A Guide to COVID-19 for Health Care Professionals

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Cambridge Scholars Publishing

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This book first published 2022

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-8750-9
ISBN (13): 978-1-5275-8750-2

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PREFACE

To say that the Covid-19 pandemic is the first major global health issue for a little over a century is to state the obvious. The continuously rolling stages of the pandemic have (as yet) made it difficult to draw firm conclusions, and any long-term effects will not be known for years to come. However, as regards summarising the pandemic, we are blessed with a number of firm official sources, notably the World Health Organisation (WHO), with its global view, and the Office for National Statistics, the UK Health Security Agency (formerly Public Health England) and the Government Department of Health, reporting data from the United Kingdom. Although no source of information is perfect, these outlets are nonetheless the best we have. On a different level, the scientific community regularly publishes peer-reviewed data in learned academic vehicle, such as the New England Journal of Medicine, The Lancet, and the British Medical Journal. An additional valued source is the UK's National Institute for Health and Care Excellence (NICE).

The objective of this book is to provide the health care professional, be they a nurse, scientist, medic, pharmacist, or physiotherapist, a balanced, authoritative, and up-to-date (as much as in possible) academic report on the effects of the pandemic on the British population. In doing so, data cited will come only from sources of the quality described above. The timing of this book, in the Spring of 2022, is linked to the annual report of the Office for National Statistics on all deaths that have occurred in 2020, which, in comparison with previous years, will show the precise cost of the infection in terms of mortality. However, these data do not tell us the weight of morbidity caused by the virus, and whose implication will be long-lasting, with the recognition of Long-Covid.

The book will achieve its objectives in a series of chapters that will describe the epidemiology, pathophysiology, diagnosis, management, and consequences of COVID-19 using hard facts provided by validated and authoritative scientific sources, and so provide the reader with a sound understanding of this disease.

The contents of these chapters are as follows:

- Chapter 1: A complete understanding of SARS-Cov-2 and COVID-19 disease needs to place it in terms of other population infections, themselves being caused by infectious micropathogens.

- Chapter 2 outlines the process by which we defend ourselves from these micro-organisms, that being the function of the immune system.

- Chapter 3 focusses on the biology of viruses.

- The development of the disease at a global level, and its spread from China to Europe, and ultimately the UK, will be discussed in Chapter 4.

- The diagnosis and management of COVID-19 forms the basis of Chapter 5.

- Chapter 6 will examine the principal medical defence from COVID-19 – vaccination.

- A development during 2021 was the appearance of variants of the original 'Wuhan' strain of the virus, and the long-term effects of an infection were also being recognised. These issues will be developed in Chapter 7, which will conclude with an examination of long COVID and general overview of the larger effects of the pandemic on the health of the nation.

CHAPTER 1

PATHOLOGY, MORBIDITY, AND MORTALITY

Each of us will face our final destination – death – and accordingly a great deal of effort is expended in delaying this ultimate arrival, and this fact weight heavily on statistics and resources. The viral infection known as COVID-19, caused by SARS-CoV-2, is the latest in a series of infectious disease that have, literally, plagued humanity for millennia. However, death is commonly preceded by ill-health, and in comparison, data on morbidity is collected poorly, although that for COVID-19 is improving.

A complete understanding of SARS-CoV-2 and COVID-19 needs to place it in terms of other population infections, themselves being caused by micropathogens, which this chapter will provide. We start, in section 1.1, with an exploration of the causes of death, followed in section 1.2 by a historical perspective of infectious disease through the ages.

Learning objectives

Upon completion of his chapter, you should be able to….

- Describe the major causes of death
- Explain the differences between epidemic, endemic and pandemic
- Identify the four major groups of micropathogens
- Recognise that these micropathogens have been plaguing our species for millennia
- Understand the place of SARS-CoV-1 and MERS-CoV in the biology of COVID-19

1.1: Life, death, and infections

The causes of death

You are going to die – I absolutely guarantee it. But how? In the UK, the Office for National Statistics (ONS) publishes annual data on the numbers of deaths according to the underlying disease. Many of those for 2021 are shown in table 1.1, with COVID-19 (where the virus was actually identified) being the third most frequent. Notably, a death cannot be counted twice, so that other respiratory disease is still a major killer. Not shown in table 1.1 are deaths due to certain infectious and parasitic diseases, which killed 5,476 (2,487 men, 2,989 women), the leading cause (2,894 deaths) being bacterial sepsis. There were 151 deaths due to tuberculosis, 175 due to viral hepatitis and 140 caused by HIV, all of which pale into insignificance compared to that of SARS-CoV-2, which caused 67,057 deaths, slightly down from 69,679 in 2020.

