibiotics, may help restore the microbiome and perhaps reduce risk of allergic disease. Preventive efforts must focus on early life.

4. Multiple Sclerosis

The question is why this increase may be occurring. The etiology of MS is complex and likely involves several genes and their interactions with environmental factors. Although there is a growing body of evidence suggesting that this disease is mediated by an autoimmune reaction among susceptible people to a widespread pathogen (Epstein-Barr virus? Candida species? that is ubiquitous in the developed world, none of the current hypotheses on the etiology of MS are completely convincing. Vitamin D production in the skin during sun exposure may potentially explain the increased prevalence of MS at higher latitudes, but this does not explain the overall increase in incidence. The hygiene hypothesis has also generated a large number of studies. What seems clear is that recent reports suggest that the latitude gradient could be disappearing and that the female-to-male ratio among patients with MS has increased in the past decades.

Julián Benito-León

Are the Prevalence and Incidence of Multiple Sclerosis Changing?

Neuroepidemiology 2011;36:148–149

"Conclusions: our findings indicate that over the next 20 years there will be an expansion of morbidity, particularly complex multi-morbidity (4+ diseases). We advocate for a new focus on prevention of, and appropriate and efficient service provision for those with, complex multi-morbidity"
Changing the Way we Think...

- Systems thinking and interconnectedness
- The tools and drivers are often the same - food/sleep/movement/relaxation/environment
- Root cause... "Think why - not what"

The Personal Framework

The Symptom Web

[Diagram of systems and interconnectedness]

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The 4 Pillars

FOOD
MOVEMENT
SLEEP
RELAXATION
Environment

The Lifestyle Prescription

Symptom Web – lays it ALL out
4 Pillars – the tools
How? What? When? – thinking about changes
Lifestyle Prescription – a simple list
The Healthcare Web

Summary

- Increasing global rates of NCD
- Most are preventable and treatable with targeted lifestyle measures
- Tools and drivers are same
- Can present nebulously
- Start with the Symptom Web
- Think of this as ‘loose screws’ that need tightening up
- It’s easy – hard to “get it wrong”/ low risk/ enjoyable

The Aetiology of Type 2 Diabetes

Dr Rangan Chatterjee
MRCPsych, BSc(hons) Immunology, MRCP, MRGCP
Learning Objectives

1. Identify the many different causes of insulin resistance
2. Overview of science on gut dysbiosis and role of lipopolysaccharides
3. The contribution of non-dietary factors
4. The science on time restricted feeding
5. The four primary areas of lifestyle change and using The Personal Framework
6. Specific lifestyle interventions and how to personalise for individuals
7. Case studies to demonstrate concepts

The Gut Microbiome

The gut microbiome is the term given to describe the vast collection of symbiotic microorganisms in the human gastrointestinal system and their collective genetic content. Recent studies have suggested that the gut microbiome performs numerous important biochemical functions for the host, and disorders of the microbiome are associated with many and diverse human disease processes.

Systems biology and omic technologies have established the importance of the gut microbiome in the disease pathogenesis for numerous systemic disease states, such as obesity and cardiovascular disease, and in intestinal conditions, such as inflammatory bowel disease.
Diseases Influenced by Gut Microbial Metabolism

- Gut-brain hypothesis
- Asthma/atopy
- Hypertension/myocardial heart disease
- Peripheral vascular disease
- Colon cancer
- Biliary disease
- Altered xenobiotic/drug metabolism
- Obesity/metabolic syndrome
- Inflammatory bowel disease

The Hadza: Complexity of Microbiome vs Western Microbiome

"Seasonality in diet and lifestyle is a universal thing that modern societies dropped. The high fibre consumption is likely to have been universal, too. The same for the intimate relationship with environmental microbes."

Gut Microbiota Therapies

Rapid environmental transition and modern lifestyle have led to changes in the biodiversity of the human gut microbiota. With clear effects on physiological, immunological, and metabolic processes in human health, alterations in the gut microbiome and intestinal homeostasis have the capacity for multisciplinary effects. Changes in the gut microbiota are implicated in the increasing propensity for a broad range of inflammatory diseases, such as allergic disease, asthma, inflammatory bowel disease (IBD), diabetes, and associated noncommunicable diseases (NCDs).
The field of gut microbiome research has already moved from the idea of describing the core species to identifying the core ecological functions various microbes perform. Many potential species may fulfill any given role. Now another concept may be emerging, which might be called the "keystone relationship." The interaction between fiber and microbes that consume it is the fundamental keystone interaction that everything else is built on in the gut. It may lie at the heart of the symbiotic pact between microbes and humans.

The Peacekeepers

How Many?!

Lipopolysaccharides

Diabetes and obesity are two metabolic diseases characterized by insulin resistance and a low-grade inflammation. Seeking an inflammatory factor causative of the onset of insulin resistance, obesity, and diabetes, we have identified bacterial lipopolysaccharide (LPS) as a triggering factor. We conclude that the LPS/CD14 system sets the tone of insulin sensitivity and the onset of diabetes, and that lowering plasma LPS concentration could be a potent strategy for the control of metabolic diseases.
"About 75% off the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota."

Stig Bengmark

Food Choices

Gut Bugs Immune System

Minimally processed wholefood diet
Healthy microbiome
Immune system balanced
Automatic regulation of body function
Good health

Highly processed modern diet
Disrupted microbiome
Immune system unbalanced
Low grade inflammation
Poor health

PREScribing Lifestyle Medicine

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55

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**Time-Restricted Feeding**

- Time-restricted feeding (TRF) confines food access to 9–12 hrs during the active phase.
- TRF is a therapeutic intervention against obesity without calorie restriction.
- TRF protects against metabolic diseases even when briefly interrupted on weekends.
- TRF is effective against high-fat, high-fructose, and high-sucrose diets.

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While subjects randomized to time-restricted feeding had meals at 1 pm, 4 pm, and 8 pm, those who were in the normal diet group had meals at 8 am, 1 pm, and 8 pm. At the end of 8 weeks of 16 hours of fasting, the time-restricted feeding group had a significant reduction in fat mass, leptin, triglyceride, total testosterone, insulin growth factor-1, and interleukin-1β levels and had a significant increase in adiponectin levels compared to the normal diet group.

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Based on the findings of studies conducted on human subjects, dawn-to-sunset fasting has the potential to be a cost-effective intervention for obesity, metabolic syndrome, and NAFLD.
Melatonin treatment inhibits insulin secretion

The Symptom Web

Type 2 Diabetes

Exercise
Sleep
Diet
Stress

Muscle Mass and Insulin Resistance

Higher muscle mass is associated with better insulin sensitivity and lower risk of PDM.

Dosing exercise as brief, intense 'exercise snacks' before main meals is a time-efficient and effective approach to improve glycaemic control in individuals with insulin resistance.


Sitting vs Standing

Breaking sitting with standing and light-intensity walking effectively improved 24 h glucose levels and insulin sensitivity respectively in individuals with type 2 diabetes to a greater extent than structured exercise. Thus, the results suggest that breaking sitting and standing with light-intensity walking may be an alternative to structured exercise to promote glycaemic control in patients with type 2 diabetes.

