

# The Wadham Journal

Issue 1, Trinity 2012

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*Sharing the fascinating work of Wadham graduates with the MCR, alumni and the wider College community.*

*This Journal was made possible by the generosity and kindness of The Wadham Society.*

# Editor's Comments



Ever wondered what Wadham graduates get up to? Well, now there is an answer.

Welcome to the first ever issue of *The Wadham Journal*! In this issue we have some fantastic papers for you to read. Rachel Everett, a pathologist, will discuss why her research shows that humans can contract meningitis, but rodents can't...maybe they are the superior race?! Margarita Vaysman, our Russian expert, highlights the myth of Nikolay Chernyshevsky over two captivating pages, and Andrew Brown, who recently successfully defended his thesis, has dusted off the laptop and produced a passionate Classics discussion on the common voice of the people in the Greek world. And finally, one of Wadham's many biomedical engineers, Alisa Selminovic, presents some fascinating work on cerebral aneurysms.

*The Wadham Journal* exists as a place where MCR students can share their research with the wider college community; with the result being that we are all more aware of the achievements and interesting work performed by our peers. Wadham students study and research a phenomenal breadth of topics and this will be brought to you in the form of a few papers each term.

In addition to the work of the MCR, going forward it is hoped that *The Wadham Journal* will also feature the work of an undergraduate, to showcase project work or essays that are noteworthy of recognition.

Furthermore, in future issues we would like to list any of your special achievements. Have you recently won an award? Published an exceptional article? Published your own book? Started your own company? If the answer is yes to any of the above, then please send me an email.

If you are interested in publishing some of your work then please get in touch. I hope you enjoy the issue!

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# Why rodents win hands (paws) down against us: investigations into host specificity of bacterial meningitis

Rachel Everett, DPhil Pathology



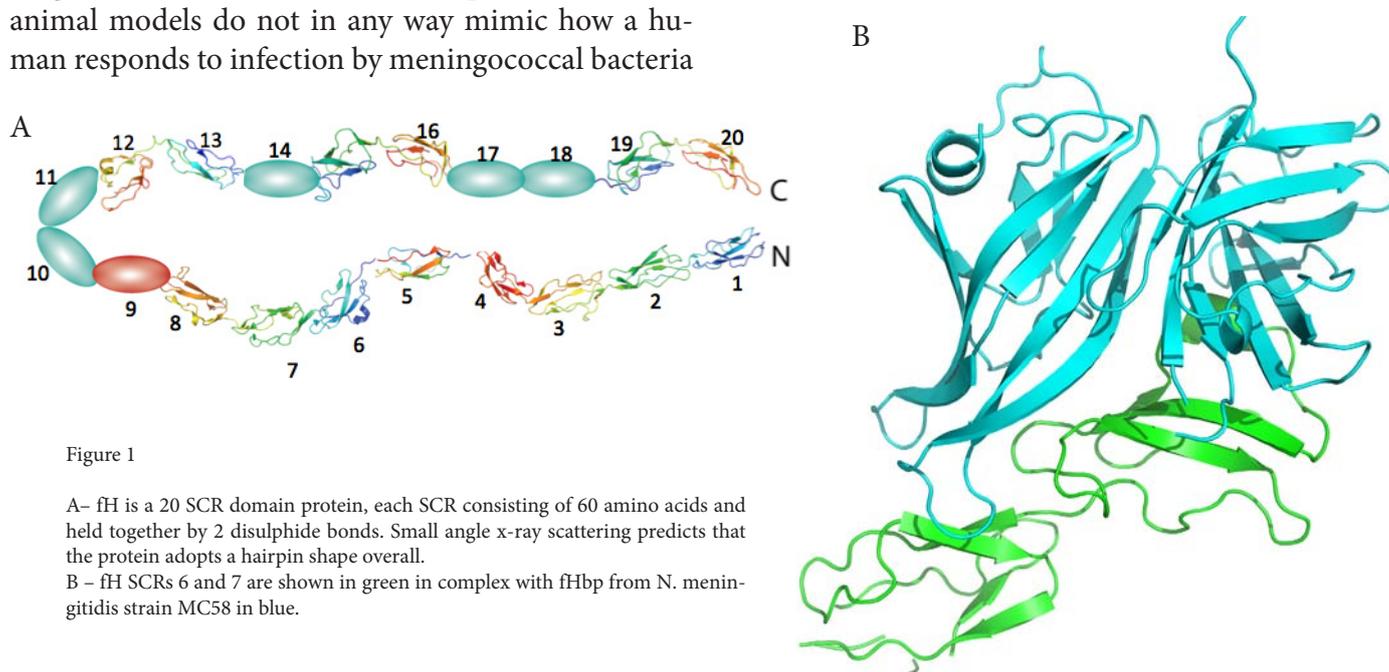
The hunt for a broad spectrum vaccine against all strains of meningitis has long proved challenging. This disease is specific to humans so testing any vaccine in an animal model does not give us any true indication of how this vaccine would work in people. This project attempted to understand why, at a molecular level, meningitis is a human specific disease with a view of characterising the mouse immune system. Through examination of immune protein structures and complementary binding analysis studies, we have postulated a potential mouse model which could be engineered to become susceptible to meningitis infection and thus allow effective testing of such vaccines.