Table 1: Causes of death in England and Wales in 2021

	All deaths	%	Male	%	Female	%
All causes	585,484	100	297,488	100	287,996	100
Cancer	148,109	25.3	78,969	26.5	69,140	24.0
Circulation	134,174	22.9	72,498	24.4	61,676	21.4
COVID-19	67,057	11.4	36,627	12.3	30,430	10.6
Respiratory	54,799	9.3	28,064	9.4	26,735	9.3
Mental and behavioural disorders	41,076	7.0	14,729	4.9	26,347	9.1
Nervous system	37,888	6.5	16,226	5.5	21,662	7.5
Accidents	16,180	2.8	9,490	3.2	6,690	2.3

Source: www.nomisweb.co.uk

Table 1 also points to a major risk factor for deaths – the male sex, linked to an increased risk of 3.3% compared to females, a sex difference second only to a fatal accident and far exceeding the risk of death by cancer or circulatory disease. However, 11,618 more women died of a mental and behavioural disorders (such as dementia and Alzheimer disease), and 34% were more likely to die of a disease of the nervous system. But as regards this book, SARS-CoV-2 killed 20.4% more men than women. We will return to data of this nature in chapters to come.

Key point: In 2021, in England and Wales, COVID-19 was the third most frequent cause of death, slightly exceeding respiratory disease.

Types of infections

We share this planet with millions of different species, and all compete for resources. The larger competitors we can mostly address, but those very small organisms are more of a problem. Several of these cause disease, i.e. are micropathogens, the study of these being microbiology. We can address our relationship with these organisms with a number of terms.

Endemic disease
Generally, we co-exist with various micropathogens (bacteria, viruses, parasites, and fungi), and due to the laws of natural selection and the normal distribution, some of us will be resistant to these pathogens, while others will be susceptible, and so succumb to their particular disease. In such cases the disease is said to be endemic – always present in a small number of people. Examples of these diseases in the UK include measles, chickenpox, and seasonal influenza, whilst hepatitis B and C viruses are endemic in certain parts of the world. Tuberculosis is a relatively minor health issue in the UK, but is globally endemic, causing over 1.5 million deaths in 2020, making it the second leading cause of death from a single infectious agent after COVID-19 (at least 5 million).

Herd immunity
Generally, an organism fails to infect an entire population (i.e. the herd) because a sufficiently large number of individuals are naturally resistant, or have suffered a relatively mild infection, and so are immune to a second infection (discussed fully in Chapter 2). Thus herd immunity describes a situation where the disease is held at bay by those with a defence, such that those susceptible to the infection have a degree of protection. One way of improving herd immunity is to actively promote a low level of the infection, the most efficient method being vaccination, as discussed in Chapter 2.

Epidemic disease
Should herd immunity fail, perhaps because the particular organism is more infectious and/or is new to the herd, then a large number of the population will become infected, and there will be an epidemic. The study

of this process is epidemiology, although it now encompasses other health issues not always those of microbiology. However, as the herd as a whole handles the disease, and develops mass immunity, the infection will sooner or later abate, and may become endemic.

Pandemic disease
A pandemic is an epidemic that spreads out from a local population into a far larger geographic area. At some point the epidemic/pandemic may be so severe, bringing a considerable risk of morbidity and mortality, that it is referred to a plague.

Plague (noun): That which smites, wounds, or troubles; a blow; a calamity; any afflictive evil or torment; a great trial or vexation.
Webster's Dictionary (1913 Edition)

Micropathogens

As a society, we have (generally) addressed those large organisms that would do us harm (lions, tigers etc.), but have much work to do as regards harm from small organisms (i.e. microbes). In as much as you (biologically) are your body (self), the purpose of the immune system is to protect you from microbiological attack, by recognising what is not you (that is, non-self), and then destroying it. Factors that cause disease are pathogens, of which several types are recognised, and one method for classifying these disease-causing objects is by size. Atoms are too small to be recognised by the immune system, although several are toxic (arsenic comes to mind), as are certain other molecules. Prions are pathogenic and infectious proteins that are regarded as self by the immune system, and are consequently not the object of attack.

Pathologists focus on four groups of pathogens that include thousands of different micro-organisms. A further point is that all of these microbial pathogens are parasites (that is, an organism that benefits at the expense of another). In some cases, infections can be mild and merely irriatiting, but in other instances they can be fatal.

Viruses
Viruses are a section of DNA or RNA enclosed within a protein coat, and which can only reproduce within a cell. Examples include smallpox, polio, measles, mumps, rubella, influenza, hepatitis viruses and HIV as well as SARS-CoV-2. Generally sized around 0.1 μm, viruses can only be viewed directly by electron microscopy. The fine details of the biology of viruses are addressed in Chapter 3.

Bacteria
Generally with a size of 0.3-5 μm, bacteria can be viewed by light microscopy individually, or as clusters or chains of spherical (cocci), rod-shaped (bacilli) or spiral (spirilla) organisms. The vast majority are so called 'free-living', whilst a small proportion (such as *mycobacterium tuberculosis*) must pass a portion of their life cycle as intra-cellular parasites. In contrast to the protein of viruses, their outer layers (the cell wall) are composed of complex polysaccharides cross-linked by peptides, and which defines their 'non-self' nature.

