Morphostasis: a revolution?

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Progress in science has, from time to time, been swept up a blind alley on a presumption. Precepts that seem *obviously obvious* may be adopted without question. For example, the earth ***is*** flat isn't it? it ***is*** at the centre of the universe isn't it? biblical creationism ***is*** accepted fact isn't it? time ***is*** the same everywhere isn't it? The existence of a flaw is heralded by a growing crisis; *ad hoc* explanations are needed to prop up old paradigms that don't, anyway, ring true. Revolution will follow once the flaw is exposed. Where conceptual skyscrapers have been built upon insecure foundations, the upheaval will be severe.

Gestalt psychology reminds us that the whole is not simply explained by the sum of its parts. Our cultures ensure that we interpret all facts in the light of some preconceived and distorting perspective. This matters little when the distortion is in phase with the grand principle, for then it is simply a caricature; but it leads to crisis when it is not. Science grows through many discrete bubbles of expanding knowledge. These bubbles eventually meet and coalesce but, before doing so, the perception of a particular discipline may be both parochial and distorting. So, has this happened with the 'immune system'? Have we made huge, gruesome mistakes in its perceptual construction? My proposition is that we have.

The error is, I contend, implicit in that title [(1)]. It is accepted, more or less without question, that T-cells and antibodies have both evolved and been designed to identify, then eliminate, foreign organisms. This is, after all, *obviously obvious* isn't it? But, consider this point. Not all micro-organisms make us ill. Those that do are pathogens. These, by definition, make a mess in the colony of cells that constitute an animal. So, if the 'system' is primarily designed to identify and tidy up tissue mess it may pay little regard to the sorting of self from non-self. Pathogens need to reproduce and in the process, most create a mess. When sentinel cells tidy up this cellular debris, pathogens and their debris will be present too. This cocktail of mess is processed for presentation to lymphocytes. Lymphocytes then direct aggressive responses onto the most unusual constituents of this processed mess.

So, have we made fundamental errors in laying down the foundations of our science? Are we now trying to interpret all we observe from a corrupt perspective? And what is the better perspective?

The cells in an animal originate from its zygote. This zygote-derived-colony needs a system to maintain form by removing waste and carrying out repairs. The conventional view regards the process as an 'immune system' that discriminates self from non-self. I propose, instead, that it is a 'morphostatic system' (morphostasis is tissue homeostasis) that discriminates mess from non-mess. This metamorphosis in perspective requires uncomfortable mental gymnastics but it is rewarded with a greatly enhanced understanding.

The standard view of the immune system was, till recently, lymphocentric (*i.e.* the lymphocytes were regarded as central). It presupposed that these cells, somehow, work out what is self and what is non-self and that they avoid attacking self to prevent autoimmunity. This viewpoint is oblivious to core elements of a 'morphostatic system'.

- Morphostasis is rooted in the individual cells of the zygote-derived-colony. The cell has complex systems to carry out internal surveillance. It uses checkpoint controls to sense when things go wrong and it aims to restore the original (and healthy) *status quo*. It notifies adjacent cells of what is happening inside itself by flagging up evidence of these events on its surface.