Meningitis is a disease characterised by the inflammation of the membranes which protect our brain and spinal cord, collectively known as the meninges. Both bacteria and viruses can cause this disease, resulting in large scale septicaemia upon initial infection. Without treatment, the consequential invasion of the meninges, usually leads to death or severe permanent disability, for example; blindness, deafness, limb loss or brain damage. 3000 cases of meningitis are diagnosed every year in the U.K., 90% of which the causative pathogen is *Neisseria meningitidis* serogroup B (meningitis B) against which there is currently no vaccine. After the first signs of characteristic symptoms such as fever, aversion to bright lights and vomiting; *N. meningitidis* can kill in just 4 hours if no treatment is immediately received (Meningitis U.K.). Knowing the symptoms of this disease is crucial for the prevention of fatalities by rapid medical intervention. However, to eradicate meningitis completely, a broad-coverage vaccine preventing such cases in the first case is the answer medical research must provide.

Testing these vaccines is problematic. Meningitis has long been known to be a human specific disease so animal models do not in any way mimic how a human responds to infection by meningococcal bacteria

(Granoff, 2009; Johansson, 2003). To prevent mouse models simply fighting off the infection, large amounts of free iron (a limiting factor to bacterial growth in the bloodstream) and physiologically irrelevantly high titres of *N. meningitidis* must be injected.

In the human bloodstream, meningitis is able to evade the human immune system by binding onto a protein, present at high levels in our serum, called factor H (fH). This occurs via a surface exposed lipoprotein called fHbp, present on all strains of *N. meningitidis*. fH is a 20 domain or short-consensus repeat (SCR) protein which functions as a down-regulator of the alternative pathway of the complement system (figure 1A). This constitutively active arm of this evolutionarily ancient part of the immune system elicits the initial immune response upon pathogen detection within our bodies. fH normally binds sugars called glycosaminoglycans, present on the surface of host cells and tissues, to prevent inappropriate complement activation towards these host structures. By binding SCRs 6 and 7, *N. meningitidis* provides itself with the same initial protection in the blood



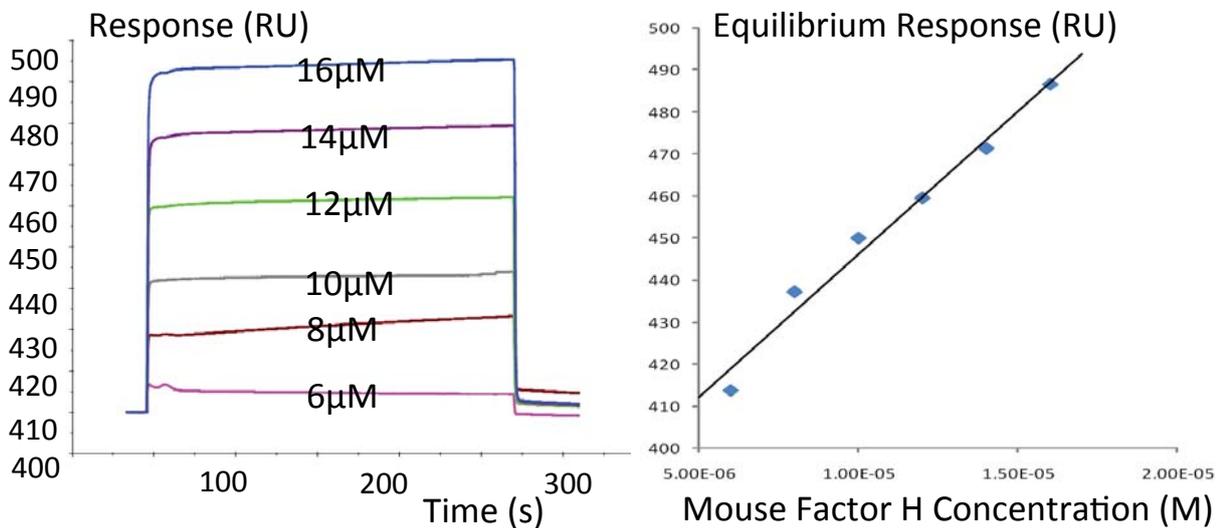


Figure 2

SPR analysis of mouse fH SCRs 6 and 7 with fHbp: The graph of equilibrium response vs. mouse factor H concentration is a straight line, indicating the range of concentrations assessed in the analysis is far below that of the value of the KD for this interaction.

stream, allowing it to replicate to extremely high levels, causing septicaemia as described previously.

The structure of human factor H SCRs 6 and 7 has been solved and the KD value (an estimation of affinity) of the interaction of this complex determined to 2nM, indicating extremely tight binding of these two proteins to each other (figure 1B) (Schneider et al, 2009). We hypothesised that one of the reasons mice have a natural immunity against meningococcal infection is that their fH is unable to bind the fHbp presented on the surface of the bacteria, thus providing the pathogen with no protection in the bloodstream against the rest of the immune system. To further investigate this, we aimed to analyse the interaction, if any, of the mouse fH SCRs 6 and 7 with the fHbp and also to determine the structure of the relevant part of the mouse fH to determine a structural reason for the host specificity of meningitis.