The precise composition of the bacterial cell wall varies and enables identification of difference species, such as Gram's stain as positive (as in *staphylococcus* and *streptococcus* species) or negative (as with *E coli* and *salmonella* species), and the Ziehl-Neelsen stain for myobacteria. In contrast to a historical view, where all bacteria were considered be pathogenic, there is increasing evidence that a collective of certain species, the microbiome, is, in fact, beneficial, especially in the abdomen.

Fungi
These saprophytes (plants living on dead material) may also to be found as individual units or as colonies. Amonst the latter are aspergillus species (of which there are hundreds), and which characteristically grow in long chains (hyphae), and which preferentially infect the lung, causing aspergillosis. The most prevalent non-colonical species include *candida albicans* (yeast, causing the infection thrush), and *pneumocystis jirovecii*, a common infection in AIDS, but which can also cause pnemonia in those free of this disease.

Parasites
Larger, more complex parasites can be protozoa (single celled organisms) and metazoa. The former include the plasmodium species that cause malaria (*P. falciparum, vivax, ovale, knowlesi* and *malariae*) and infect red cells, amoeba (*Entamoeba histolytica*, often causing amoebic dysentery), and trypanosomes. Metazoan parasites include filaria, schistosomes, and

various worms (tapeworm, liver flukes). Many of these parasites gain entry to the body, others remain on the outside of the body as ectoparasites (such as leeches and certain arthropods [fleas, ticks and lice]).
The role of the immune system in combating infection is discussed in Chapter 2.

A global view of infectious disease
In 2017, there were almost 56 million deaths worldwide. Table 2.2 shows those 4.2 million (~7.5%) caused by infectious agents. The first COVID-19 death was reported on 6th January 2020. As of 20th July 2022, the WHO reported 6,367,793 deaths due to SARS-CoV-2, with over 560 million confirmed infections.

Table 2: Global deaths due to infectious disease in 2017

Infectious agent	Deaths
Tuberculosis	1,183,700
HIV/AIDS	954,500
Malaria	619,800
Hepatitis B virus*	384,000
Hepatitis C virus*	332,300
Typhoid fever	116,800
Syphilis	113,500
Measles	95,300
Whooping cough	91,800
Acute hepatitis B virus	89,600
Other unspecified infectious disease	79,300
Haemophilus type B (meningitis)	75,700
Salmonella	59,100

From GBD 2017 Causes of Death Collaborators.
*both causing cirrhosis and chronic liver disease

Key point: SARS-CoV-2 has become the most lethal infectious agent in the modern era.

1.2: Infectious disease throughout the ages

The ancients

Perhaps the earliest and most authoritative description of a micropathogen plague was made by Thucydides in Greece around 430 BC, and which killed perhaps a quarter to a third of the population. It has been speculated that it was not caused by any single pathogen, but a combination of viruses (smallpox, measles, scarlet fever) and bacteria (*Mycobacterium tuberculosis, Bacillus anthracis, Salmonella typhimurium* and *Yersinia pestis*). Notably, he observed that "*the same man was never attacked twice – at least never fatally*", he himself suffering once from the infection.

The first millennium AD

Aelius Galenus described the Antonine plague of 166-169 AD, the cause now reputed to be smallpox (possibly because of the scabby and scaly rash). In and around Rome, it brought a mortality rate of 7 – 10%, although others suggested a rate of 50%. This, and the plague described by Thucydides, most likely had only local effects, perhaps to a relatively small geographical area, and so can be described as epidemics. The Justinian plaque of 541-544, and lasting until 750, is possibly the first and best-described early pandemic, causing tens of millions of deaths around the Mediterranean region and in Europe. Analysis of DNA from victims of this plague point to *Yersinia pestis* (hence: pest and pestilence) as the causative agent. The Japanese smallpox epidemic of 735-737 brought a mortality rate of between a quarter and a third.

Many commentators refer to *the* plague as any infection caused by this organism, whereas others often fail refer to this or any other organism, describing *a* plague, without a defining causative micropathogen.

The second millennium AD

The Black Death
This pandemic decimated many Asian and European populations, peaking between 1335 and 1355, reaching England in August 1348, killing a third to half of the population of ~25 million. Analysis of DNA from bodies found in plaque burial pits found incontrovertible evidence that the causative agents was *Y pestis*. A key clinical feature was the development

of '*buboes'*, hence bubonic plague, modern medicine now recognising these as lymphadenopathy, although the precise pathophysiological nature cannot be determined. An additional term is pneumonic (=relating to air or gas) plague, wherein the infection centres on the lungs. With further benefits of the modern age it is now generally believed that *Y pestis* was transmitted by fleas carried by rats. An increase in the number of these rodents is believed to be due to a reduction in numbers of its leading predator (the cat).

