

The activated neutrophil — formidable forces unleashed

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The human neutrophil is the small, aggressive, front-line, circulating phagocyte. The enormous intrinsic destructive potential of neutrophil is captured in the following quotation, which dramatically emphasises the critical requirement for latency and self-limiting activation of these cells:

'Unlike cytotoxic lymphocytes and the complement system, which destroy their targets with a drop of poison, the professional phagocytes kill like Attila the Hun, deploying a battery of weapons that lay waste to both the target and the nearby landscape with the subtlety of an artillery barrage.'¹

In this review recent advances in neutrophil physiology and function, as well as mechanisms of inflammation-related tissue injury and carcinogenesis, are highlighted.

Neutrophil production

About 55 - 60% of bone marrow is dedicated to the production of one cell type — the neutrophil, the most abundant professional phagocyte.² During maturation in the marrow the neutrophils undergo progressive differentiation and loss of biosynthetic activity. After the myelocyte stage these cells become end-cells and enter a large storage pool from which they are released into the circulation after about 5 days, where they have a half-life of about 6 hours.² Although they are end-cells, mature neutrophils retain some residual biosynthetic capacity which is activated on exposure to leuco-attractants or the cytokines GM-CSF and TNF,³ enabling limited adaptation to a changing micro-environment. The steady state production of mature neutrophils is about 1×10^9 /kg body weight per day, but this is dramatically increased by co-operative interactions between leucocytosis-promoting cytokines (TNF- α , IL-1, IL-3, IL-6, IL-8, G-CSF and GM-CSF) and leuco-attractants (C5a, PAF and LTB₂).⁴

Neutrophil cytoplasmic granules

The most notable structural features of the neutrophils are the abundant, heterogeneous cytoplasmic granules and the highly dynamic plasma membrane; these make this cell ideally suited to the performance of its primary function, viz. adherence to locally activated vascular endothelium, extravasation, rapid migration to sites of infection and engulfment and intracellular destruction of invasive microbial pathogens.

With regard to function, the plasma membrane is equipped with adhesion molecules, receptors for leuco-attractants, opsonins and cytokines, as well as the unique

private chalets with luxuries such as central heating; rest and fresh air were the basic treatments. He was well able to afford these amenities, not only on account of the extraordinary success of *Animal Farm* but because *Ninety Eighty-Four*, published that year, had been selected Book of the Month in the USA. Orwell comments in his notebook that 'one cannot help feeling the difference in the texture of life when one is paying one's own keep', as opposed to that in the government-subsidised institutions he had experienced. He appreciated the quietness with 'none of those abominable rattling trolleys' as everything was brought by hand. There was 'not much noise of radios either — all the patients have headphones', and the left-wing socialist evidently enjoyed the benefits of capitalism! However, his radicalism came to the fore in a notebook entry commenting on the 'cultivated accents' of 'upper-class English voices' of visitors to this most expensive block of chalets. 'And what voices! A sort of over-fedness, a fatuous self-confidence, a constant bah-bahing of laughter about nothing, above all a sort of heaviness and richness combined with a fundamental ill-will . . . People one instinctively feels . . . are the enemies of anything intelligent or sensitive or beautiful.'

As Orwell's progress was not satisfactory he was moved to University College Hospital⁸ in London. The consultant reported 'severe disease of the left lung and a relatively slight amount on the right' and as his 'prognosis was hazardous' he was warned that 'if he ceases to try to get well and settles down to write another book he is almost certain to relapse quickly'. Another book would not have been necessary financially as *Nineteen Eighty-Four* had the prospect of bringing in £10 000 - 15 000 and he could afford the £17 per day for his private room.

Despite his poor condition he married Sonia Bronell, a journalist, in a ward ceremony in October 1949. She was 31 and they had been friends for some years. He was 46. They had been married for 95 days when he died suddenly and alone of a massive haemoptysis on 21 January 1950. At the time arrangements were in progress to move him by chartered aircraft to a sanatorium in Switzerland, a venture regarded by his physician and friends as a forlorn hope. Cyril Conolly,⁹ friend and writer, offered this perspective on Orwell's illness:

'The tragedy of Orwell's life is that when at last he achieved fame and success he was a dying man and knew it. He had fame and was too ill to leave his room; money and nothing to spend it on; love in which he could not participate; he tasted the bitterness of dying. But in his years of hardship he was sustained by a genial stoicism, by his excitement about what was going to happen next and by his affection for other people.'

Epilogue

Orwell's funeral arrangements (Crick,⁸ p. 403) epitomise his ambivalent character. These were left in the hands of his friends and fellow writers, Anthony Powell and Malcolm Muggeridge, his executors, whom he had requested to arrange that his 'body shall be buried (not cremated) according to the rites of the Church of England in the nearest convenient cemetery . . .' with 'Eric Arthur Blair' on a plain brown stone.⁸ This created a problem, as Orwell had had no connection with any church. A vicar who had never heard of Orwell was found to perform the ceremony in the

country churchyard of All Saints, Sutton Courtenay, near the family estate of David Astor and through his good offices. He was the owner of the newspaper *The Observer* and had befriended Orwell during his last years. It required the influence of a newspaper magnate to get the left-wing sceptic buried in sacred ground.

Contrary to the international ethics of left-wingers, Orwell was essentially nationalistic in his love for England, especially its language and the liturgies of the English Church. Furthermore his personal tastes, as quoted by Crick,⁸ were closer to capitalism than socialism:

'I like English cookery and English beer, French red wines, Spanish white wines, Indian tea, strong tobacco, 'coal fires, candle-light and comfortable chairs. I dislike big towns, noise, motor cars, the radio, tinned food, central heating and "modern furniture".'

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50 years ago . . .

Measures by British doctors of the Indian Army Medical Corps on the Indo-Burmese Border during World War II have resulted in three important discoveries. These will profoundly influence future military malaria control.

. . . They are:

- (a) The use of suppressive mepacrine, which must lead to a considerable reduction of malaria once its administration is finally placed on a firm basis.
- (b) The introduction of D.D.T., which will enable a more rapid and a more complete control of larger areas than has been possible with the methods hitherto employed.
- (c) The use of repellent fish-nets, which will protect patrols and troops in contact with the enemy, malaria in whom has so far been difficult if not impossible to prevent.

It is felt that the narrow margin of safety conferred by the anti-malarial measures hitherto employed [including anti-larval drainage and pyrethrum spraying] will be greatly widened by the introduction of the above three methods of protection, but strict and expert supervision will still be necessary if the ultimate goal of one hundred per cent. protection is to be attained.

(Brigadier M. K. Afridi and Lieut.-Col. J. Hay Arthur, *S A Medical Journal*, 13 October 1945, p. 361.)