Both the mouse fH SCRs 6 and 7 and fHbp (N. meningitidis strain MC58) were made recombinantly in *Escherichia coli* (strain B834 (DE3)) and purified to homogeneity. Using a method called surface plasmon resonance (SPR) we can determine the rate at which these proteins specifically associate and dissociate with each other. Such analysis determined a KD value significantly larger than 5µM (figure 2). This renders the interaction physiologically irrelevant as fH is present in serum at approximately 5µM. Other fHbp molecules from different strains were also analysed for their binding characteristics with mouse fH SCRs 6 and 7 though the KD values determined were even greater than 5µM. Overall we can conclude that mouse fH interacts far too weakly with the fHbp in the bloodstream to then confer immune resistance to

the bacteria through its down-regulatory activities.

To understand why mouse fH SCRs 6 and 7 interacts so differently with the meningococcal fHbp compared to human fH SCRs 6 and 7, we determined the structure of mouse fH SCRs 6 and 7 using x-ray crystallography (figure 3A). This method requires growing crystals of the mouse fH SCRs 6 and 7 protein, collecting the diffraction pattern as high intensity x-rays pass through. The diffraction patterns collected from the crystal can then be deconvoluted to determine the atomic resolution structure of the individual protein unit which makes up the crystal i.e. the exact position, identity and connectivity of all of the atoms of this protein molecule. The structure was determined to 1.6Å (1.6 x 10<sup>-10</sup>m) resolution. Comparison of the mouse and human structures shows that the angle that SCR 6 is orientated with respect to SCR 7 differs greatly between these two fH molecules (figure 3B). Given the structure of the complex of human fH SCRs 6 and 7 with fHbp, overlay analysis would indicate that this difference in domain angle would sterically occlude the binding of fHbp by mouse factor H. Even on the basis of the amino acid sequence of the mouse protein we can see disparity in residues which were identified in the human fH SCRs 6 and 7 as being key for this binding interaction. Previous work mutating these residues in the mouse protein to the sequence found in the human protein was shown not to increase the binding capacity of mouse fH SCRs 6 and 7 for the fHbp. From the structure we can see that this is due to a complete re-organisation of the fHbp binding site in the mouse protein compared to the human.

Overall, this study provides the evidence for the disparity in host evasion by meningitis between mice