Other outbreaks of the Black Death appeared sporadically: in 1499 around 40,000 died in one year in Paris, in 1564 around 1,000 Londoners died weekly, and in 1603 a further epidemic killed 38,000 and lasted for eight years.

The Great Plague

This disease also rolled in from the East, and was present in several European countries in 1665: 300,000 died in Naples, whilst in London it killed over 68,000 from a population of 460,000 (i.e. ~15%). An early example of public health data collection were 'Bills of Mortality', collated by John Graunt. A summary of one Bill from 1665 is presented in table 1.3, which shows the major forms of 97,307 deaths, omitting the 68,596 (70.5%) that died of the plague.

Several of these causes of death are recognisable, but others are obscure. Note also several are of an infectious aetiology, and others not present in the table include 15 from plurisie, 2 from shingles and smallpox, 2 from leprosy and 7 from measles. Other plagues were present in the Near East: in 1834 in Turkey and Egypt, 1840 in Syria, 1871 in Kurdestan, and in 1875 in what is now Iraq and Iran. Numerous other plagues were reported in the Middle East (India, Pakistan) and Far East (China, Hong Kong). This period saw the development of anti-microbial measures by Pasteur, Lister, Calmette and others, whilst in the 1890s, work at the Dharwar Plague Hospital in India showed that 71% of cases once inoculated recovered, and 81% of those twice inoculated recovered (section 3.3.2 has details of inoculation). Those not inoculated had a recovery rate of 38%.

Other measures around this time to reduce the incidence of *Y pestis* plague included the destruction of rats. The frequency and wide geographical distribution of outbreaks over the millennia have led to the view that *Y pestis* is globally endemic.

Table 3: Bill of Mortality for 1665 (plague excluded)

Cause of death	Number	%*
Ague and feaver	5257	18.3
Consumption and tissick	4808	16.8
Teeth and worms	2614	9.1
Convelsion and Mother	2036	7.1
Spotted feaver and purples	1929	6.7
Aged	1545	5.4
Dropsie and Timpany	1478	5.1
Griping in the guts	1288	4.5
Chrisomes and infants	1258	4.4
Surfet	1252	4.4
Flox and smallpox	655	2.3
Childbed	625	2.2
Abortive and stillborn	617	2.1
Rickets	557	1.9
Rising of the lights	397	1.4
Stopping of the stomach	332	1.2
Impostume	227	0.8
Bloody flux, scowring and flux	185	0.6
Canker and Thrust	185	0.6
Apoplexy and suddenly	116	0.4
Collick and winde	134	0.5
Jaundice	110	0.4
Scurvy	105	0.4
Stone and stranguary	98	0.3
French pox	86	0.3
Kings Evill	86	0.3
Sores, ulcers, broken and bruised limbs	82	0.3
Cold and cough	68	0.2
Cancer, gangrene, and fistula	56	0.2
Drowned	50	0.2

*% is of non-plague deaths

The effects of migration

The principal reason that the two diseases just described were particularly devastating was their rapid introduction by infected travellers into a relatively immunologically-naïve population. This same process was to prove as damaging globally in centuries to come.

The introduction of smallpox into Mexico in the early 16th century by the Spanish, and the epidemic that followed, is reputed to have killed some 8 million Aztecs, and may have contributed to the collapse of this

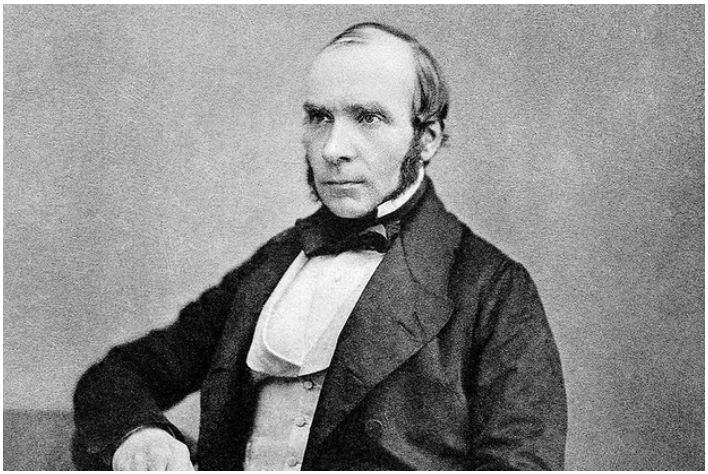
civilisation. Similarly, various organisms brought into North America by European settlers also caused widespread morbidity and mortality in the native population. In reverse, syphilis was carried from the Caribbean to Europe, and there caused epidemics, which then became endemic, as the microbe became established within the population.