Specific Advice for Insulin Resistance

- Walk More and Sit Less
- Focus on Muscle Mass
- Exercise 'Snacks'
- High Intensity Interval Training
The Symptom Web

Exercise

Stress

Sleep

Type 2 Diabetes

Exercise

Stress

Sleep

Diet

Type 2 Diabetes

The Symptom Web

Sleep

Type 2 Diabetes

Exercise

Stress

Importance of Sleep

Chronic sleep deprivation causes:

- Increased gut permeability
- Increased inflammation
- Increased visceral fat
- Increased leptin levels
- Increased insulin resistance

Sleep Deprivation

Partial sleep deprivation during only a single night induces insulin resistance in multiple metabolic pathways in healthy subjects. This physiological observation may be of relevance for occurrence of dysregulation in patients with Type 1 and Type 2 diabetes.
Sleep Deprivation in Healthy Individuals

- Participants who slept 4 hours per night for 6 nights, were 40% less effective at absorbing a standard dose of glucose compared to when they were fully rested
- Some would now be diagnosed as prediabetic
- Sleep deprivation causes insulin resistance
- Chronic sleep deprivation is a major contributor to the development of type 2 diabetes

The Symptom Web

Exercise

Sleep → Type 2 Diabetes → Stress

Diet
In recent years, the roles of chronic stress and depression as an independent risk factor for decreased insulin sensitivity and the development of diabetes have been increasingly recognized. We hypothesized that acute psychological stress may cause the development of insulin resistance, which may be a risk factor in developing type 2 diabetes.

Stress and Insulin Resistance

- Glucose enters cells via GLUT-4 receptor
- Stress disables GLUT-4 – this is insulin resistance
- Oxidative stress possible mechanism
- We are well adapted to a short term increase in cortisol and glucose

Sleep, Stress and Metabolism
T2DM can now be understood to be a metabolic syndrome potentially reversible by substantial weight loss, and this is an important paradigm shift. The observations carry profound implications for the health of individuals and for the economics of future health care.

Type 2 Diabetes & VLCDs


10% of total UK NHS expenditure goes on treating diabetes (9 billion of which 1 billion spent on antidiabetes drugs)

• Medical costs are x2 to x3 greater than the average for people with diabetes

Diabetes management is beginning to focus on reversible underlying disease mechanisms rather than treating symptoms and subsequent multisystem pathological consequences

Recognising remission of diabetes can be a powerful motivator for patients to maintain weight loss.

Type 2 Diabetes & Lifestyle Medicine


Unwin D et al. Low carbohydrate diet to achieve weight loss and improve HbA1c in type 2 diabetes and pre-diabetes: experience from one general practice PRACTICAL DIABETES VOL. 31 NO. 2 (2014)

Remission of Type 2 Diabetes

It could be said that starchy foods such as bread, pasta or rice are just concentrated sugar, and as such may represent a block to good diabetic control even when termed "wholegrain" or "wholemeal" (GI index 71) than table sugar itself (GI index 68). This is the basis for the low carbohydrate diet currently gaining popularity via the internet.

A low carbohydrate diet was trialled in a primary care setting for 19 diabetic or pre-diabetic patients, bringing about improvements in health markers over an eight month period. Blood glucose control improved...

Patients reported the diet was surprisingly easy to comply with and also noticed increasing energy levels. Seven patients were able to come off medication of one form or another.
Type 2 Diabetes Remission
- Roy Taylor’s work
- 1g fat loss in pancreas
- Multiple methods
- Low Calorie
- Low Fat
- Low Carb
- Patients need choices!

Case Studies
- Rachel, 36 year old female
- Andrew, 55 year old executive

Case Study – Rachel
- 36 year old female
- Weight - 19st 10lbs
- Struggling to lose weight
- Lacking motivation and mood often low
- Mother had T2DM
- HbA1C – 7.3%
- Joint pains
- Fatigue
Case Study - Andrew

- 55 year old executive
- 2 years Hx DM
- On Metformin 500mg BD
- HbA1c initially 8.0 - tried a 'low carb' diet and HbA1c came down to 7.0. Tired restricting carbs further, but HbA1c remained at 7.0
- Frustrated by lack of improvement
- Gym twice per week - cardio
- Working hard professionally and NO off time
- No relaxation
- Sleep impacted

Lifestyle Intervention or Metformin?

Conclusions: lifestyle changes and treatment with metformin reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin.
Learning Objectives

1. Appreciate the core role of inflammation in NCDs
2. The value of personalised lifestyle interventions
3. Three core biological mechanism contributing to NCDs
4. Innate vs. Adaptive Immunity
5. The microbiome and inflammation
6. Environmental pollutants and the impact on health
7. The benefits of community, environment and social prescribing
8. Strategies for behaviour change

Replacing "happiness" with "inflammation" in Thomas Merton's quotation holds true for the processes that govern our immune response and health.

The balance between pro- and anti-inflammatory signals regulates inflammatory responses, leading to either restoration of health or the development and progression of disease, depending on whether it creates equilibrium or dysfunction.

"Happiness is not a matter of intensity but of balance, order, rhythm and harmony."

Many layers of evolutionarily conserved interactions exist between immune response and metabolism. Proper maintenance of this delicate balance is crucial for health and has important implications for many pathological states, such as obesity, diabetes, and other chronic non-communicable diseases.
Inflammation

In summary, these data are consistent with a causal role of gut-produced SCFAs, specifically butyrate and propionate, with respect to energy balance and glucose homeostasis in humans.

Sanna et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Bioessays* 2019 *Nature Genetics*

Increasing evidence indicates that the human gut microbiome plays a role in immune function and metabolic diseases.

Manipulation of the gut microbiome offers an alternative to pharmacological interventions, provided that altering microbiota composition and/or function (for example, through personalised nutrition) can be demonstrated to have clinical benefit.

Mechanisms of Overarching Model

1. Does this person need to be rid of something? (toxic, allergic, infectious, poor diet, stress)
2. Does this person have some unmet individual need required for improved function?
Agreed Action

1 What does the patient think he or she can do to change?
Agree to change as a partnership with the patient leading.

Shared decision making (SDM) is a collaborative process in which practitioners and patients/clients work together to select tests, treatments and health management or support packages, based on clinical evidence and their informed preferences and values. [https://www.england.nhs.uk/shared-decision-making/](https://www.england.nhs.uk/shared-decision-making/)

The Lifestyle Prescription

- FOOD
- MOVEMENT
- SLEEP
- RELAXATION
- Environment

On The Shoulders....

Although the promise of targeted, personalised medicine with the microbiome as a therapeutic targeting is now on the horizon, we may do well to heed the words of Gustav Wislicenus, physician and microbiologist who wrote in 1933

“For dysbiosis cannot be cut out of the structure of life for independent treatment, nor can (eu)biosis be treated intelligently except in its totality, its all-embracing oneness…”

As noted over 50 years ago by Rene Dubos, the true value of microbial contributions to health often becomes apparent only when their normal operations are disrupted by various environmental factors.