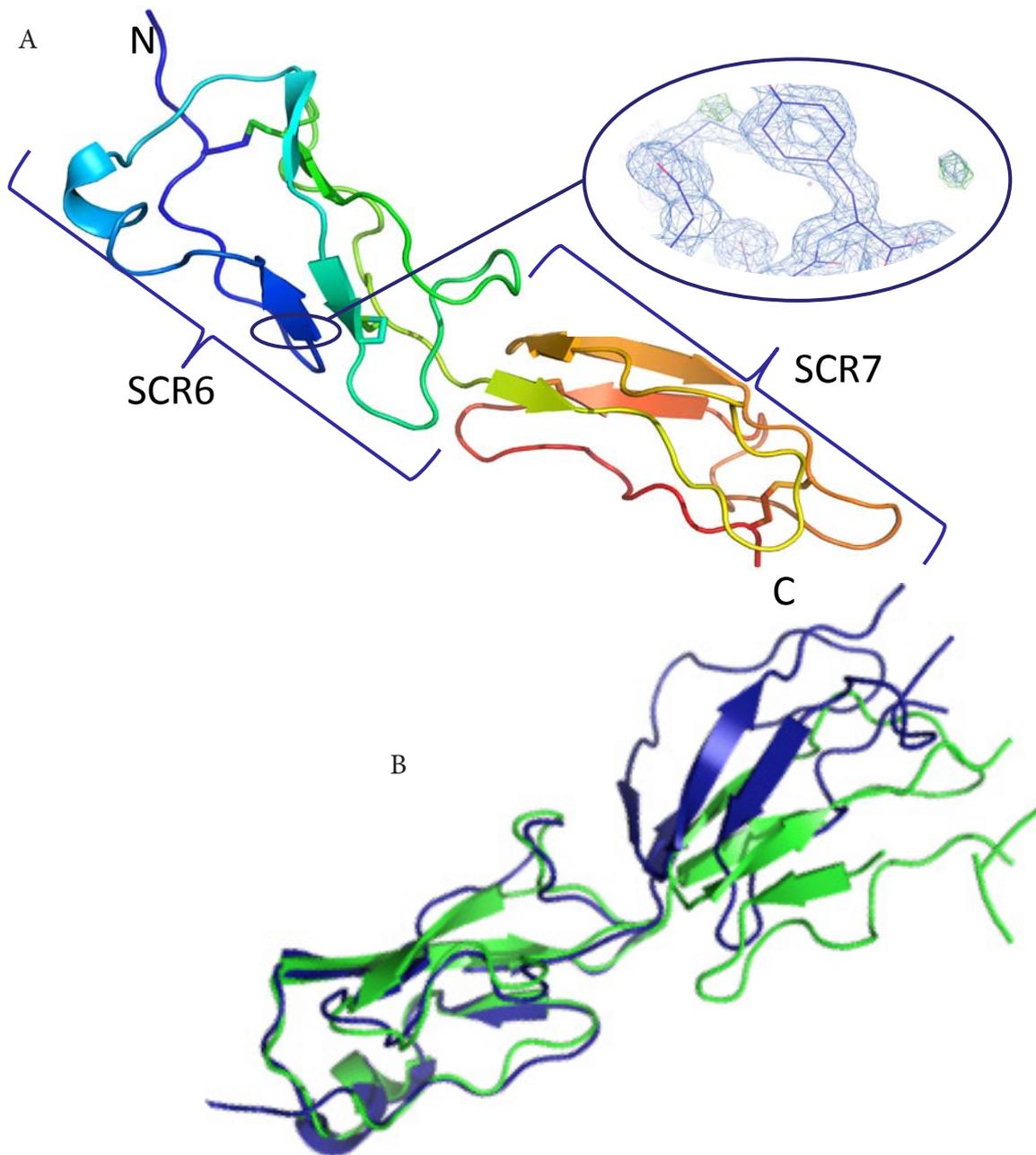


Figure 3

A - The structure of mouse fH SCR6 and 7 to 1.6 Å resolution.

B - Mouse fH SCR6 and 7 shown in blue overlaid on human fH SCR6 and 7 shown in green. Whilst SCR 6 overlays very well, SCR 7 is clearly orientated differently with respect to SCR 6 when comparing the 2 structures.

and humans at the molecular level. We can speculate that by making a genetically modified mouse which expressed a chimeric form of fH where SCR6 and 7 were replaced with the human form, the binding characteristics of human fH would also be conferred, making this mouse vulnerable to *N. meningitidis* infection. This model would be far more relevant to study this human specific disease as the pathogenesis of the infection should display much more human-like characteristics, and therefore would be a much better model to also assess new vaccine candidates in. Meningitis is not the only bacterial pathogen to evade an immune response by recruiting fH. *Streptococcus pneumoniae*, *Borrelia burgdorferi* and *Staphylococcus aureus* all also recruit complement to evade an immune response. This mouse model could therefore be a better model to study these pathogens in too. Other factors are known to contribute to the host specificity of *N. meningitidis*.

For example, CD46, a cell surface bound regulator of the complement system has also been shown to be a host-specific factor for meningococcal infection susceptibility. Such proteins are now future lines of enquiry to fully understand and determine exactly why bacterial meningitis is a human specific disease.

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# A Man and a Steamship: Truth and Fancy In Creating The Myth of Nikolay Chernyshevsky, The Great Soviet Writer

Margarita Vaysman, DPhil Modern and Medieval Languages (Russian)



Nikolay Chernyshevsky, Vladimir Lenin's favourite writer and adopted mentor, has been on the forefront of Russian revolutionary propaganda from the time his novel "What is to be done?", was first published in 1863. An iconic figure and 'an early saint of the Bolshevik calendar' (Tom Stoppard), Chernyshevsky is an example of ideological manipulation of literary reputation and biography. His figure and works have been an object of consistent manipulation of that kind first by the Imperial Russian government in the 19th century and then by the Soviet State. Branded as a 'spider, aspiring to be an eagle' by contemporary critics, Chernyshevsky was then praised by the Soviet propaganda as the inventor of social realism and as an early martyr of the Revolution. These assessments were based not on literary merits of Chernyshevsky's writings, but rather on political and ideological impact they had on Russian society. My research examines universal ways in which personal myths are constructed, how they are integrated into more general national ones and how portraying and re-interpreting the past in academia, literary criticism and arts could serve ideological purposes.

In his 1926 poem *To Comrade Nette, A Man and a Steamship* Russian poet Vladimir Mayakovsky described a peculiar feeling he had after seeing an actual ship, named after someone he knew personally. *To Comrade Nette* illustrated a tradition of naming ships after national heroes, practiced in many countries. However, in the young Soviet state of 1920s, where new heroes were born daily, it created a peculiar effect of ghostly, inanimate presence (figure 1). Almost a century afterwards the object of my research, Nikolay Chernyshevsky, a person and a historical figure, is now no more than a ghostly presence, paling in comparison with a myth of Nikolay Gavrilovich Chernyshevsky, The Great Socialist Writer – a myth which it has taken more than hundred and fifty years to create. It was created for a purpose – as soon as Russian philosopher, journalist and writer Nikolay Chernyshevsky became a public figure in 1860's his image has been an object of consistent ideological manipulation.

In the curious case of Nikolay Chernyshevsky the process of turning a real historical figure into a steamship or, in other words, into a myth had started even earlier than

the official Soviet propaganda began employing his image as one of its major ideological weapons. Moreover, it went on after the Soviet state ceased to exist.

Nikolay Chernyshevsky, archbishop's son from a small town in the South of Russia, established quite a career for himself in St Petersburg of the 1860s. He graduated from the University of St Petersburg in 1851, went home to Saratov to teach at a boy's school for three years, married the prettiest girl in town and came back to St Petersburg to work first as a journalist and then as an editor at one of the most influential journals of the time – *The Contemporary*. In a short period of time this young scholar overtook the journal's editorial board, radically changing the balance of power of Russian literary scene (figure 2).

In 1862 Chernyshevsky was put into a Peter and Paul Fortress – his imprisonment would last for the next twenty years. Arrested on charges of 'seditious activity', in 1863 he published his first and most successful



Figure 1



Figure 2



Figure 3

novel *What is to be done?*, written in prison in the period of four months. It became one of the most significant publications of the 1860s. Dealing with issues at hand, the novel offered a whole generation an example of how to channel their revolutionary aspirations into productive activity. The protagonists, so called 'new people', were busy setting up sewing workshops and brainstorming on the problems of working class instead of organising clandestine meetings and blowing up governmental officials. The novel was immediately banned but nonetheless widely read, and the first foundations of a myth of Chernyshevsky, a great martyr of Revolution, were laid – the author had, after all, sacrificed his freedom in order to be heard (figure 3).