Cholera

The Victorian era also saw the widespread appearance of plagues cause by *Vibrio cholerae*, a bacterium principally infecting the intestines. The organism releases a toxin that interferes with water and electrolyte (sodium, potassium) homeostasis, resulting in a watery diarrhoea and so a dehydration that can be fatal. Earliest reports described the disease in the Middle East (India, circa 1820), it then migrating to the Far East, Russia, Europe (reaching the UK in 1832) and the Americas. Subsequent outbreaks claiming hundreds of thousands of lives developed all over the world in the decades that followed, thus also leading it to be described as a global pandemic.

In 1854 physician John Snow (figure 1) plotted the number of cholera deaths in Soho, a region of London, concluding that its origin was in a water pump, which he convinced the local authorities to disable.

Figure 1: Dr John Snow



This is cited as possibly the first act of an evidence-based public health initiative. Snow also collected data on cholera and water supplied by different providers, finding up to a six-fold difference in mortality rates. Although flawed by today's more exacting standards of data collection and analysis, Snow's work is nevertheless perhaps the earliest example of population-based epidemiology, and led directly to Government interventions in public health.

Cholera continues to cause epidemics, such as that in Central and South American in 1991-1993, that killed around 8,000 from almost a million cases, and in Bangladesh, with some 8,900 deaths.

Influenza

Although influenza was known of in the Victorian era, the pandemic of 1918-1919 was the first such event caused by a virus, and has been estimated as causing 17.4 million deaths. Notably, adjusted death rates in the 20-39 year olds were ~1,200 per 100,000 compared to ~750 per 100,000 in the age range 50-59. The particular variant of the virus is described as A/H1N1 (H from haemagglutinin, N from neuraminidase). Other variants appeared in 1957-1958 (A/H2N2) and in 1968-1967 (A/H3N2), whilst H1N1 reappeared in 1977-1979, causing an estimated 700,000 death globally. Influenza is generally endemic and seasonal, but certain variants are more transmissible (virulent) and cause more demanding symptoms that in some susceptible individuals are lethal. There can also be variation in the deaths caused by influenza from year to year. In England and Wales, from 2017 to 2020, there were 458 (0.09% of all deaths), 1,596 (0.29%), 1,213 (0.23%) and 510 (0.08%) deaths respectively.

The human immunodeficiency virus

The final major pandemic of this millennium was that of HIV/AIDS, which started in 1981. It is still considered on-going by the WHO, having killed some 36 million people, with slightly more currently infected.

Key point: Although difficult to verify, the majority of epidemics up to the Victoria era were caused by bacteria, a reduction in which thereafter is likely to be due to combination of factors in public health, such as clean water and better sanitation.

The third millennium AD

Some epidemics in the present millennium disappointingly reflect those of the past, such as cholera and bubonic plague, whilst new agents have appeared. Dengue fever (caused by the dengue virus) epidemics have been reported all over the globe, whilst other viral epidemics included those of Zika (originating in Brazil, linked to congenital malformations, especially microcephaly), Ebola (over 13,000 deaths in Africa), measles (over 7,000 globally) and yellow fever (almost 800 deaths).

SARS-CoV-1

This virus, arising in bats, and causing a potentially fatal severe acute respiratory syndrome (SARS) spread from China to many parts of the globe during 2002-2003, infecting a little over 8,000, and killing 811. The WHO took a leading role in international management, naming the organism by its pathology and structure – the 'Co' referring to its membership of the coronavirus family, V for virus. By 2004 the epidemic appeared to be over, and subsequent research showed that the entry of the virus into cells is mediated by the affinity between a spike protein that includes a receptor-binding domain recognising membrane-bound angiotensin-converting enzyme-2 (ACE-2). As with many viral infections, immunologists were unsurprised to learn that those surviving an infection carried an efficient 'memory' of that infection, and subsequent literature described the development of vaccines to counter further epidemics.

MERS-CoV

In September 2012 a case report focused on a 49-year old Qatari male with SARS, and similar infections soon came to light, all originating in the Arabian Peninsula, but spreading to Europe and elsewhere. The causative agent was found to be another coronavirus, and so was named MERS-CoV, also arising from bats. Despite a smaller infected cohort of 2,574, the World Health Organisation (WHO) reported that virus caused proportionally more deaths (34%) than SARS-Cov-1. However, molecular genetics showed that the receptor for MERS-CoV is the enzyme dipeptidyl peptidase IV, expressed by endothelial and epithelial cells of the respiratory tract. As with SARS-CoV-1, the scientific literature spoke of the development of vaccines.

The previous two subsections explain why the health care industry's response to SARS-CoV-2 was so rapid and successful.

Summary

- In 2021, COVID-19 was the third most frequent cause of death in England and Wales
- Infectious disease in populations can be described in terms of epidemics, endemics, and pandemics
- The four groups of micropathogens are viruses, bacteria, fungi, and parasites.
- SARS-CoV-2 / COVID-19 is the latest in a series of epidemics and pandemics stretching back millennia, caused by microbes such as *Y pestis, V cholerae* and influenza.

