A MEDICAL HYPOTHESIS: AUTOIMMUNITY IS A POSSIBLE CONSEQUENCE OF LYMPHOCYTE EVOLUTION. A TRIBUTE TO THREE GREAT MENTORS

ALAN S. COULSON M.D [1] | ANGELA F. COULSON A.A [2]

INTRODUCTION

The first person we would like to pay tribute to, is Professor J M Yoffey, (Fig 1) whose name is virtually synonymous with classic lymphocyte research. Neither Angela nor I actually worked with him at Bristol University in England, but we corresponded. I still treasure one of his letters from the 1968 asking me to send him material for his book.(Fig 2) To my mind one of the most important publications in last century, in the field of lymphocyte research, is Yoffey's article, "The Lymphomyeloid complex" (Ref 1), in which he discusses the evolution of the lymphocytes, and in particular the strange fact that they seem to be continuing to evolve in the vertebrates. "The lymphomyeloid complex is the total mass of tissue concerned with the formation of blood cells, and also to a large extent with antibody formation. It is present throughout the vertebrate series, but shows a sequence of evolutionary changes of whose precise significance we are not as yet aware."

Fig 1. Professor Joseph Yoffey, (1902 – 1994) my mentor by mail, and the acknowledged guru of lymphocytes.

UNIVERSITY OF CALIFORNIA
SAN FRANCISCO MEDICAL CENTER

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO — SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE
LABORATORY OF RADIOBIOLOGY

SAN FRANCISCO, CALIFORNIA 94122

April 25, 1968

Dr. A. S. Coulson
Guy's Hospital Medical School
S.E. 1 London
ENGLAND

Dear Dr. Coulson:

Greetings from San Francisco, where I have just received the reprint of your paper "Review of Early Work on Mammalian Blood Lymphocyte Tissue Culture". It was forwarded to me by surface mail hence it has taken an unconscionably long time in reaching me.

I think it is a very constructive exercise to review the controversy over the lymphocyte which goes back to Ehrlich's time. I think it was Ehrlich's hasty observation of blood lymphocytes on a warm stage, when he observed them to be motionless, that gave him what one might term an anti-lymphocytic bias for the rest of his days. It was the force of Ehrlich's great authority which made all hematologists reluctant to contradict him.

In England the Medawars also became violently anti-lymphocytic after their brief attempt to repeat Bloom's culture experiments. As recently as 1957, Medawar dismissed in a brief and contemptuous footnote the idea that lymphocytes could grow and transform. I was reading this paper only the other day. It makes strange reading in 1968, yet even stranger is the fact that he was merely expressing what was the generally held view until 1960, when what I have termed the great Phytohaemagglutinn Explosion occurred. Incidentally, I am now embarking on a new book together with Colin Courtice entitled Lymphatics, Lymph, and the Lympho-Myeloid Complex. I shall be grateful if you could let me have copies of your recently published papers for inclusion where pertinent.

Kindest regards.

Yours sincerely,

Joseph M. Yoffey
Visiting Professor in Anatomy

JMY:dp

Fig 2. One of the letters I saved from Professor Yoffey. His insights were invaluable.

At the time I read this, I remember thinking: Then are lymphocytes truly part of the vertebrate's body? Or are they just passengers, a part of what was later termed the "microbiome", that vast population of microorganisms that lives in and on our bodies? And where did lymphocytes evolve from? They seem to have arrived "out of the blue" in the lampreys, and, what is more, as we found out later, they arrived almost fully equipped with biological weapons (2). Lymphocytes also exhibit strange non-vertebrate behavior patterns: they readily migrate through vertebrate cells, a dynamic not even perpetrated by developing vertebrate embryo cells, and they display a distinctive non-vertebrate way of movement.

These thoughts provided the stimulus for a previous article, in which it was argued that a strong case could be made for the origin of lymphocytes, or at least their unique functions, from marine protozoan parasites (3), and that this event probably occurred about the time of the origin of the lampreys, 530 million years ago, long before lymphatics and lymph nodes had evolved. It was envisaged that the aggressive patrolling and killing actions of these parasites were originally self-serving, aimed at protecting their "turf", their host fish, from other competing invaders.