In the next twenty years *What is to be done?* became a part of an underground culture of resistance, going through the hands of numerous young idealists including a fourteen-year-old Vladimir Ulyanov-Lenin. But it was after the first Russian revolution of 1905 that the true potential of Chernyshevsky as an inspirational figure was first realised. Not restricted by censorship, numerous publications about Chernyshevsky found their readers. Written both by genuine admirers and political activists, these biographies and pamphlets described Chernyshevsky's life in a way that was sometimes very far off from real historical facts. Realising the importance of correct interpretation of the great writer's life and oeuvre, Lenin himself took a special interest in the works on the subject, promoting some and banning the others.

The state leader's open admiration granted Chernyshevsky and his novels a privileged status in Soviet

academia. Research has been encouraged, and an image of Chernyshevsky as a relentless revolutionary and the best 'socialist thinker of the pre-Marxist era' was established. His metaphors, such as 'the fair future', entered the vernacular. The story of the novel's protagonist, Vera Pavlovna, and her dreams became an ideological cliché, a part of an official, even if imposed and artificial, literary canon.

As soon this canon collapsed along with the whole machine of Soviet ideology in 1991, Chernyshevsky and *What is to be done?* acquired another, peculiar status. An iconic work of literature during Soviet times, it was now considered 'one of the worst novels ever written', an esthetical disgrace and simply a very dull book to read. Generations of students that have sweated over their school essays and learned the descriptions of 'the fair future' by heart were now happy to see their children escape this tragic fate. The long pent-up vehemence that was unleashed after 1991 was quite understandable – all the unthinkable things could finally be said aloud, written down, published as academic papers. Removal of Chernyshevsky's works from the school curriculum in 1990s Russia, along with other works of the so-called social-realism, was considered to be a sign of an important political change.

Interestingly enough, another writer's final and much-awaited return to Russian literary canon coincided with Chernyshevsky leaving it, as it seemed at the time most probably for good. Vladimir Nabokov's novel *The Gift* (first published in Russia in 1988) presented a notoriously unflattering image of Chernyshevsky that did not help constructing his post-soviet and post-ideological persona. Nabokov's protagonist writes a biography of Chernyshevsky, an undertaking that baffles his friends and colleagues. It is 'an exercise in shooting', he maintains, a way to deal with cultural legacy of Imperial Russia, the legacy that brought the country to such an inglorious end. Following Nabokov's lead post-Soviet Russia treats Chernyshevsky much in the same way. Marketing campaigns, fine art, political technologies and folklore all reflect that Chernyshevsky is still an important part of modern Russian life – as a cultural artifact, a symbol of a bygone era (figure 4). Also in accordance with Nabokov's text, Russian politicians are now invoking Chernyshevsky's name as a symbol of political resistance. Thus, the story of a real man and his works, having gone through a three-step process of ideological manipulation, has made a full historical circle, once again bringing Russia's past closer to its present.



Figure 4

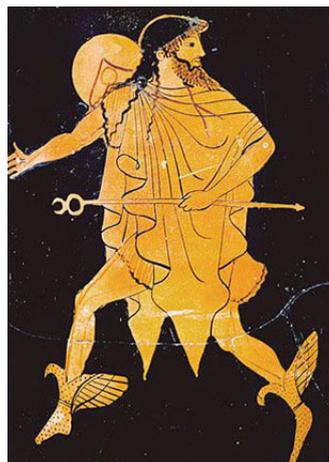
# The Common Voice of the People: The Importance of Heralds and Proclamations in the Archaic and Classical Greek world

Andrew Brown, *DPhil Classics*



Shortly after submitting my doctoral dissertation for examination Russell Tucker asked if I might be willing to write a short little note regarding the nature of my research and its conclusions for this wonderful Wadham Journal. As any grad student who has recently finished or is nearly finished can attest the dissertation becomes to its author a monstrous creation that dominates one's life, and having just recently freed myself of the clutches of Ancient Greek communication I initially balked at the idea as the thought of revisiting my research led me to the brink of despair. However, I eventually realized that perhaps it would be best if I at least considered what my thesis was about before I walked into the impending viva, and so I present to you a quick and dirty summary of the aims and general conclusions of my study, *The Common Voice of the People*, regarding the role of ritual proclamation and oral communication within the Classical Greek city-state of the fifth and fourth centuries B.C.E.