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CHAPTER 2

IMMUNOLOGY

As discussed in Chapter 1, infectious disease is an important feature in both morbidity and mortality, and we fight a constant battle with the microscopic pathogens that surround us. Our ability to hold these organisms in check relies on a functioning immune system. One of the most severe examples of the failure of this process is HIV/AIDS, a further example being the pneumonia and other consequences of the SARS-CoV-2 infection we describe as COVID-19. However, we cannot understand how this virus causes the disease without a comprehensive understanding of the working of the immune system.

The leading objective of this chapter is to explain this crucial aspect of physiology (section 2.1), with its cellular and humoral components (sections 2.2 and 2.3). Section 2.4 will look at the immune response itself, which will, in turn, provide the opportunity to consider, in section 2.5, immunological disease - immunopathology.

Learning objectives

Upon completion of his chapter, you should be able to….

- Understand the roles of the organs of the immune system
- Recall the major aspects of cell-mediated immunity
- Explain humoral immunity
- Identify key features of innate and adaptive immunity
- Recognise leading elements in immunological disease

2.1: Defence

Introduction

In order to understand the workings of the immune system, we must first examine its component parts, which can be easily classified in two parts. Cellular immunity involves white blood cells (leukocytes) such as the

neutrophil and the lymphocyte, whilst humoral immunity focusses on molecules such as antibodies and cytokines. Key organs of the immune system include the bone marrow, liver, thymus, skin, spleen and lymph nodes, full details of which follow in sections 2.2 and 2.3. One of the proofs of the working of the immune system is inflammation, which can have both desirable and undesirable effects on the body, should it become chronic.

These two parts of the immune system come together functionally in two forms; innate immunity and adaptive immunity, as will be explained in section 2.4. But a final major aspect of immunology considers how we recognise what is foreign (such as a virus), and therefore may be dangerous. Central to this is the concept of 'self', so that anything regarded as 'non-self' is likely to be attacked, The key molecules responsible for defining self (and non-self) are those of the human leukocyte antigen system, abbreviated to HLA, highly expressed on lymphocytes. One of the descriptors for a molecule that is non-self, is an antigen, that being a substance that invokes an antibody response, although some immunological cells respond to certain antigens in the absence of antibodies.

The armed forces

Parallels can be drawn between the immune system and the armed forces. Both defend us from invaders/attackers, one on a micro-scale, the other on a macro-scale. The metaphor has a number of advantages that we can relate to with relative ease, and so will be returned to as this chapter develops. Just as the armed forces consist of a huge number of specialists acting in concert, so too does the immune system. We can explore these aspects in more detail, as in table 2.1, envisaging soldiers, sailors and aircrew as being different types of white blood cells, each of which are highly specific for a certain function.

Sailors do not fly aircraft, nor do aircrew operate submarines, and certain white blood cells (lymphocytes) do not engulf pathogens any more than others (neutrophils or monocytes) generate antibodies. Nevertheless, each specialist has a crucial role to play in the overall defence plan, and the system is weakened if any of the players are absent or malfunctioning. There are different types of bullets and shells, and so there are different types of antibodies.

Table 3: Parallels between the armed forces and the immune system

The armed forces	The immune system
The training camp	The bone marrow
Armed forces personel	White blood cells
The infantry	Neutrophils
Bullets and shells	Antibodies
A fortress and bullet factory	Lymph nodes
Messengers carring orders	Cytokines
Barracks	The spleen
A specialist arms factory	The liver
Specific uniforms and insignia	The HLA system

Communications are vital between the various strata of armed personel, and within our bodies small proteins (cytokines) circulate to instruct white blood cells and other cells to undertake certain functions. In both situations, failure to deliver a message, or the wrong message, or an incomplete message that may be misunderstood, can have serious consequences.

When faced by a possible microbial attack, an early immunological process is the acute phase response (discussed in section 2.4), in which a large series of cells and humoral factors are put on alert with the release of numerous non-specific molecules such as C-reactive protein (CRP), an important marker of inflammation. A parallel with the armed forces is a general increase in visible security, perhaps with soldiers actually patrolling the streets, which translates immunologically with more leukocytes in the blood.

2.2: Cellular immunity

Organs of the immune system

The bone marrow

All blood cells (red cells, white cells, and platelets) are produced within the bone marrow by the process of haemopoiesis, itself driven by growth factors. In the neonate this can be in many bones, but in the adult it is in the sternum and pelvis, the site of stem cells that give rise to each type of white cell. As they develop, cells pass through several immature ‘blast’ stages (hence myeloblast, lymphoblast) before becoming mature.

Lymph nodes
Over 100 of these small bean-like bodies are found all over the body, and are connected by a specific vascular system - the lymphatics. These vessels allow the passage of lymphocytes and a fluid (lymph) from node to node, a process that enhances the immune response. Lymph nodes are important as they are the primary site of antibody production, and are located in anatomical regions often under microbial attack, such as in the inguina (groin) and axilla (armpit), which collect lymph from the limbs.