René Jules Dubos (February 20, 1901 – February 20, 1982) was a French-born American medical microbiologist, experimental pathologist, environmentalist, and winner of the Pulitzer Prize for General Non-Fiction for his book So Human An Animal of Giants….

Today….

most of the progress in the field comes from new knowledge about the functional properties of these microorganisms in physiology and their effect in mucosal immunity and distal inflammation. This review summarizes the preclinical and clinical evidence on how dietary, probiotic, prebiotic, and microbiome based therapeutics affect our understanding of wellness and disease, particularly in autoimmunity.


Other non-specific factors

- Complement system
- Phagocytosis
- Epithelial barriers & digestive functions
- NK cells, acute phase proteins
- Enzymes, transferrin, etc

Neutrophilic granulocyte

Eosinophilic granulocyte

Monocyte/macrophage, dendritic cells

Cell-mediated immunity

Humoral immunity

T lymphocytes

B lymphocyte

Plasma Cell

Activation

Antigen-presenting

Th Immuno-globulins

Stimulate cell-mediated immunity & phagocytosis

Antigen-presenting

CD8+ cytotoxic T cells

CD4+ Th1 cells

CD4+ Regulatory T cells

CD4+ Th2 cells

IL-4

IL-5

IL-10

IL-13

Stimulate humoral immunity & eosinophils

Inflammation

Oxidation
Nutrition science is moving away from focusing on isolated nutrients, deficiency diseases, calorie counting, and simple surrogate outcomes and toward foods, chronic diseases, diet quality, and complex biological mechanisms and pathways.

For both the patient in our clinic and the population around us, it is appropriate to act on reasonable conclusions based on the totality of existing evidence and expected risks versus benefits. As in all fields, application cannot await flawless evidence or perfect understanding.

Mozaffarian D, Forouhi NG. Dietary guidelines and health—Is nutrition science up to the task? BMJ. 2018 Mar 16

The microbiota and its metabolic machinery produce a myriad of metabolites that serve as important messengers between the diet, microbiota, and host. Short-chain fatty acids affect immune transcription and epithelial integrity via G-protein coupled receptors and excretory mechanisms. By increasing our understanding of interactions between diet, immunity, and the microbiota, we might develop food-based approaches to prevent or treat many diseases.

GPRs have been of long-standing interest as pharmacological targets, as they regulate various diverse physiological processes and have druggable/nutrient sites that are accessible at the cell surface.

https://www.nimml.org/nutritional-immunology
Effects of Various Diets on Microbiota and Immunity

Foods (food components)

Microbiota...

- Food components
- Microbiota-dependent
- Involved pathways
- Effect on immunity

Inflammatory

Red meat, eggs, milk (contain phosphatidylcholine, L-carnitine)

+ a TMA

TMAO

Atherosclerosis↑ (proinflammatory cytokines, forward cholesterol transport)

High-fat diet + a Intestinal permeability

↑ TLRs

Endotoxemia

Intestinal cytokine expression

↑ Intestinal and systemic inflammation

Milk-derived fat + b Expansion of pathobions (eg, B wadsworthia)

Proinflammatory cytokines

↑ Th1-driven inflammation

Salt?

p38/MAPK pathway

Th17-driven inflammation

↑ Anti-inflammatory

Cruciferous vegetables (carbazoles) + b AhR ligands

IL22↑, maintenance of intraepithelial lymphocytes and innate lymphoid cells

Vegetables, fish (tryptophan) + b AhR ligands

c GPCRs

d IL22↑, mucosal protection from inflammation

Soluble fibre (complex carbohydrates) + Generation of SCFA

GPCRs (Gpr41, Gpr43, Gpr109a)

Mucus production

↑ IgA production

Proinflammatory cytokines↓

Tregs↑

Mediterranean diet (enriched in ω-3 fatty acids)

? Gpr120

Proinflammatory cytokines↓

Knowledge, opportunity, income, education, social community—can be changed by GP intervention
Chronic inflammatory diseases are stimulated by current lifestyle: how diet, stress levels and medication prevent our body from recovering.

**Nutrition and Inflammation**

Mitochondria and Diet

Mitochondria are responsible for oxidative metabolism and converting substances from the foods we eat into energy for essential functions. Dietary biofactors that optimise mitochondrial function work by either activating mitochondriogenesis or inhibiting apoptosis. This in turn improves oxidative defences and has a major impact on efficient energy utilisation by cells.

**Assimilation (digestive function)**

Gastrointestinal Remedies - UK - May 2016

"86% of all British adults have suffered some form of gastrointestinal (GI) problem or ailment in the last year.*

But when it comes to preventing GI problems, for some it seems they adopt the mantra 'you are what you eat'. Of those who have experienced GI problems in the last 12 months, 43% say they know what foods to avoid to prevent GI problems, while 23% say they put a lot of effort into their diet to prevent GI issues. However many GI sufferers are still uncertain, over half (57%) say they are unsure whether their diet is the source of their problems.

Refers to digestion and absorption of nutrients in the gut, as well as the health, diversity, and balance of the microbes that inhabit the digestive tract.
Circadian Rhythms

Preclinical research has demonstrated that the bacteria in the GI tract vary over the course of a day, with relative abundances of bacterial taxa, proximity of bacteria to the gut wall, and microbial metabolism all exhibiting circadian rhythms. Time of eating is considered a potential modulator of circadian rhythms with an effect on both bacterial abundance and function. Furthermore, the gut microbiome appears to have a reciprocal relationship with the human body’s circadian clock and eating patterns. Emerging research suggests that some of the observed health effects related to eating patterns, such as time-restricted feeding (TRF) and meal frequency, may also be related to the GI microbiome.

The Microbiome and Health

**What we know**
- Probiotic supplementation has several beneficial effects on human health
- The resident murine gut influences human-microbiome interplay
- Diet and medication have a strong influence on gut microbiota composition
- Microbiota composition influences response to chemotherapy and immunotherapy
- Microbiota composition affects glucose response to foods and can be used to personalize diet

**What we don’t know**
- Are natural probiotics in food better than probiotic supplements? Should we take them preventively?
- Can probiotics influence food choices and appetite?
- How do probiotics in food affect human health?
- What is the effect of pesticides in food on the gut microbiome? Is organic food better for the gut microbiota?
- Should all new drugs and food chemicals be tested on the gut microbiota?

Ingested bacteria can provide a temporary complement to resident bacterial communities as part of our transient microbiome. The extent of integration is, to some extent, species- and strain-dependent and may vary depending on dietary context and baseline microbiota structure. Ingested bacteria can influence the composition of the microbiota of the small intestine and may alter the genetic diversity of the gut microbiota. Clinical data have provided evidence that ingested bacteria may modulate production of short-chain fatty acids and inhibit some opportunistic pathogens.
**Possible Mechanisms Contributing To Restoration Of The Microbiota**


**Biotransformation & Elimination**

Chemical changes of a xenobiotic, phytochemical or endogenous compound that render it less toxic and/or more readily excreted.