In so doing these parasites improved the chances of survival of their hosts, by keeping out more pathogenic organisms, a process not unlike the protection afforded by normal gut flora in present day humans. In addition, with the passage of time, it was suggested, the parasite paradigm changed, so that possibly by the incorporation of key protozoan components into host stem cells, or some type of cell fusion, valuable endosymbionts were produced, the creatures we now call 'lymphocytes'.

Lymphocytes are remarkable cells that continually scan their host's tissues, and are able to recognize any defective cells, which they promptly eliminate; and similarly, they are able to recognize any other new or foreign protein that might herald an invasion by parasites, or viruses or bacteria. Such detection of foreignness triggers a violent coordinated cellular and biochemical 'blitz' attack, a part of the body's key self preservation function. In this way the lymphocytes, 500 million years later, now serve primarily to protect their chordate hosts.

AUTOIMMUNITY

Professor R.R.A. Coombs, (Fig 3) the world renowned Cambridge immunologist, used to get very upset whenever he heard the word 'autoimmunity'. To his way of thinking the term was a complete misnomer, a veritable oxymoron. In the world of medicine, the word 'immunity' meant 'protection' since the 1870's; hence the use of the term 'autoimmunity' introduced in the 1950's, was something of a disservice to immunological terminology. While we were in Cambridge, in Professor Coombs' presence, we learned to use instead the word 'autoallergy', because, as he put it: How can you be protected against yourself, especially by hurting yourself? Which in turn also made me think: lymphocytes, cells that might not be 100% chordate in origin; could they revert back to their original parasite mode, and then hurt their host which differs in some fundamental way from themselves? Could some of them be "the enemy within", the immunological francs-tireurs?

Nonwithstanding all these theoretical considerations, the medical problem of autoimmunity Is enormous; according to Fairweather et al (4), after cancer and heart disease it is the third most common class of disease in humans.

Autoimmune diseases are a diverse group with one thing in common, the patient's lymphocytes, instead of visiting their violence on pathogens, choose to attack various normal components of its human host; thereby embarking on a course of what amounts to incremental self immolation, and incidentally, one that is completely devoid of any evolutionary advantage. To put it simply: autoimmunity flies in the face of the Red Queen evolutionary law (5). Common examples in humans are systemic lupus erythematosus, rheumatoid arthrits, and Hashimoto's thyroiditis.

PERIOD OF COMITY

If we accept that lymphocytes originated in fish (2), then they have had a period of some 500 million years to adjust to an environment bristling with fish antigens as their new adoptive 'home' milieu. To put it in very simple terms, it would seem as though, as a result of evolutionary selective forces, lymphocytes were originally "trained" to be primarily "guard dogs" for fish, which would explain why autoimmune disease has not been described in fish. The lymphocytes have grown too accustomed to fish antigens; and using this same argument in reverse, for the lack of millions of years of time, lymphocytes are still having problems adjusting to all the new antigens found in chordates that evolved after fish. This would also explain why the targeted tissues in mammals, that bear the brunt of the autoimmune attacks, are primarily those that were not present in fish.

In the case of humans, for about the first 20 to 30 years of life there seems to be a period of relative immunological comity, during which the patient's lymphocytes maintain a rapprochement with their host tissues, and confine their assaultive activities to infected cells, or cells showing malignant changes, and to microorganisms such as bacteria and viruses. They seem to tolerate the non piscine antigenic structures in their hosts. But then, after what amounts to an extended immunological "honeymoon period", as many as eight per cent of humans are attacked by the very same cells that previously defended them, a situation not unlike the actions of the Praetorian Guards when they turned on their Emperors, in Roman times.

Why only some humans suffer autoimmune disease, and not all, brings us to Professor Shumway, (Fig 4) the world famous pioneer heart transplant surgeon at Stanford University. His kindness to me will never be forgotten, nor his amazing sense of humor. With a twinkle in his eye, he was fond of remarking on the anatomic variability of humans, and one night this made me think: Could there be a similar variability in the function of patients' lymphocyte populations? This was a new concept at the time, (1974), nevertheless we went on to determine the quantified response profiles, of the lymphocytes, of a series of heart transplant recipients, and found that indeed there was just such a variation (6). This phenomenon might also explain why only eight per cent of humans get autoimmune diseases, they could be the ones with the hyperreactive immune systems.