The liver
This large organ is the site of production of inflammatory cytokines such as interleukin-1 and interleukin-6 (IL-1, IL-6) as well as acute phase reactants such as CRP. It may also be the site of production of antibodies.

The spleen
Antibodies may also be produced in this organ, but a further function is of a reservoir of certain types of white blood cells, principally neutrophils

The thymus
This small organ, situated between the heart and the sternum, is essential for the development of a type of lymphocyte, the T cell.

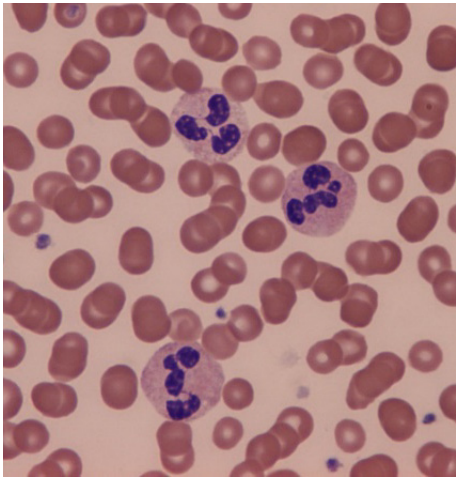
Skin
This organ is our first line of defence from many pathogens, forming a thick physical barrier. However, within the various dermal layers are specialised sentinel white blood cells. Secretions such as sweat and mucus also have defensive properties.

Cells of the immune system

Light microscopy can identify five different types of white blood cells (leukocytes), which in order of frequency in the blood are the neutrophil, lymphocyte, monocyte, eosinophil, and the basophil. Rarely, there may be a sixth cell, a blast, or an atypical cell.

The neutrophil
These cells make up around 75% of all white blood cells, a key morphological feature being that the nucleus is arranged into a number of irregular lobes (figure 2), and accordingly may be described as polymorphonuclear leukocytes.

Figure 2: A blood film showing three neutrophils



Note the irregular nucleus (here stained blue).
The small purple dots are platelets

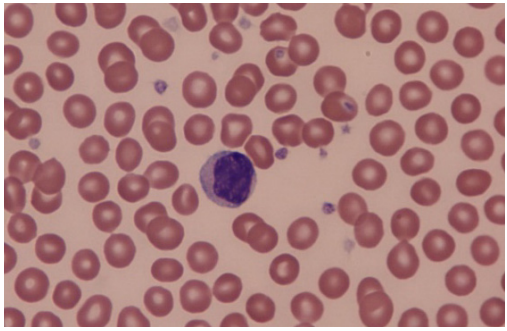
A second feature is of granules in the cytoplasm, so that they may also be described as granulocytes. One of their major functions is to attack and digest bacteria by the process of phagocytosis: the micro-organism is first 'swallowed' by the cells, and then destroyed/digested by enzymes and other molecules, some present in the granules, others generated by biochemical pathways, such as reactive oxygen species.

The lymphocyte

The second most frequent blood leukocyte (around 20-30%), this cell is smaller than the neutrophil, and is further characterised by its regular roughly circular nucleus, which may take up perhaps 80 to 90% of the cell (figure 3). It may therefore be described as a mononuclear leukocyte.

Sub-types of lymphocytes, principally T cells, B cells, and NK cells cannot be distinguished by morphology alone, but can be enumerated by the presence of certain molecules (such as CD3 for T cells and CD19 for B cells) at the cell surface by a machine called a fluoresence activated cell scanner, or FACS. B lymphocytes (or B cells) generate antibodies, whilst T lymphocytes (T cells) have a number of functions, one of which is to kill cells that are infected with a virus. Therefore, low numbers or poor function of lymphocytes may lead to increased risk of viral infections.

Figure 3: The lymphocyte



In contrast to the neutrophil, the nucleus of the lymphocyte is regular and circular.

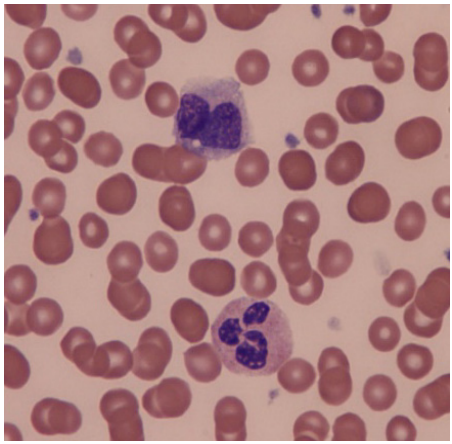
Key point: T-cell immunity is important in our defence from viruses, co-operating with B lymphocytes to make antibodies, and in killing cells infected with a virus.