**Individual Variation**

1. Overwhelming toxic load
2. Poor elimination
3. Intestinal dysbiosis
4. Nutrient deficiencies
5. High sugar, low protein diets
6. Oxidative stress
7. Chronic inflammation
8. Stress, emotional trauma
9. Polymorphisms in phase I & II enzymes

Chemical intolerance occurs in 1 of 5 primary care patients yet is rarely diagnosed by busy practitioners. Symptoms may resolve or improve with the avoidance of salient chemical, dietary (including caffeine and alcohol), and drug triggers.


20%
There is evidence that pollutant toxicity can be modulated by nutrition and lifestyle choices. Western diets, abundant in processed foods, excess caloric content and proinflammatory fatty acids, may contribute to the development of obesity and cardiovascular diseases and enhance pollutant toxicity. Conversely, diets rich in bioactive food components, such as polyphenols and omega-3 fatty acids (i.e. the Mediterranean diet), are associated with reduced risk of inflammatory diseases and can attenuate the negative health effects of pollutant exposure.


Environmental pollutant exposure is associated with numerous health complications ranging from cardiovascular disease, diabetes, and metabolic syndrome.

Intestinal barrier defects have been associated with a broad range of diseases, including both GI (e.g. celiac disease (CeD), inflammatory bowel disease (IBD), skin carcinoma) and extra-intestinal disorders (e.g. chronic-liver disease, type 1 diabetes, obesity). For all these diseases, it is commonly hypothesized that dysfunction of the intestinal barrier and an uncontrolled flux of antigens across the intestinal epithelium may challenge the immune system of susceptible individuals and affect the host-microbial balance, as such initiating inflammatory mechanisms in the gut or more distant organ systems.


Intestinal barrier covers a surface of about 400 m² and requires approximately 40% of the body’s energy expenditure. It prevents against loss of water and electrolytes and entry of antigens and microorganisms into the body while allowing exchange of molecules between host and environment and absorption of nutrients in the diet.

Why do we need a gut barrier? The intestinal barrier is a complex multifaceted system, consisting of an outer “physical” barrier and an inner “functional” immunological barrier. The interaction of these 2 barriers enables equilibrium to be maintained.
Gut Microbiome Diversity
Relates to

- Gut microbiome diversity is inversely correlated with the number of sugary drinks per day the Pioneers report consuming ($p=1.3\times10^{-5}$).
- Low gut diversity is associated with disease such as obesity and inflammatory bowel disease.

4 sugary drinks induce dysbiosis & Change barrier integrity


Signalling and messaging
Refers to hormones, neurotransmitters (the chemicals nerve cells use to communicate with one another), and inflammatory mediators called "cytokines."

Hormone imbalances are often tied together into what is called the hypothalamic-pituitary-adrenal-thyroid-gonadal (HPATG) axis. This is because the different hormone systems are connected to one another, and operate in a hierarchical fashion with the demand for cortisol, the stress hormone, taking preference.

The axes can influence each other by cross-talk from hormones or hormone-mimicking compounds.

Behaviour Science
Stages of Change Model developed by Prochaska and DiClemente

- Stage 1: Pre-contemplation (Not Ready)
- Stage 2: Contemplation (Getting Ready)
- Stage 3: Preparation (Ready)
- Stage 4: Action
- Stage 5: Maintenance

Relapses are patterns of behaviour reversal and need Ongoing support: coaching or peer management

Relapses are patterns of behaviour reversal and need Ongoing support: coaching or peer management
• Receives an explanation that makes sense to them
• Feels safety in the presence of aid or the expression of care and concern
• Experiences an intervention they expect will resolve the problem as they understand it
• Gains skills and knowledge that allows control or mastery over the experience


Effective & Modifiable Factors in Managing Inflammation, Oxidation, Immune Dysfunction

3

- Stress (immune response)
- Hormonal Imbalances
- Food (AhR, GPR, HDA)
- Environment
- Damaged Mitochondria
- Sleep (Circadian Rhythm)
- Infections (sterile inflammation)
- Exercise

Step 1 – Symptom Web
PMH + ask about a “typical day”

- Environment (working/learning/commute)
- Exercise (movement type)
- Sunlight (Exposure)

- Sleep (quality/amount)
- Symptoms

- Infections (see trigger/parasites)
- Diet (nutrition)

- Genetics (polymorphisms)
- Stress (personality/external factors)
Simple Questions: Causes and Function

2. DO YOU need to be rid of something? (toxic, allergic, infectious, poor diet, stress)

2. Do YOU have some unmet individual need required for improved function?

Step 1 – Symptom Web
PMH + ask about a “typical day”

Consultations in Practice
Dr Ayan Panja MRCGP
1. Understanding the “super generalist” approach  
2. Using the personal framework with worked real life examples  
3. Familiarity with the symptom web  
4. Getting used to the process of generating the lifestyle prescription  
5. Understanding that symptoms arise from systemic malfunction  
6. Quick tools that are used in practice  
7. Molecular mimicry as a concept and clinical impact  
8. Real data for you to help you start to work on a case

Learning Objectives

A Vision for Population Health

A recent report from The King’s Fund (A VISION FOR POPULATION HEALTH) argues that reversing the stall in life expectancy will require a shift from our current focus on diagnosing and treating illness to promoting the health and wellbeing of the entire population.

“Social prescribing initiatives are an encouraging move towards giving us the tools to address social determinants but need to target people only after they present with a problem.”

“Nothing is at the heart of our nation’s health” emphasises the central role of primary care… but we feel poorly equipped to influence them in our current system.

The new NHS long-term plan has promised additional funding for general practice and proposed an expansion of primary care networks – how this can translate into a greater emphasis on prevention is not clear, but it would be a lost opportunity if we don’t utilise our potential to address population health in the future. As GPs, we need to rediscover ways of keeping one eye on the individual patient sitting in front of us and another on the wider community.
The Lifestyle Prescription

FOOD
MOVEMENT
SLEEP
RELAXATION
Environment

Turning ‘What?’ into ‘Why?’