In recent decades the importance of communication within the ancient Greek World has become a subject of great interest to modern scholars. These attempts to analyze the importance of communication systems within and between the poleis have become a means of exploring how the citizens of ancient Greece interacted with one another, with their community at large, and with the greater world on an international scale. Recent works have explored the importance of monumental inscriptions and written communication, archives, regional networks of city-states, and the very nature of news dispersal within the community. However, despite this increased attention on the role of communication within the city-state there has been little direct work on the importance of oral communication, and specifically proclamations, as a means of spreading information and as an important aspect of ritual action. The source of these civic proclamations, the herald (known often in modern England as a town-crier), appears in Greek history from the earliest fragmentary records of Bronze Age Pylos to the epics of Homer, the histories of Herodotus and Thucydides, and in the abundance of late Classical, Hellenistic, and Roman inscriptions from Athens and the rest of the Greek world. Heralds made proclamations within every major aspect of Greek society from the official level of governance, religion, and



military organization to private matters of slave manumissions, family affairs, and mercantile advertisement. However, despite this breadth of involvement in the life of the polis, the herald has been largely marginalized, glossed over, or completely overlooked by modern scholarship. Aristotle speaks to

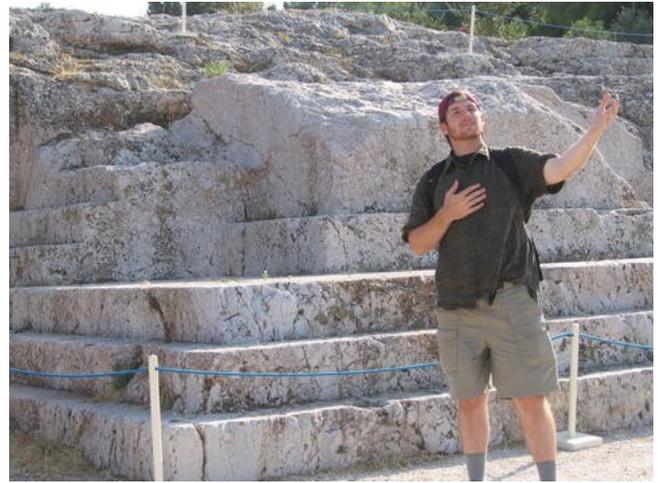
the centrality of the herald to the Greek way of life when he notes that a city must not be so large that its citizen body cannot be reached by the voice of a herald. However, despite Aristotle's allusion to the centrality of the herald and his voice to the proper size and functioning of a polis, he himself does not go into depth about the roles of heralds and their proclamations within the everyday life of the community, but he does mention them amongst the important officials of the polis. Aristotle, like many ancient authors, took his readers' general knowledge of heralds for granted, and likely felt it was unnecessary to explain such a basic and highly visible official shared throughout the Greek world.

My dissertation seeks to fill the void of modern scholarship on the importance of heralds and their proclamations within the systems of communication of the classical Greek community. The goal is not to overturn previous scholarship on the spread of information, or the rise and place of written communication in the Classical World, but instead the dissertation seeks to dovetail with previous scholarship on communication in ancient Greece, and to explore how proclamation directly affected citizens and residents (in particular) of ancient Athens. The abundance of heralds and the multitude of official proclamations in various aspects of life within Athens testify to their importance to the proper functioning of the state, but it is not immediately clear what was the exact nature of this importance. The thesis asks: What is the importance of proclamation and the herald to civic life? More specifically, in the increasingly literate world of late Archaic and Classical Athens, did formal oral communication in the form of herald proclamations play a role in conveying information to the greater community? Were there aspects of communication where heralds and proclamations appear to have been unimportant, and what might this indicate about Athenian attitudes towards heraldic

proclamation? Might proclamation have further purposes in the form of direct effects upon communal life through speech acts, rituals of legitimization, or perceived direct communication with the divine? Were some of these proclamations simply ritualized remnants of a pre-literate society which relied upon orality as a means of communicating in a memorable fashion? The dissertation attempts to answer these questions by exploring the specific place of proclamations and heraldic activity within a range of aspects of life central to the community. Beyond a simple antiquarian list of roles and places for proclamations and heralds the work attempts to understand their importance within the context of the Classical city-state.

The first, and most basic, conclusion I drew from the amassed evidence is the impressive depth of heraldic involvement within the domestic and international institutions of Athens. While most previous scholarship has largely focused on heralds as either literary characters in Athenian drama or diplomatic agents bearing messages of peace, war, or battlefield truces, the truth as revealed in my dissertation is that they also served prominent roles within local government bodies such as legislatures and courts, smaller aspects of government such as boards of magistrates and officials, and in private sector capacities where they facilitated the ability of individual citizens and businesses to communicate to the greater community by publicizing news regarding civic regulation, organizing assemblies and crowds, and pronouncing instructions to the greater public. The consistency of heraldic involvement throughout society leads me to believe that the herald's cry must have been one of the most common human sounds in the community. The limited nature of requirements needed to be a herald, effectively a loud and clear voice, meant that nearly any able bodied man might find some sort of employment as a herald. This possible oversubscription of the herald employment pool meant that the socio-economic position of heralds ran the gamut from wealthy and respected professionals who served as auctioneers, prominent civil heralds of the legislature, sacred heralds who took part in ritual sacrifice, or who won competitions at athletic festivals to those less experienced and skilled men who might be hired on a daily or hourly basis to announce individual or commercial information.