Fig 3. Professor Robin Coombs, (1921 – 2006). He did not like the tem "autoimmunity".

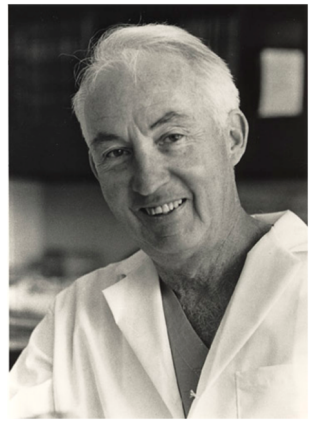

Fig 4. Professor Norman Shumway, (1923 – 2006). His kindness to me will never be forgotten.

DEVONIAN IMMUNOLOGICAL SCHISM.

The concept that lymphocytes were primarily designed to protect fish was mentioned earlier, and this leads us to expect that those organs and tissues not present in fish, but which emerged later in chordate evolution, would be the most likely victims of the turncoat lymphocytes. In which case this phenomenon would have started in the Devonian period, about 400 million years ago, when the amphibians first emerged, a hypothesis we would like to term the "Devonian immunological schism". This schism would also mark the beginning of autoimmunity.

The evolution of mammals, and the adaptation to life on land, in the Triassic period, about 200 million years ago, would only exacerbate this problem and worsen the schism.

Cells that constitute skeletal muscle, cartilage and bone in fish would be "familiar faces" from the lymphocytes' perspective. These structures are similar in fish and man, so, as might be anticipated autoimmune attacks on these tissues in man are extremely rare,(7,8). On the other hand new tissues and structures associated with life on dry land could be expected to provoke a heightened response because of their novelty. And this indeed proves to be the case: the synovium lining joints is frequently attacked resulting in rheumatoid arthritis, but as mentioned above, nearby bone escapes unscathed.

A consideration of endocrine system is particularly interesting; the human parathyroid glands may be attacked causing hypoparathyroidism, the pancreas is the target in type 1 diabetes, and the thyroid in Graves Disease and Hashimoto's Disease. (Although primordial thyroid cells and pancreas cells are present in fish, they are not organized into discrete glandular structures), (9). Thymus destruction causes myasthenia gravis, and auto immune attacks on the adrenals cause Addison's disease.

Conversely the pituitary gland because it is present in fish, is rarely the subject of auto immune attack in man, and the same is true for the testis, which is also found in fish. (TABLE 1)

TABLE 1: FREQUENCY OF OCCURRENCE OF AUTOIMMUNE DISEASE IN SELECTED HUMAN ORGANS AND TISSUES. RELATIONSHIP TO PRESENCE IN FISH.

ORGANS/TISSUES PRESENT IN FISH BEFORE THE DEVONIAN		
ORGAN/TISSUE	**FREQUENCY OF AUTOIMMUNE DISEASE**	**REFERENCE**
Muscle	very rare	7
Cartilage	rare	8
Testis	very rare	10
Hypophysis	very rare	11
ORGANS/TISSUES NOT PRESENT IN FISH		
Skin	3,000 cases per 100,000 population	12
Thyroid	350 cases per 100,000 population	13
Thymus	18 cases per 100,000 population	14
Synovial Joint	1,000 cases per 100,000 population	15
Adrenal	14 cases per 100,000 population	16

As might be expected, other structures rarely found in fish before the Devonian, such as the lungs, are also stricken with a variety of auto immune diseases viz: Goodpasture's Syndrome, Wegener's granulomatosis, systemic sclerosis, interstitial pneumonitis, sarcoidosis and Churg-Strauss syndrome, to name but a few. In much the same way, the lacrimal glands and salivary glands, obviously unnecessary under water, are similarly afflicted by autoimmune disease; in this case Sjogren's syndrome, which reflects a continued prehistoric testimony to the redundancy of these structures in fish.