Exercise
Sunlight
Stress
Genetics
Infections
Sleep
Environment

The Cases

- Gary – age 37, intractable heartburn and TATT
- Claire – age 18, fatigue/low mood
- Zarin – age 52, cognitive decline
- David
Gary – Heartburn and TATT

- Age 37
- Hairdresser
- Heartburn for 10 years on and off
- Gave up smoking in 2014
- Normal endoscopy late 2016
- H-Pylori – ve
- On esomeprazole 40mg bd
- Cannot cope with level of daily discomfort
- Tired all the time despite gym
- No change in stress / diet recently
- Recurrent otitis media as child / myringotomy

“Typical day”
- Co-owns salon – very busy
- Wakes up at 7:00am
- Latte + Croissant walking on way to work (30 minute walk)
- 9:30am starts work
- Another Latte and biscuits on the go at 10:30am
- Works through until 1pm
- Lunch is quick sandwich and water – takes turns with colleague
- Has tea and biscuits on the job
- On the go until 6:30pm
- Home by 7:00-7:30pm
- Sits on sofa until 9:00pm
- Dinner 9:30pm (Curries/pasta/chicken)
- Bed by 10:30pm (often asleep on sofa)

Claire – Fatigue / low mood

- Age 18
- High level sportsperson - always super healthy
- 4-5 months feeling tired, anxious, low, bloated, poor appetite, achy joints and muscles
- Normal standard bloods
- Told “probably viral” …. Hmm…..
- Stress – fell out with best friend 9 months ago
- UTI x 3 recently
- Unable to compete in sport
- Overwhelming tiredness
- Heart rate variability abnormal
- Weakness / cramps
- Unable to train
- Heart rate variability abnormal

“Typical day”
- Breakfast – cereals / toast + milk
- Tired all day
- Poor mood
- Poor sleep
- Poor strength / cramps
- Unable to train
- Classic teenager diet + fruit

Tips and tools (evolving autoimmunity)

- Claire – Stress > UTI (flora) > food sensitivity > systemic symptoms including autonomic dysfunction (HRV) > ? HLA DQ2 or DQ8 (keratosis pilaris)
- A word on gluten as an example – 90% of coeliac patients are HLA DQ2 +ive, rest are HLA DQ8 +ive
- NCGS is a described entity – ‘molecular mimicry’
- Not just TG2 antibodies (TG3 = skin and TG6 = brain)
- Dermatitis Herpetiformis / gluten ataxia etc
Intestinal permeability

This barrier represents a huge mucosal surface, where billions of bacteria face the largest immune system of our body. On the one hand, an intact intestinal barrier protects the human organism against invasion of microorganisms and toxins, on the other hand, this barrier must be open to absorb essential fluids and nutrients. Such opposing goals are achieved by a complex anatomical and functional structure the intestinal barrier consists of - the functional status of which is described by intestinal permeability.


Genes, Drugs (NSAIDS), Alcohol, Smoking, Stress, Nutrient deficiencies, Food Antigens, Antibiotics, Disease, Dysbiosis, Inflammation, Oxidation, Immune deficiency, Diet, Fibre
Tips and tools (Mg defy symptoms)

Mg is an intracellular cation

Does the "opposite" of calcium - inhibitory

- Palpitations
- Migraines
- Twitchy eyelids (myokymia)
- Muscle tension
- Brittle nails and hair
- Insomnia
- Fatigue
- Anxiety

Only 1% in bloodstream

Common causes

- Beige diet low in greens/nuts/avocado
- Coffee
- Alcohol
- Soil increasingly poor

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- Beige diet low in greens/nuts/avocado
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Magnesium

Furthermore, because of chronic disease, medications, decreased in food crop magnesium contents, and the availability of refined and processed foods, a vast majority of people in modern societies are at risk for magnesium deficiency. Subclinical magnesium deficiency is prevalent, and magnesium in order to prevent suboptimal magnesium deficiency, especially fortified with an optimal magnesium status. Magnesium deficiency increases the risk of numerous types of cardiovascular disease. Furthermore, an incurable amount of healthcare costs and suffering, and death is prevented by public policy. This is a simple, cost-effective strategy across the world and treat subclinical magnesium deficiency. Magnesium deficiency causes a range of symptoms.


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Zarin – TATT/ IBS/ cognitive decline/ arthritis

- Age 52, married 2 sons
- Mum had Alzheimer’s
- Takes a load of supplements (B12/ nootropics/ zinc/ probiotics) – OTC
- Could not name objects visually 4 yrs ago
- Not menopausal yet (benign breast dis/ fibroid)
- IBS out of control for years since childhood
- Pain in small and large joints (+ve ANA)
- Very motivated/ exercises a lot/ low carb diet/ healthy fat/ protein diet
- Bloods entirely ‘optimal’ except vit D 41

The Hidden Benefits to the NHS

Imagine the knock on effect of these cases in a few years time in terms without a lifestyle approach of....

1. Patient outcomes?
2. Cost of appointments
3. Cost of prescriptions
4. Cost of referrals
5. Time spent on follow ups

- Extending this by getting patients to share their stories
- Local support groups

Summary

- Look at the big picture – The Personal Framework
- Start with the symptom web, think of past medical history and “timeline”
- 4 pillars
- How? What? When?
- The Lifestyle Prescription
- Go for quick wins based on history, examination and daily routine
Step 1 – Symptom Web
PMH + ask about a “typical day”

- Environment (working/living/commutes)
- Sunlight (Exposure)
- Sleep (quality/quantity)
- Symptoms
- Infections (can trigger/paradigm)
- Genetics (FHx/phenotype)
- Stress (personality/environment/trauma)
- Diet (nutrition)
- Exercise (movement type)

The 4 Pillars
- EAT
- SLEEP
- MOVE
- RELAX

How? What? When?

Part 5
Food as information

Michael Ash
BSc(Hons), RNT
Learning Objectives

1. Understand that food is more than fuel: contains ‘positive and negative’ molecular patterns
2. How food affects health
3. The role of the microbiota and related genetic components in metabolising foods
4. How food choices induce an immune response
5. How to generate and sustain immune tolerance
6. The immune system and its role in NCDs and functional disorders

Personalised Nutrition

- Personalised nutrition uses information on individual characteristics to develop targeted nutritional advice, products, or services to assist people to achieve lasting dietary change in behaviour that is beneficial for health
- Personalised nutrition is based on the concept that individualised nutritional advice, products, or services will be more effective than more traditional generic approaches
- The personalisation may be based on biological evidence of differential response to foods/nutrients in subgroups or individuals characterized, analysis based on current behaviour, preferences, barriers and objectives
- Personalised nutrition is based on the concept that individualised nutritional advice, products, or services will be more effective than more traditional generic approaches
- The overall consensus is that much research and regulation is required before personalised nutrition can deliver the expected benefits

For every person they do help (blue), the ten highest grossing drugs in the USA fail to improve the conditions of between 3–24 people (red)

https://www.nature.com/news/personalized-medicine-time-for-one-person-trials-1.17411
Mechanisms of Overarching Model

Simple Questions: Causes and Function

1. Does this person need to be rid of something? (toxic, allergic, infectious, poor diet, stress)
2. Does this person have some unmet individual need required for improved function?

Agreed Action

What does the patient think he or she can do to change?
Agree to change as a partnership with the patient leading.

Shared decision making (SDM) a collaborative process in which practitioners and patients/clients work together to select tests, treatments and health management or support packages, based on clinical evidence and their informed preferences and values. [https://www.england.nhs.uk/shared-decision-making/]
The emerging appreciation that certain inflammatory diseases are initiated by multispecies communities, wherein constituent organisms contribute to disease collectively rather than individually, challenges the notion that bacteria can be divided into two categories: commensals and pathogens. Their spectrum that ranges from commensalism to pathogenicity, dependent upon the nature of its interactions with other community members and the host’s condition, includes newly recognised categories such as ‘accessory pathogens’, ‘keystone pathogens’, and ‘pathobionts’.