While heralds do appear to make proclamations at a variety of levels throughout the community, there is a surprising lack of evidence for heraldic proclamation of new Athenian laws or decrees within the community. This is extremely surprising as when I



begin my research I expected a state herald to be responsible for making regular state proclamations in the central square and marketplace and throughout the community. This absence within Athens is doubly surprising considering the Athenian use of heraldic proclamation to communicate decrees to militarily occupied populaces and to their fifth century imperial allies. This evidence, coupled with the Homeric citations mentioning orders and decrees being proclaimed by heralds, suggest that other city-states might have institutionalized systems of proclamation for new legal statutes. Additionally, the above examples seem indicative of more restrictive forms of governance (military occupation, imperial domination, Homeric kingship), and I would propose that restrictive forms of government likely maintained heralds as the official mouthpiece of the ruling authority in order to relay information to the general population. It is clear from an investigation into public notice that some cities employed heralds on a more expansive basis than Athens for certain issues, and it is not unreasonable to imagine they likewise did so in some cases for central state communication as well. This raises the question as to why Athens does not appear to employ heraldic proclamations, and I have postulated that the Athenians consciously removed such a role from common use precisely because of an association with more restrictive governments such as tyranny or oligarchy. The position of heralds and their proclamations appears to have been double-sided within the Athenian polis. On the one hand heralds existed in a variety of roles throughout private and public life making proclamations that could both directly inform and have a real effect upon individuals and the community, and on the other there was an absence of heralds and official proclamations in those areas of statutory communication where many have assumed they would have played an active and important role.

# Physiological growth models of cerebral aneurysm evolution

Alisa Selminovic, DPhil Engineering Science



A cerebral aneurysm (CA) is best described as an abnormal distension of the wall of an artery in the brain, often forming a bulbous sac which may rupture and lead to stroke. While structural changes characteristic of CA development are extensively documented, the link between mechanical stimuli –in particular the forces arising from the motion of blood through arteries (known as hemodynamic forces) –and these processes remains poorly understood. This work explores the hypothesised link between low levels of shear force (SF) –the force arising from the movement of blood against the arterial wall –and CA growth. A computational model of CA evolution<sup>1</sup> incorporating the interactions between haemodynamic forces, the growth and remodelling (G&R) of cells comprising the arterial wall, and the physical deformation of the artery during CA development is embedded within images of real, patient-specific arterial geometries using a novel method for constructing virtual surfaces. Interestingly, blood-flow simulations showed that in one case, the evolved model aneurysm geometry was qualitatively similar to the physiological aneurysm geometry.

## Introduction

CAs are relatively common, and affect 2% to 5% of the adult population. Most remain asymptomatic; however, 0.1% to 1% of detected CAs rupture annually, with a 30% to 50% chance of fatality<sup>[1]</sup>. The aetiology of the disease is believed to be the result of a combination of multiple contributing mechanisms, including biological, genetic, life-style and patient-history factors. High incidence, high mortality rate in the case of rupture, and the improvement in imaging techniques have resulted in an increase in interventional treatment of detected asymptomatic aneurysms. However, the low incidence of aneurysm rupture coupled with the non-negligible risks of interventional treatments provide motivation for identifying and treating only those aneurysms that are most likely to rupture. In turn, this provides motivation for computational modelling of cerebral aneurysm evolution, so as to provide insight into the mechanisms underlying the disease, as well as to allow clinicians to predict the behaviour of a detected aneurysm.

It has recently been accepted that hemodynamic forces play an important role in aneurysm development, although the exact mechanism is not yet understood. In-vitro studies have shown that the direction and magnitude of SF affect the orientation of cells that form the inner-most layer of arteries, and modulate cell-signalling and gene expression<sup>[2]</sup>. In particular, recent clinical observations suggest that regions of arterial geometry exhibiting permanently low levels of SF correlate well with the site of CA development<sup>[3]</sup>. Therefore, low SF may be a driving force for CA evolution. In this study, a novel algorithmic method was developed to embed a mathematical model for CA evolution<sup>[4]</sup> within images of real patient arterial geometries. We assume that low SF drives the

degradation of elastin and in turn the growth and remodelling of collagen (the key structural components of the arterial wall), thereby facilitating CA growth. To test this hypothesis, we compare the evolving model aneurysm geometry to the clinically observed CA geometry.

## Methods

To integrate the model within patient-specific arterial geometries, the original CA is removed in software, and replaced with a cylindrical section (aneurysmal section) to represent an idealised section of healthy artery. The aneurysmal section is reconnected to the up- and downstream sections of the artery using a novel, automated algorithmic method.

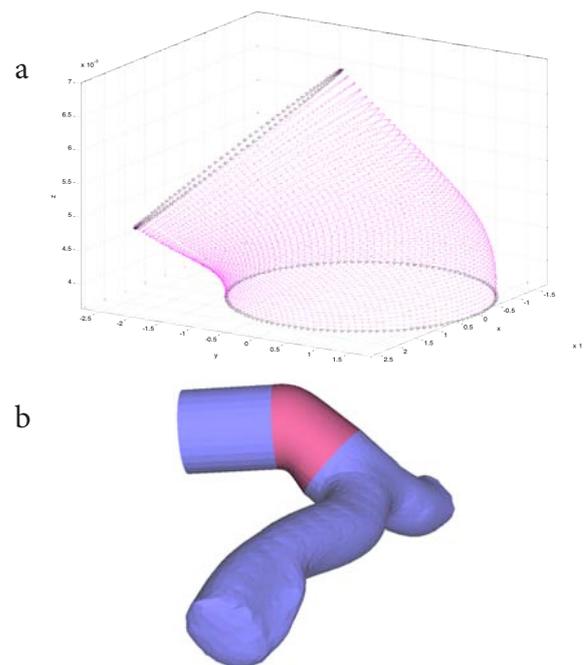


Figure 1

- (a) Algorithmically-generated curves (pink) between two geometry boundaries (black), and
- (b) the triangulated, reconstructed surface (pink) connecting the cylinder model geometry (blue, left) and the downstream arterial geometry (blue, right)

