

Microbes, molecular mimicry and molecules of mood and motivation

James A Morris, consultant pathologist (retired), formerly University
Hospitals of Morecambe Bay NHS Trust and Lancaster University.

Anorexia nervosa

- Hypothesis: anorexia nervosa is an autoimmune disease, with auto-antibodies to regulatory peptides and neuronal proteins related to appetite control. The autoimmune process is triggered by molecular mimicry with proteins on the surface of pathogenic bacteria of the normal microbial flora.
- Background: age incidence and female excess

Microbial flora: trillions without

- Approx. 10 trillion bacteria growing on the body surface.
- They gain their food supply from bodily secretions – mucus in colon and respiratory tract, keratin on skin, glycogen from non-keratinised stratified squamous epithelium of oral cavity, oesophagus and vagina.
- They do not invade the tissues and do not cause disease.
- They compete with pathogenic bacteria and therefore prevent disease
- There are probably over 500 different species and over 1000 different strains.

Microbial flora: billions within

- There are billions of pathogenic bacteria growing within the tissues.
- They invade the tissues, grow within them, derive their energy from blood glucose, cause cell damage and trigger inflammation.
- They have genetic mechanisms to prevent elimination by the immune system.
- There are probably less than 100 different strains.

Pathogenic bacteria growing within.

- Periodontal pathogens: grow within the tissues around the teeth, slowly destroy the tissue and the cementum leading to tooth loss. Mainly gram negative anaerobic bacteria. They can spread by blood to other sites including heart, brain, amniotic fluid.
- Associated with Alzheimer's disease, atherosclerosis, type 2 diabetes mellitus, obesity; also cancer of oesophagus, colon, breast, pancreas, and prostate.
- *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*.

Pathogenic bacteria within

- Pharyngeal bacteria: *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*.
- Life threatening infections following viral respiratory tract infections.
-

Autoimmunity: a decision theory model.

- Human genome has 20,000 genes coding for up to 250,000 proteins
- Bacteria have 3000 to 5000 genes coding for 3000 to 5000 proteins.
- Genes are conserved in evolution so we share our genome with the rest of creation.
- Decision problem is to distinguish self from non-self
- False negative: fail to respond to that which one should respond, increases the risk of death.
- False positive: respond to that which one should not, increases the risk of autoimmune disease.

Autoimmunity: a decision theory model

- There are approx. 3 male deaths for every 2 female deaths from infection throughout life from SIDS to Myocardial infarction.
- Organ specific autoimmune disease is much more common in women than in men: autoimmune thyroiditis, primary biliary cirrhosis, pernicious anaemia, myasthenia gravis
- Anorexia nervosa, chronic fatigue syndrome, irritable bowel syndrome, anxiety neurosis.

Autoimmunity: a decision theory model

- The risk of dying rises as a power function of age: the risk doubles every 7 years. The incidence and the prevalence of conditions such as Alzheimer's disease, ischaemic heart disease, and the common cancers (lung, colon, breast, prostate etc) show the same power relationship.
- Common bacteria and viruses are met early in life, probability of first exposure falls roughly exponentially from birth.
- Age incidence of autoimmune disease is the product of those two curves (one falling exponentially, and one rising as a power function).

Sergei Fetissov:

- Demonstrated IgG antibodies in sera of anorexia nervosa (AN) and bulimia nervosa (BN) patients to neurons in the rat hypothalamus and pituitary : alpha melanocyte stimulating hormone, adrenocorticotrophic hormone, gonadotrophin releasing hormone. Increased frequency of auto-antibodies in AN and BN compared with controls.
- Demonstrated auto-antibodies to alpha melanocyte stimulating hormone, ACTH, oxytocin and vasopressin using ELISA. Occurred in AN and BN patients as well as some controls. There was a positive correlation between level of auto-antibodies in AN and score on the Eating Disorders Inventory – 2 (EDI -2).
- Subsequently Ig G and IgA serum auto-antibodies to leptin, insulin, peptide YY, ghrelin, NPY, agouti related protein, galanin, orexin, melanin concentrating hormone, alpha MSH, ACTH, corticotrophin releasing hormone. Found in healthy controls as well as patients with AN and BN.
- Sequence homology between 14 peptides and a number of common commensal and pathogenic bacteria: *E. coli*, *H. pylori*, *C. albicans*, *Lactobacilli*, *Bacteroides*.

Streptococcus pyogenes

- The cause of rheumatic fever, Sydenham's chorea, Immune complex mediated acute proliferative glomerulonephritis, guttate psoriasis
- Acute exacerbation and remission
- Acute rheumatic fever was the commonest autoimmune disease of childhood but is now uncommon in the western world. Probably because Streptococcus pyogenes has retained sensitivity to penicillin.
- Streptococcus pyogenes is now less common, but not uncommon. However the conditions it causes, such as rheumatic fever, are rare.

Hygiene Hypothesis:

- Eczema, asthma , hayfever
- Type 1 diabetes mellitus
- Anorexia nervosa, chronic fatigue syndrome, irritable bowel syndrome, anxiety neurosis
- Multiple sclerosis and other autoimmune conditions
- ?? Type 2 diabetes mellitus. obesity

Features: increasing in incidence in technologically developed countries, more marked in the higher social classes, associated with educational qualifications, live in a detached house (but not a farm), less exposure to animals, first born, don't attend nursery in the first year of life, don't share a bedroom

Anorexia nervosa: autoimmune disease, auto-antibodies to peptides relevant to appetite control, molecular mimicry with pathogenic bacteria of the normal flora.

Biopsychosocial model of disease: multiple factors interact to cause disease. This means the causative pathways to disease are complex. But if all the factors interact then removing just one of the factors will prevent the disease arising. Therefore causation is complex but prevention can be simple.

Investigation should be focussed on a quantitative assessment of the bacterial flora within.

Quantitative counts on faeces

Bacterial DNA in blood and urine.

Bacterial toxins in blood and urine using ELISA and tandem mass spectrometry

Prevention will be based on optimising the microbial flora.

A simple preventive measure with great potential is yoghurt.

Non-keratinised stratified squamous epithelium contains glycogen in the superficial cells. This has evolved to feed lactobacilli on the surface which convert the glycogen to lactic acid. The acid suppresses pathogenic bacteria. This system evolved millions of years ago.