Inflammation

- Influences gene expression via microRNA (miRNA) transfer
- Supplies Macro & Micro Nutrients
- Fibre for immune maturation, microbiota expansion and SCFA production
- Secondary metabolites (phytochemicals >5k) mediators of transcription
- Antioxidants
- Organisms (bacteria/yeast) for ecological diversity

Numerous environmental, geographical, social, and individual factors influence human food choice and intake.


Food as Information - NOT Fuel

Food is not just calories. It contains messenger molecules that communicate with every cell in your body. It provides a personalised medicine focus at the interface of immunology, inflammation and nutrition.

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Food as Information

Cauliflower

Immunological Tolerance

- Inflammatory conditions are on the rise due to changes in lifestyle, food consumption patterns, and ageing.
- Disease-prevention/targeted medical nutrition can be aimed at chronic inflammation/oxidation/immune dysfunction.
- Inflammation-associated conditions, such as atherosclerosis, type 1 and type 2 diabetes, obesity, Autoimmunity and many others, are a growing burden to health budgets.
- Inflammatory, oxidative and immune-related conditions are thought/understood in part to result from failing mechanisms of immunological tolerance.


Regulatory T cells (Treg)

Of these mechanisms, deficient suppressive activities of a specialised subset of T cells, called regulatory T cells (Tregs), are being recognised as a major factor in the failure of immunological tolerance.

Immune tolerance is the state of unresponsiveness of the immune system to substances or tissues that have the potential to induce an immune response. Self tolerance to an individual’s own antigens is achieved through both central tolerance and peripheral tolerance mechanisms.*

*https://www.nature.com/subjects/immune-tolerance
Mucosal Immunology

Since 1990 mucosal immunology has expanded from what many considered a niche discipline to one of the hottest areas in immunobiology today. Mucosal immunologists focus on the sites at which most antigens enter – the mucosal surfaces of the gastrointestinal, respiratory and urogenital tracts, which are the body’s first line of defence against an array of pathogenic/pathobiontic (dysbiotic) microbes.

They study the disease/dysfunction states that result when the mucosal immune system’s ability to distinguish pathogens from innocuous antigens fails (i.e. inflammatory bowel diseases, food allergies, gluten intolerance).

Harnessing the mucosal immune system’s unique features to prevent or treat disease is another rapidly growing area of interest that includes the development and refinement of orally administered immunotherapeutics.

http://www.socmucimm.org/

- SCFAs (Butyrate)
- HDAC
- GPCR (43,41,109A,35,120)
- ω3 EFAs
- Trycats
- Vit A & D
- Fibre & Probiotics

Proposed to induce immune maturation and anti-inflammatory mechanisms to maintain immune tolerance in the gut and systemically.

Collated from in vivo, in vitro and human studies.

An Apple a Day x 2

Apples also help to alter the pathobiont (these are commensals that alter their relationship with the host depending on environmental triggers) mix of bacteria in human guts when consumed regularly, suggesting a role for their use in mild to moderate dysbiosis leading to inflammation and loss of tolerance. In a small but clinically interesting study, healthy adults noted an increase in Bifidobacteria species and Lactobacillus numbers following a diet of 2 apples a day for 2 weeks. Healthy adults noted an increase in Bifidobacteria species and Lactobacillus numbers also rose, but Clostridium. Perfringens, Pseudomonas and Enterobacteriaceae declined on a diet of 2 apples a day for 2 weeks.

Quantitative PCR was used to measure effects of the polyphenols on the balance between the major groups of intestinal bacteria that are known to influence gut health, i.e., Bifidobacterium spp., Bacteroidetes, and Firmicutes. Fermentation of polyphenols stimulated proliferation of bifidobacteria and decreased the ratio of Firmicutes to Bacteroidetes relative to controls. ... effect is indirect, i.e., it is mediated by biotransformation products, rather than the original plant compounds.

Three commercial apple varieties—Renetta Canada, Golden Delicious and Pink Lady—were studied in a small but clinically interesting study. Healthy adults noted an increase in Bifidobacteria species and Lactobacillus numbers following a diet of 2 apples a day for 2 weeks. Healthy adults noted an increase in Bifidobacteria species and Lactobacillus numbers also rose, but Clostridium. Perfringens, Pseudomonas and Enterobacteriaceae declined on a diet of 2 apples a day for 2 weeks.

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Apples - a Tolerance Tool?

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Renetta Canada (Russett) is the variety of apple with the longest history. Grown in Europe since 1600. Delicious baked or stewed with cinnamon and raisins.

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**Anti-Inflammatory Diet**

An anti-inflammatory diet should not be prescribed according to its isolated components. A truly integrative and anti-inflammatory approach should focus on eating mindfully and in caloric balance to help decrease inflammation. The definition of an anti-inflammatory diet will likely continue to evolve with further advancements in nutrition research.

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**Table 1: Comparison of Diet Components**

<table>
<thead>
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<th>Diet</th>
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<th>Mediterranean Diet</th>
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<td>Protein sources</td>
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Nutrition, microbiome, metabolism, genetic predisposition, and the immune system interact to delineate health and disease.


This barrier represents a huge mucosal surface, where billions of bacteria face the largest immune system of our body. On the one hand, an intact intestinal barrier protects the human organism against invasion of microorganisms and toxins, on the other hand, this barrier must be open to absorb essential fluids and nutrients. Such opposing goals are achieved by a complex anatomical and functional structure the intestinal barrier consists of, the functional status of which is described by 'intestinal permeability'.

Intestinal permeability is a functional entity separating the gut lumen from the inner host, and consisting of mechanical elements (mucus, epithelial layer), functional elements (defensins, IgA), immunological elements (lymphocytes, innate immune cells), muscular and neurological elements.

This is defined as a functional feature of the intestinal barrier at given sites, measurable by analyzing flux rates across the intestinal wall as a whole or across wall components of defined molecules that are largely inert during the process and that can be adequately measured in these settings.

Normal intestinal permeability is defined as a stable permeability found in healthy individuals with no signs of intoxication, inflammation or impaired intestinal functions.

Impaired intestinal permeability is defined as a disturbed permeability being non-transiently changed compared to the normal permeability leading to a loss of intestinal homeostasis, functional impairments and disease.
The Intestinal Barrier


Flavonoids on the other hand are an example of plant-derived components with proven beneficial effects on the epithelial barrier. Flavonoids are abundant in most vegetables, fruits, green and black tea, red wine, chocolates, and coffee. The normal intake of flavonoids in the population is estimated to be below the threshold for significant beneficial effects.

Microbial Stability

Diet has a major impact on human health, whether by affecting the host directly or through changes of the microbial community. The microbial community in the mammalian gut is a complex and dynamic system with a steady state, which can be perturbed by many environmental factors, including diet, lifestyle, drugs, thereby changing the host's physiology. As a response to dietary changes, shifts in the composition of the gut microbiota occur.

A healthy gut microbiota maintains a symbiotic relationship within the gut mucosa offering essential functions in metabolism, immunology, and protection of the host.

Why Do We Care?