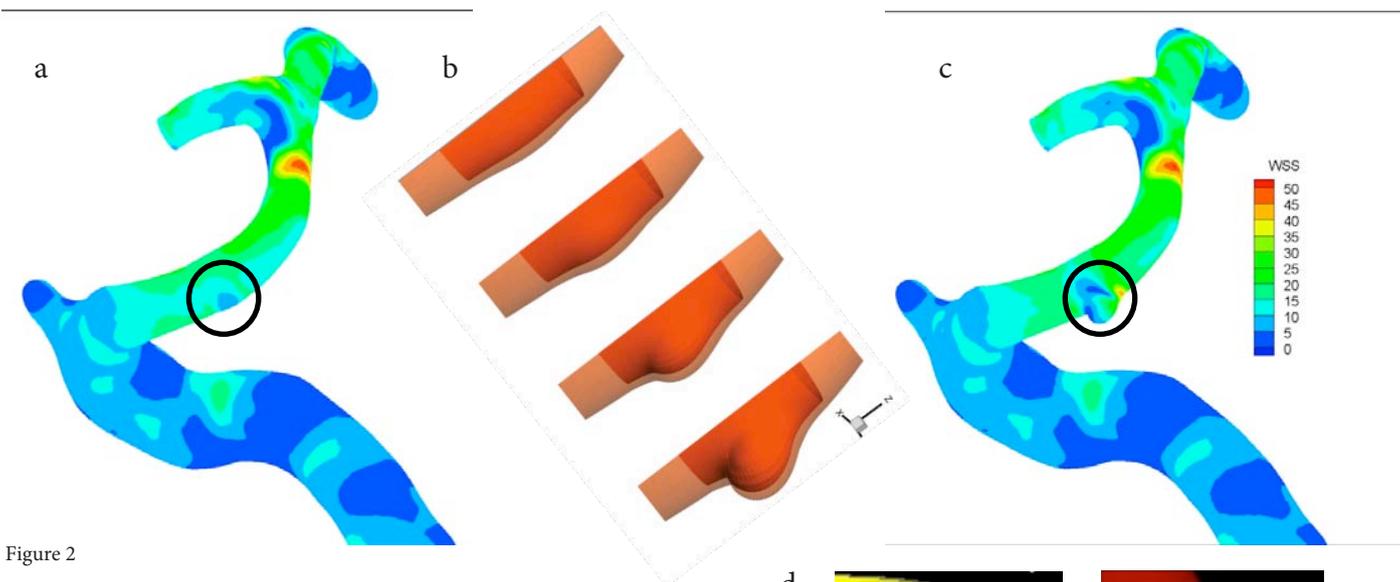


Figure 2

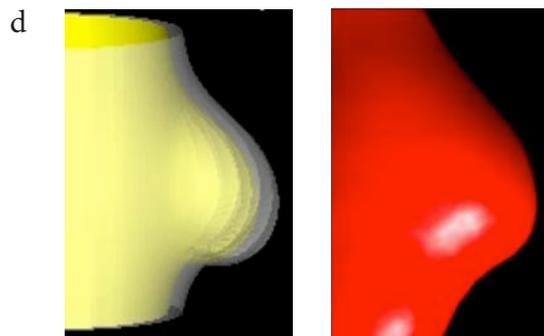
- (a) Physiological geometry at aneurysm inception, where initial perturbation results in localised low SF;  
 (b) the evolving model aneurysm geometry;  
 (c) the evolved, stabilized aneurysm;  
 (d)(i) model CA geometry compared (left) with (d)(ii) physiological CA geometry (right)

The algorithm generates a series of curves between two boundaries; the points of adjacent curves are connected to form a triangulated surface between the boundaries. Physiological pressures and blood-flow velocities are applied at the geometry boundaries. Blood-flow simulations are run, and the growth and remodeling of arterial-wall components is explicitly linked to the evolving hemodynamic environment.

### Results & Discussion

Aneurysm inception is prescribed to occur within a small circular patch on the cylinder model (Figure 2(a)). A localised degradation of elastin results in a perturbation in the arterial geometry; the collagen fabric adapts, and the artery achieves a new equilibrium configuration at each time-step (Figure 2 (b)). The initial perturbation to the geometry creates a localised region of low SF. Subsequent degradation of elastin is explicitly linked to low SF. An aneurysm evolves (Figure 2(c)).

Qualitative similarities of the simulated and removed patient CA geometries were observed (Figure 2(d)(i) and (ii)), which tentatively support the low SF hypothesis. The SF distribution (shown in Figures 2(a) and (c)) shows that the lowest levels of SF occurred at the proximal dome of the aneurysm, and were highest at the distal neck, which is consistent with other, similar computational studies[5,6]. Of course, the real story is more complex, and further sophistications (e.g. a more explicit representation of other vascular cells) are needed to more accurately model the mechanobiology of the arterial wall.



The current computational framework provides the foundations to incorporate these, and thus provides the basis to elucidate the CA aetiology.

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