Whereas fat tissue is rarely a subject of autoimmune attack, presumably because fish and human lipocytes are similar, the overlying skin structure of humans differs quite markedly from fish, hence this structure, the largest organ in the human body, displays a veritable panorama of autoimmune disease stigmata; these include alopecia areata, vitiligo, psoriasis, sclerodema, pemphigus, pemphigoid, and systemic lupus.

CONCLUSION

It has been suggested that lymphocytes evolved from marine protozoan parasites, about 530 million years ago; and that over time, the parasite paradigm changed, and they instead developed into valuable endosymbionts that protect their piscine hosts. But, with the emergence of amphibia in the Devonian period, an immunological schism started, as unrecognizable new structures developed in the amphibia, such as synovial joints. These new tissues, because they were not present in fish, became subject to the same kind of attack by the lymphocytes as other foreign protein, such as bacteria or viruses.

Autoimmunity can thus be seen as the dystopic situation where some 'rogue' lymphocytes revert back to their original parasite state, and slowly cripple their host.

If protozoan sequences could be found in the human genome in areas controlling lymphocyte function, it would led valuable support to this hypothesis

REFERENCES

1. Yoffey, JM, 1960; The Lymphomyeloid Complex, in Ciba Foundation Symposium – Haemopoiesis: Cell Production and its Regulation (eds G.E.W. Wolstenholme and M. O'Connor), John Wiley & Sons, Ltd., Chichester, UK.
2. Mayer WE, Uinuk-ool T, Tichy H, Gartland LA, Klein J and CoopeMD, 2002: Isolation and characterization of lymphocyte-like cells from a lamprey. Proc Natl Acad Sci USA. 99(22): 14350
3. Coulson AS, 2013; Possible Protozoan Ancestry of Lymphocytes. The Evolver, Newsletter of Evolution SIG of British Mensa. 43:11.
4. Fairweather D, Frisancho-Kiss S. and Rose NR, 2008; Sex Differences in Autoimmune Disease from a Pathological Perspective. Am J Pathol. 173: 600.
5. Van Valen L, 1973; A new evolutionary law. Evol. Theory.1:1
6. Coulson AS, MacMillan F. Griepp RB, Stinson EB, Dong E, and Shumway NR, 1974: Lymphocyte Tissue Culture Studies on Human Heart Transplant Recipients. II Screening the Lymphocyte Reactivity of the Recipients in vitro. Transplantation. 18: 409.
7. Prieto S. and Grau JM, 2009; The Geoepidemiology of Autoimmune Muscle Disease. Autoimmun Rev,doi:10.1016/j.autrev. 2009.11.0065
8. Hajj-ali RA, 2013; Relapsing Polychondritis. The Merck Manual Home Edition. Merck Sharp & Dohme, Whitehouse Station, N.J., U.S.A.
9. Geven EJW et al, 2007; Comparative thyroidology: thyroid gland location and iodothyronine dynamics in Mozambique tilapia and common carp. J Exp Biol. 210:4005.
10. Cihakova D.2001; Autoimmune Orchitis. Johns Hopkins Medical Institutions. Autoimmune Disease Research Center. Baltimore. Maryland. U.S.A.
11. Cihakova D. 2001; Autoimmune Hypophysitis. Ibid.
12. Basko-Piluska JL and Petronic-Rosic V, 2012; Psoriasis: epidemiology, natural history, and differential diagnosis .Psoriasis: Targets and Therapy.2:67.
13. McGrogan A,Seaman HE, WrightJW and de Vries CS,2008; The incidence of autoimmune thyroid disease: a systematic review of the literature. Clin Endocriol (Oxf). 69:687.
14. Phillips LH, 2003; The epidemiology of myasthenia gravis. Ann N Y Acad Sci. 998: 407
15. Symmons D, et al,2002; The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology (Oxford) .41: 793.
16. Charmandari E, Nicolaides NC, and Chrousos GP, 2014; Adrenal insufficiency. www.thelancet.com Published online Feb 4, 2014 http://dx.doi.org/10.1016/S0140-6736(13)61684-0