Key messages:
- Gut microbiota influences many areas of human health from innate immunity to appetite and energy metabolism.
- Targeting the gut microbiome, with probiotics or dietary fibre, benefits human health and could potentially reduce obesity.
- Drugs, food ingredients, antibiotics, and pesticides could all have adverse effects on the gut microbiota.
- Microbiota should be considered a key aspect in nutrition; the medical community should adapt their education and public health messages.
- Fibre consumption is associated with beneficial effects in several contexts.
…highlight the evolutionarily highly conserved AhR system as a previously unknown link between external environmental stimuli and the maintenance of specialized immune cell populations (IELs), as well as the control of the microbiota.

Our results provide a molecular basis for the importance of cruciferous vegetable-derived phytonutrients as part of a healthy diet in sustaining important elements of the immune system and in controlling bacterial colonization. Furthermore, we reveal an important role for AhR, independent of xenobiotics, in the physiology and homeostasis of epithelial barrier sites.

Elements are also functional in the large intestine.

Climate Change = Nutrient Change?

Loladze has investigated the effect of rising CO2 levels on the nutrient levels in food plants by analyzing data on 130 varieties of plants: his dataset includes the results of 7,761 observations made over the last 30 years, by researchers around the world.

Elevated CO2 levels were found to reduce the overall concentration of 25 important minerals—including calcium, potassium, zinc, and iron—in plants by 8% on average.

Furthermore, Loladze found that an increased exposure to CO2 also increased the ratio of carbohydrates to minerals in these plants.
Osteoarthritis

What is already known?
• Dietary supplements are widely used by patients.
• Clinical guidelines are still controversial.
• Clinical benefits or harms have not been established.

What are the findings?
• This systematic review and meta-analysis summarises all available randomised placebo-controlled trials on efficacy and safety of dietary supplements to treat hand, hip or knee OA.
• Supplements are found to be generally safe for treating osteoarthritis.
• The most widely used supplements (e.g., glucosamine, chondroitin) do not provide a clinically important effect on osteoarthritis.
• Some little-known supplements (e.g., Boswellia serrata extract, pycnogenol, curcumin) appear to have larger effects, although current data are of low quality.

Avocados

Compared to a raw carrot meal without avocado, the addition of one avocado (150 g):
• Significantly increased beta-carotene absorption 6.6 times
• More than quadrupled (4.8 times) alpha-carotene absorption
• Significantly increased (12.6 times) the conversion of provitamin A (inactive vitamin form) to vitamin A (active vitamin form)

Vitamin D....NICE

This guideline covers vitamin D supplement use in specific population groups.

Vitamin D: supplement use in specific population groups

- Children and young people aged under 4
- Pregnant and breastfeeding women
- People over 65
- People who have low or no exposure to the sun
- People with darker skin

Reduction in intestinal epithelial VDR levels promotes mucosal inflammation and vice-versa. The lack of calcium absorption causing epithelial VDR levels by vitamin D analog therapy or by anti-TNF therapy might have important therapeutic value in the management of IBD. In fact, vitamin D hormone not only induces VDR expression, but also suppresses TNF-α production. Thus, in theory vitamin D therapy can shift the balance to favor inhibition of inflammation and blockade of IEC apoptosis. This could be a mechanism by which vitamin D therapy alleviates IBD.

Vitamin D could influence colonic commensal bacterial profiles through regulation of anti-microbial peptides. Epithelial VDR signaling may also regulate autophagy, another molecular event that has been implicated in IBD. Finally, as a well-known immune regulatory factor, vitamin D-VDR signaling can certainly control mucosal inflammation by regulating the immune system.

In just four months, high-doses of vitamin D reduce arterial stiffness in young, overweight/obese, vitamin-deficient, but otherwise healthy African-Americans.

The dose, now considered the highest, safe upper dose of the vitamin by the Institute of Medicine, reduced arterial stiffness the most and the fastest: 10.4 percent in four months. "It significantly and rapidly reduced stiffness."

More than 80 percent of Americans, the majority of whom spend their days indoors, have vitamin D insufficiency or deficiency.
Vit D & Mg


All of the enzymes that metabolise vitamin D seem to require magnesium, which acts as a cofactor in the enzymatic reactions in the liver and kidneys.

There are two types of nutrient deficiencies, frank deficiencies (such as scurvy from ascorbic acid deficiency or goitre from iodine deficiency), and subclinical deficiencies (a slowly silent reduction in physiological, cellular and/or biochemical functions).

Subclinical Nutrient Status

Part 6

Case Studies and Mechanisms

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Learning Objectives

1. The need for lifestyle medicine
2. The importance of understanding threshold therapy
3. The clinician’s view of Evidence Based Medicine
4. Multiple different causes of chronic inflammation
5. Inflammatory markers in depression and lifestyle interventions
6. How stress impacts hormone production
7. The application of lifestyle interventions in cognitive decline
8. Case studies to demonstrate concepts
The ultimate goal and primary focus of lifestyle medicine is to promote healthier lives through salutary environments and healthier lifestyle choices. Treatment of lifestyle-related diseases (L RDs) includes nutritional, exercise, psychological, social, economic and environmental interventions. To successfully do this requires education, training and communication about lifestyle medicine at the professional and general public level.


Lifestyle Medicine

Physicians also have cited inadequate confidence and lack of knowledge and skill as major barriers to counseling patients about lifestyle interventions.

To begin to address the identified gap in physician armamentarium, a group of representatives from primary care medical specialties and other interested medical professional societies met and developed suggested lifestyle medicine competencies for primary care physicians.


Prescribing Lifestyle Medicine

The Threshold Approach

• Multiple small interventions
• Simultaneously
Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

Evidence based medicine is not "cookbook" medicine. Because it requires an individual approach that integrates the best external evidence with individual clinical expertise and patient's choice, it cannot result in slavish, cookbook approaches to individual patient care.

External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision.

Case Study - Lauren

- 36 year old woman
- Eats out, ready meals
- Married with 2 kids
- Feels 'very stressed'
- Minimal exercise
- No time to herself
- BMI 22
- PHQ9 19/27
- Sedentary job, habit bad snacks particularly sugary drinks
- Disturbed sleep, social media into the night
- Bad back from sitting in office chair – affects mood
- Mother diagnosed with 'depression'
- Two previous unsuccessful SSRI trials
The physiology of Vitamin D overlaps with the pathophysiology of depression. Vitamin D is expressed in key brain areas. And Vitamin D has a key role in circadian rhythms and sleep, affects glucocorticoids and neuronal growth. Growing epidemiological evidence linking depressive symptoms to low levels of 25-hydroxy Vitamin D.

So depression is an inflammatory disease, but where does the inflammation come from?

This review explores the role of inflammation and oxidative and nitrosative stress as possible mediators of known environmental risk factors in depression. A range of factors appear to increase the risk for the development of depression, and to be associated with depression. These include psychosocial stressors, poor diet, physical activity, drugs, smoking, altered gut permeability, obesity, dental care, and low levels of vitamin D deficiency.

Critically, most of these factors are amenable to therapeutic and preventative interventions.