The monocyte

The largest white blood cell, making up 5-10% of the circulating pool of leukocytes, monocytes also have a single nucleus, but it generally occupies much less of the cell, typically two-thirds, and may be indented (figure 2.3). It too may be described as a mononuclear leukocyte, but not as a granulocyte, even though there may be granules in the cytoplasm. Blood monocytes circulate for a few hours, then migrate to the tissues and organs where they become macrophages, and take on specialised roles, including phagocytosis of non-self material, such as micropathogens.

All monocytes and macrophages engulf, digest and so eliminate foreign material – the process of phagocytosis. Modified macrophages are able present antigenic parts of the micropathogens to lymphocytes, and so are described as antigen-presenting cells (APCs). These APCs are crucial intermediates in the process of instructing specific lymphocytes to perform their effector functions of making antibodies or killing abnormal cells. This is explained in section 2.4.

Figure 4: A monocyte and a neutrophil



This figure provide the opportunity to compare the morphology of the monocyte (the upper cell) and neutrophil (the lower cell).

Eosinophils and basophils

Together, these cells make up <5% of all circulating white cells. Their cytoplasm is dominated by granules, and so they may also be described as granulocytes. Basophils migrating into the tissues are described as mast cells. The granules of both cells are similar to those of neutrophils, but those of the basophil are rich in the anticoagulant heparin and the smooth muscle relaxant histamine.

Both cells have numerous functions in a number of diverse settings, such as in defence from parasites and in some instances of acute inflammation, but from a pathological viewpoint they are also involved in hypersensitivity reactions such as asthma and allergic reactions, as briefly discussed in section 2.5.

Compared to other leukocytes, eosinophils and basophils are of relatively minor interest in a COVID-19 infection.

Table 4 summarises key points of white blood cells.

Table 4: Key points of white blood cells.

Cell	Circulating frequency	Morphology	Principle function
Neutrophil	70-80%	Polymorphic lobular nucleus, intracytoplasmic granules	Phagocytosis
Lymphocyte	10-20%	Single circular nucleus	Antibody production, cytotoxicity
Monocyte	5-10%	Single indented nucleus	Phagocytosis, antigen presentation
Eosinophils and basophils	<5%	Bi-lobed nucleus, often obscured by granules	Defence from parasites

The white cell count and differential

A key feature of an immune/inflammatory response is an increase in numbers of circulating white blood cells (a leukocytosis), which can vary according to the extent of the inflammation and in other disease. The proportions of the different white cells is called the differential, and although there may be a general increase in all cell types, in practice it is usually in numbers of lymphocytes, neutrophils, and monocytes. Bacterial infections are generally characterised by an increased neutrophil count (a neutrophilia), whereas a viral infection (such as in infectious mononucleosis [glandular feature]) is often marked by an increased lymphocyte count (a lymphocytosis).

However, in the leading white blood cell malignancy, leukaemia, the differential may be markedly abnormal, and increased numbers of cells reflect the type of the leukaemia (such as myeloid or lymphoid - table 5). Both leukaemias are characterised by increased numbers of immature blast cells in the blood, a sign of malignancy as they are generally only found in the healthy bone marrow.

The white cell count and COVID-19

The preceding section is important because a major laboratory feature of this infection is reduced numbers of lymphocytes (lymphopenia). As we shall see in sections to follow, this lack of lymphocytes predicts the clinical aspects of the disease, including hospital admission and death.

Table 5: The white cell count and its differential in health and disease

Cell type	Health (reference range)	Acute inflammation	Lymphocytic leukaemia	Myeloid leukaemia
Total white cell count	4.0 - 10.0	15.7	25.0	30.0
Neutrophil	2.0 – 7.0	11.0	8.5	15.0
Lymphocyte	1.0 – 3.0	2.5	10.5	2.8
Monocyte	0.2 – 1.0	1.5	1.5	2.1
Eosinophil	0.02 - 0.5	0.5	0.1	0.2
Basophil	0.02 – 0.1	0.1	0.2	0.1
Blast	<0.02	0.1	5.9	10.5

Units are 10^9 cells/litre of blood.

Key point: The leading cells of the immune system – neutrophils, lymphocytes and monocyte/macrophages - are present in different numbers in the blood, and respond specifically to different types of pathogens. The differential tells us which white cells are the most frequent in the blood, which can be a clue to the form of an infection.

2.3: Humoral immunity

The second part of our immune system involves molecules.

Antibodies

Produced by B lymphocytes, these proteins are constructed to a common 'Y' shape, consisting of two light chains and two heavy chains joined by disulphide bonds. At one end the precise make-up of the terminal ends of the light and heavy chains can vary (hence variable region), forming a 'slot' which can bind to an antigen, hence Fab. The remainder of the light and heavy chains do not vary, and so are described as constant. The other end (in many cases) is engineered to be able to fit into specific receptors expressed by certain leukocytes, named the Fc region (figure 5).