- Nucleated cells are able to commit suicide (apoptose) when they become too sick for repair. In doing so, a cell sanitizes its contents - trashing both its own and any invader's genes plus other intracellular structures. Apoptotic debris melts tidily away. Problems arise when zygote derived cells fail to complete a 'controlled shutdown' and so end up spilling their cytoplasms and making a mess.
- The membership rules in the zygote-derived-colony require individual cells to monitor their own health and only communicate through gap junctions when they are fit. Gap junctions are transmembrane channels that link the cytoplasms of adjacent cells. These structures are a cornerstone in the function and subsequent evolution of metazoans. All metazoans have either gap junctions or their plant counterparts - plasmodesmata. This stark uniformity has attracted scant emphasis. It is this ability to construct gated bridges of cytoplasm that separates primitive multicellulate life forms (*e.g.* slime moulds) from the explosive diversity and complexity of species that sprang up following the arrival of gap junctions (about 700 million years ago). Cells sever gap junctional communication from adjacent cells when they become sick; it is likely that this response evolved early as an extracellular response to intracellular disease.
- There have been few studies of gap junctional intercellular communication in phagocytes and lymphocytes. When my second paper was accepted for publication there was sparse evidence for such communication (this is anticipated particularly between healthy self-cells and 'angry' macrophages). But this is now substantiated [2,3]. Further, the molecule that leads on to the construction of gap junctions belongs to a group of cell adhesion molecules that play a crucial role in the function of immune cells (antigen presenting cells; natural killer, cytotoxic & helper T-cells; and B-cells).
- The adaptive immune system (the main executors of which are the cytotoxic and helper T-cells together with B-cells) is a sophisticated memorising system. It seems to spring into the evolutionary arena - Minerva like in full armour - around about the origin of the *jawed* vertebrates. It has been a broad assumption that lymphocytes are needed to fight infection because, in mammals, the failure of adaptive immunity leads to life threatening infections. Now this is manifestly untrue of many invertebrates. So what is going on? The answer may be that, when vertebrates elaborated their morphostatic systems, they moved a lot of 'morphostatic-eggs' into this 'adaptive-immunity-dependant-basket'. Macrophages (or other antigen presenting cells) categorise encounters with debris into threatening-messy-lytic or safe-tidy-apoptotic. Lymphocytes with appropriate specificities are conditioned to memorise this context. Antigen presenting cells progressively relinquish autonomy of action and increasingly become dependent on primed lymphocytes to activate macrophage aggression.
- It used to be difficult to imagine any gradual evolutionary path to this adaptive system. Logic suggested that a large repertoire of different receptors was needed before it could fulfil any useful function. However, it is becoming increasingly clear that natural killer cells act in a way that is a functional inversion of the cytotoxic T-cell system. Natural killer cells avoid attacking self-cells by interacting with self histocompatibility antigens. This mechanism must, somehow, generate receptor specificity. So, a system of receptor selection arose in natural killer cells that promoted receptors able to recognise self and suppress the rest. The adaptive system was now ready to be catapulted onto the scene by 'flipping' natural killer cell function over to cytotoxic T-cell function near the origin of the vertebrates [4].

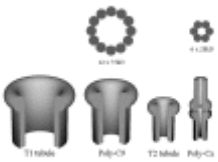
Once these perceptual adjustments have been made, large tracts of pathology and immune phylogeny invite novel interpretations. Autoimmune disorders, infection and cancer can all be viewed from a different and more enlightening perspective. Processes that were once confusing enigmas gain clear explanations.

More detail and longer bibliographies can be found in my papers - two in print, another in press and a fourth, tidying up the concept, has been submitted [4,5,6].

References

1. *To be fair, the etymology of this term - from the Latin 'immunis' meaning 'freedom from burden or taxes' – is broad enough to encompass the new concept. The problem is that its accepted usage has been irreversibly constricted to mean 'freedom from infection'.*
2. *Hillis GS. Duthie LA. Brown PA. Simpson JG. MacLeod AM.Haites NE. Upregulation and co-localization of connexin43 and cellular adhesion molecules in inflammatory renal disease. J Pathol 1997; 182(4):373-9*
3. *Krenacs T. van Dartel M. Lindhout E. Rosendaal M. Direct cell/cell communication in the lymphoid germinal center: connexin43 gap junctions functionally couple follicular dendritic cells to each other and to B lymphocytes. Eur J Immunol 1997; 27(6):1489-97*
4. *Cunliffe J. Morphostasis and Immunity.*
5. *Cunliffe J. Morphostasis: an evolving perspective.*
6. *Cunliffe J. From terra firma to terra plana - danger is shaking the foundations.* Deconstructing the immune system.

Jawed - this has been added after publication. Arena was inadvertently omitted in the original.



First picture: *Gap junctions - reproduced from J Cell Biol (1977) 76:643*
Second picture: *Complement, perforin and gap junction holes - reproduced from Morphostasis: an evolving perspective*
Third picture: *Tidal Forces - created by James D. Cunliffe. James is currently animating characters for the forthcoming film Happy Feet and was, prior to this, lead animator with Free Radical Design. FRD have released several games including TimeSplitters2 (PS2, XBox and Game Cube formats).*
Fourth picture: *A cartoon of the author that appeared in this article, drawn by Matthew Lawrence, a freelance caricature artist.*