Markers for Depression

This study suggests that one can predict which patients suffering from depression will respond to conventional antidepressants by looking at markers of inflammation in their blood. They found that patients with high degrees of inflammation do NOT respond to conventional antidepressants. Depression might be a symptom of biological changes in the body that are driven by inflammation rather than simply changes in brain chemicals. In these cases, addressing the body’s inflammation rather than using a drug to raise serotonin levels would seem to be common sense.

One of the markers used to determine levels of inflammation in this study is the cytokine IL-1β—this cytokine is also elevated in many other chronic conditions such as obesity, type 2 diabetes and metabolic syndrome.

Inflammation underpins many different conditions.

Nutrition in Mental Health

Although the determinants of mental health are complex, the emerging and compelling evidence for nutrition as a social factor in the high prevalence and incidence of mental disorders suggests that diet is as important to psychiatry as it is to cardiology, endocrinology and gastroenterology. Evidence is mounting for the potential role of diet in mental health, and the need for nutritional-based therapies to address deficiencies, or as monotherapies or augmentation therapies.
Depression and Diet

A randomised controlled trial of dietary improvement for adults with major depression (the SMILES trial) - BMC Medicine (2017) 15:23

These results provide preliminary RCT evidence for dietary improvement as an efficacious treatment strategy for major depressive disorder. The results of this trial suggest that improving diet according to current recommendations targeting depression may be a useful and accessible strategy for addressing depression in both the general population and in clinical settings. A pertinent observation was that improvements in depressive symptoms were independent of weight change. These findings were expected as the diet intervention was ad libitum and did not have a weight loss focus, but provide further support for the beneficial role of dietary improvement per se. The extensive observational evidence linking diet quality to mental health has repeatedly shown that the observed relationships exist independently of various measures of body composition.

There are many other biological pathways by which dietary improvement may influence depression (e.g., previous discussions have centered on inflammatory and oxidation stress pathways, as well as brain plasticity, and the new evidence base focused on the gut microbiota).

• Statistically significant differences
• Modified Mediterranean Diet
• Reduced empty carbs, highly processed foods, refined starches

Better sleep may reduce mental illness symptoms: study finds

BMJ 2017;358:j4163

https://doi.org/10.1136/bmj.j4163

Improving sleep with online digital cognitive behavioural therapy (CBT) is associated with significant reductions in paranoia and hallucinations, a randomised trial in UK university students with insomnia has found. This trial indicates the importance of sleep difficulties for mental health in the general population and the need for a reconsideration in clinical services of the priority given to improving sleep.


“…clinical research has shown that sleep problems may actually precede conditions such as anxiety and depression.”

“...a more integrated consideration of sleep disturbance in both directions will result in a deeper understanding of the broader health problems that are associated with these conditions.”
Disrupted Circadian Rhythmicity

Interpretation: Circadian disruption is reliably associated with various adverse mental health and wellbeing outcomes, including major depressive disorder and bipolar disorder.

Case Study - Smita

- 48 year old lady Asian background
- Married with 2 kids
- Always on the go
- Hot flushes and low mood
- 15/17 score British Menopausal Society Symptom questionnaire
- Recommended HRT by her GP, she declined
- BMI 33

Magnesium

Furthermore, because of chronic diseases, medications, diabetes,生活方式,high fruit consumption, and the availability of refined and processed foods, the vast majority of people in modern societies are at risk for magnesium deficiency. Certain individuals will need to supplement with magnesium in order to prevent subclinical magnesium deficiency, especially if trying to obtain an optimal magnesium status to prevent chronic disease. Subclinical magnesium deficiency increases the risk of numerous types of cardiovascular disease, costs nations around the world an incalculable amount of healthcare costs and suffering, and should be considered a public health crisis. That an easy, cost-effective strategy exists to prevent and treat subclinical magnesium deficiency should provide an urgent call to action.
The Steroid Pathway

- Stress is pro-inflammatory
- Stress increases aromatase which increases oestrogen
- Stress increases 5 alpha reductase, increases Dihydrotestosterone, therefore, hair loss
- Insulin does similar things
- How many patients are inflamed, under stress and elevated insulin – perfect storm to diminish androgens and oestrogens
The Personal Framework

Reversal of Cognitive Decline?

Biological effects of stress on the hippocampus
Case Study – June

- 86 year old lady
- Diagnosed with Mild Cognitive Impairment due to Alzheimer’s disease
- Daughter (age 63) noticed mother struggling to remember numbers and trouble with knitting
- Vegetarian whole life (no alcohol, no smoking)
- Fibroids in 40s
- High stress life
- Strong family history of Alzheimer’s disease
- Lost interest in life
- On and off use of PPIs for reflux

Bloods
- MCV 95
- Serum B12 220ng/L (145-910)
- Vitamin D 20 nmol/L (>50 adequate)

Exercise and Cognitive Function

Interventions of aerobic exercise, resistance training, multicomponent training and tai chi, all had significant point estimates. When exercise prescription was examined, a duration of 45–60 min per session and at least moderate intensity, were associated with benefits to cognition. The results of the meta-analysis were consistent and independent of the cognitive domain tested or the cognitive status of the participants.

Physical exercise improved cognitive function in the over 50s, regardless of the cognitive status of participants. To improve cognitive function, this meta-analysis provided evidence to recommend that patients obtain both aerobic and resistance exercise of at least moderate intensity on as many days of the week as feasible, in line with current exercise guidelines.


Tips for getting a good nights sleep

- Stick to a sleep schedule
- Exercise is great, but not too late in the day
- Avoid caffeine and nicotine before bed
- Don’t take naps after 3pm
- Relax before bed
- Take a hot bath before bed
- Have a good sleeping environment
- Have the right sunlight exposure
- Don’t lie in bed awake
- See a health professional if you continue to have trouble sleeping

National Institutes of Health - https://medlineplus.gov/magazine/issues/summer15/articles/summer15pg22.html
Summary

- Inflammation as key mediator of depression
- The importance of multipronged interventions for chronic disease
- Primum non nocere
- What is the long term outlook for Lauren, Smita and June?
- The impact on their lives, your time and NHS resources

Part 7

Putting it all together...

'Non-Communicable Disease'

Key processes and systems

- Oxidative stress
  - damage to DNA and cell membranes via free radicals
- Inflammation
  - inappropriate responses activated by oxidative stress
- Immune dysfunction
  - gut microbiome health, environmental insults
Turning ‘What?’ into ‘Why?’

Exercise (movement type)
Sunlight (exposure)
Genetics (FHx/phenotype)
Stress (personality/external factors)
Diet (nutrients)
Infections (can be trigger/harbinger)
Sleep (quality/amount)
Environment (working/living/community)

Symptoms

The Lifestyle Prescription

FOOD
MOVEMENT
SLEEP
RELAXATION
Environment

Case Study – Role Play
Summary

- You have enough tools to start making **big differences with small changes**
- The framework is **repeatable** and will get easier
- Peer support via the FB group + additional research
- Share your successes and **ask each other for help**
- Network with like minded clinicians in your area – a local PLM group
- Enjoy adding this dimension into your practice