induction and the subsequent combination with a proliferation signal inhibitor could potentially generate protolerogenic immunological effects (like so-called prope, or near, tolerance and upregulated T regulatory cells). Prevention of cumulative alloimmunological injury to the graft from subclinical rejection and acute and chronic (donor-specific) antibody-mediated rejection could potentially translate into measurably better graft function and survival after 5 years. Alemtuzumab with sirolimus could reduce nephrotoxicity and cardiovascular and metabolic adverse effects through avoidance of calcineurin inhibitors. However, given the complexity of cardiovascular morbidity and mortality after renal transplantation, improvement in a few laboratory results in a clinical trial is a long way from achievement of improvements in the disease course over 5 years. Ideally, these goals would all be achieved without excess malignancies and opportunistic infections.

Irrespective of the current and anticipated long-term results of the 3C Study, investigators will question the cause of the results. This will be a difficult question to answer because the 3C investigators changed all parts of the standard of care immunosuppressive regimen (the type of induction drug, the dose of calcineurin inhibitor and mycophenolate, and even the use of corticosteroids) rather than one element only.6 months later, they changed the regimen again. Therefore, the 3C Study will not only address its own predefned hypotheses, but will also represent a test case for what type of trials in clinical transplantation are needed to regain some of the academic vigour and pharmaceutical impetus towards development of new pipelines for novel immunosuppressive drugs.

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Genome sequencing of an early World War 1 isolate of *S. flexneri*, which Kate Baker and colleagues describe in this issue of *The Lancet*, gives an in-depth view of the microbe’s evolution over the past 100 years. The changes mimic those of the ancestral *Escherichia coli* as it developed into *Shigella*, species that are still regarded as a clade of *E. coli*. The differences reported between *E. coli*, the descendant enteroinvasive *E. coli* (EIEC), and *Shigella* are often indistinct (analysis using matrix-assisted laser desorption/ionisation with time-of-flight mass spectrometry is unable to distinguish these microbes) and they share a common core genome. Molecular-clock calculations suggest that *Shigella* diverged from several *E. coli* species between 35,000 and 270,000 years ago. Was this a result of early paleolithic man’s habits, the way food was prepared or stored, or perhaps diet? Or, if about 35,000 BCE is accepted as the date for *S. flexneri’s* appearance, did it occur when man migrated from Africa to Europe? The low infective dose of *Shigella* might explain how hunter-gatherers could have taken a small amount of contamination with them when moving to new environments.

After the evolution of *E. coli* to *Shigella*, two predominant genetic events were reported. Old characteristics were deleted—as a form of reductive evolution—with the addition of new characteristics that increased pathogenicity, such as the loss of genes relating to motility, the flagellar genes, and the consequent absence of *H* antigens. Some fermentative catabolic pathways disappeared, accompanied by a loss of lysine decarboxylase, the end-product of which is cadaverine, which impedes intracellular dissemination of *Shigella* by blocking bacterial escape from phagocytes. Changes in the bacterial cell envelope resulting in no *K* (capsular) antigens have also been reported. However, many more insertion sequences, including those related to genomic pathogenicity islands, appeared. Insertion sequences constitute 7% of the *Shigella* genome, compared with 1.5% of *E. coli* K12. Specific virulence factors, such as adhesins and EIEC toxin, which damage intestinal mucosal epithelium and precipitate bleeding, were also acquired. Antigenic variation of the O antigen helps the bacterium to avoid the immune response, and genetic changes in the large virulent plasmid (which is responsible for different pathogenic determinants such as the T3 secretory system) tend to parallel those found in the bacterial chromosome.

Baker and colleagues show the same trend occurring over the past 100 years in the *S. flexneri* isolate from World War 1, with insertion sequences facilitating the gain of some antimicrobial resistance elements and the discovery of unique pseudogenes. New virulence factors also appeared, such as shigella enterotoxin 1, and the number of pathogenicity islands increased. The occurrence of a new serotype *Xv* from China, replacing the more common Asian serotype of *S. flexneri* type 2a but remaining in the same serotype cluster, renders any immunity obtained from the old 2a serotype irrelevant. The large plasmid was lost in the World War 1 isolate, presumably because of serial passage. Since this plasmid carries many virulence genes, such as those promoting type 3 secretion system effectors and SK2, which assists intercellular and intracellular spread of *Shigella*, only chromosomal changes could be investigated. The mutation of the variant (*v*) portion in the (*S. flexneri* 2a) Xv Chinese serotype, unlike all the other genes for serotypes, is a plasmid mutation.

Good hygiene, especially when preparing food, and reliable sanitation are the best prevention against bacillary dysentery. There are no significant non-human hosts, which makes vaccination an ideal solution for elimination of the disease. However, although many studies are in progress, vaccines are not yet available. Multiple antibiotic resistance of *Shigella* means treatment is not straightforward, even though some regional variation in resistance exists.

The focus on the treatment of soldiers has more recently been extended to civilian populations of war zones. Admirable in itself, this approach also reduces the sources of infection to which soldiers are exposed, underlining the role of the military in humanitarian work. Nowadays epidemics of bacillary dysentery in the armed services are not often reported; rather, they tend to occur in refugee camps and in impoverished urban slums.

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We declare no competing interests.

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On World Thrombosis Day

The International Society on Thrombosis and Haemostasis (ISTH) has declared Oct 13 to be World Thrombosis Day, to be held annually from 2014 onwards. The purpose is to work together with and assist local and regional organisations to increase awareness of and education about thrombosis.

This date has been chosen because it is the birthday of Rudolf Virchow (1821–1902), the founder of cellular pathology, who worked in Berlin and Würzburg, Germany. He was a remarkable man, paving the way for modern medicine along with the Viennese pathologist Carl von Rokitansky. Virchow worked not only as a pathologist but also did animal experiments, treated patients, and advocated public health—pursuing his socially minded ideas with such vigour that he was forced to leave Berlin at one stage (although re-instated at the Charité hospital, in Berlin, 6 years later). Virchow was the first to show by autopsy studies that pulmonary emboli originate from thrombi in the deep veins of the leg, and he suggested three groups of causes for thrombosis which were, liberally translated, stasis, hypercoagulability, and vessel wall pathology. Being the first to use the words thrombosis and embolism, Virchow is rightly seen as the father of modern research into thrombosis.

The need to raise awareness of thrombosis becomes clear when one reads the paper on the global burden of thrombosis published in the Journal of Thrombosis and Haemostasis, and copublished by Thrombosis and Haemostasis, Seminars in Thrombosis, Thrombosis Research and Arteriosclerosis, Thrombosis and Vascular Biology. Arterial thrombosis (ie, ischaemic heart disease and ischaemic stroke) causes more than 10 million deaths per year worldwide. When years of life lost to premature death and years lived with disability are looked at jointly, ischaemic heart disease is the leading cause of death worldwide. Moreover, the death toll of arterial thrombosis has increased by 25–35% during the past 20 years, which is determined by two rapidly diverging trends: a decrease in industrialised countries and an increase in developing countries. These are staggering numbers, but, as the report points out, a third major contributor to the global burden of thrombosis is venous thrombosis (deep vein thrombosis and pulmonary embolism). Unfortunately, there is much less detailed information available about deaths and disability caused by venous thrombosis. The Global Burden of Diseases, Injuries, and Risk Factors Study by WHO did not include venous thromboembolism as a specific cause of death or disability.

Because of the scarcity of data and awareness, the ISTH report focuses on venous thrombosis and, in a painstaking effort, all published reports have been reviewed and used to assess the global burden it causes. What emerges is a bleak picture. The incidence of venous thrombosis is not much different from that of