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Perspective

Communicable Diseases in *Homo sapiens* for Immunologists

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Introduction

In 1917 the American Public Health Association, (APHA), began to publish a manual dedicated to the Control of Communicable Diseases in man. The publication has been updated about every five years. The 20th edition was published in 2015 and the next edition is scheduled to come out in 2021. What follows is largely based on the 20th edition [1] though over the years the present author has looked at the manual in its 11th, 17th and 18th editions, this last in disc format. This remarkable and extremely useful document is intended primarily for Public Health practitioners and includes detailed guidance for them in relation to the steps to be taken in the event of an outbreak of any of the diseases considered. For immunologists interested in infectious disease it offers a wealth of opportunities for research and could help them to gain a better perception of the biological significance of the immune response. It also could help them better to recognise the two systems of immunity, innate and adaptive, the former an attribute of all animals with an alimentary canal and the latter found only in vertebrates. The functional relationships between the two systems of immunity are important but differ in relation to the scale of generation of immunopathological effects regulation of which is increasingly seen as important in dealing with infectious disease.

The recent outbreak of disease associated with Covid-19, the worst symptoms of which are associated with so-called cytokine storms, suggests that the simple model of thinking of immunity, as consisting of antigens originating from infectious organisms, eliciting the formation of specific antibodies which can help the rejection of the invader, needs revision. Much high-quality immunological research conducted since the Second-World War has had a reductionist flavour, very sensibly, as cutting down uncontrollable variables is seen as an integral part of experimental biological research. For example, measurement of adaptive immunity has often involved analysis of antibody arrays following the introduction of highly simplified antigenic epitopes often perched on the backs of carrier proteins which are supposedly not involved actively in the specification of the reaction to the target epitope which they convey. A problem also not addressed by the immunological communities is how the immunologically responding organism deals with the complex array of epitopes capable, using analytic methodology, of eliciting a specific antibody response without overloading the responsive system. There has also often been only restricted means of following the physiological consequences of the activation of the large numbers of the cells which are part of the overall immunological processes including, importantly, non-specific activation of the innate system following the creation of dead dying and damaged cells as a consequence of infection.

Many experimental immunologists faced with the measurement of a response to an antigenic array which is increasing exponentially from the time of first contact, as happens with many infections, will be hard pushed to predict the outcome. Their experiences will often be largely concerned with non-living antigenic arrays given once or twice to demonstrate the scale of a response and that by evocation, it is argued, of various memory cells the adaptive immune response is usually more reactive on second contact with the antigens concerned. That this paradigm is useful it not to be denied as it supports the whole fabric of the vaccinologists and has led to the eradication of small-pox as a highly dangerous disease world-wide and, in many countries, the extirpation of what can be the unpleasant consequences of contact with poliomyelitis virus. Nevertheless, it is becoming increasingly apparent that the proportion of the total array of potentially infectious organisms which cause disease, particularly viruses and bacteria, is tiny. In addition, it is being argued that humans and similar triploblastic animals carry thousands of species of bacteria and an unknown multitude of viruses. Most of which of these foreign organisms should probably be regarded as commensal or symbiotic though it also includes a few potential pathogens. This enormous array of organisms, which are an integral part of us, can under some circumstances do harm but, in the sense that overall, they do good rather than damage, should perhaps not all be termed infections which, by definition, carries the intent to do harm. It is becoming increasingly important that we better understand the precise terms of the often stable and symptom free relationship between these foreign invaders and the host organisms.

The APHA manual, from which much can be learned, deserves more attention from the immunologists interested in infectious disease. The present paper, intending to extract from the manual

generalisations and initiate explorations of the mechanisms of disease processes, will be of help to immunologists interested in the field of infectious disease. Whether it will be of help to the public health practitioners, for whom the manual is primarily intended, remains to be seen. It should be made clear that what follows is in no way intended to replace the Manual but simply to draw the attention of immunologists to read through it and to pay attention to some issues which should interest them and which, otherwise, they might not be aware of. The Manual is compiled from the writings of many specialists in relation to the 250 or so diseases that are considered in outline. Often the experts on, say, malaria know little about diseases caused by viruses and this compartmentalisation can restrict the development of useful generalisations about the processes involved in disease. What will be offered is intended for immunologists to help them, not only better to frame such generalisations and, hopefully, to better understand the complexity of their subject as a mutually reactive device acting at the interface between many living organisms and, in the broad sense, their environment.

It should be noted that all infectious organisms will be labelled parasites which often, by parasitologists is a nomenclature reserved for multicellular eukaryotic organisms. The implication is that if the host of an invader can be damaged at the expense of the host whatever the nature of the invader a state of parasitism exists. In addition, it should be made clear that what follows has a large subjective element emerging from the mind of an individual who, with the support of many scientific colleagues over the last sixty years or so, has been an experimental immunobiologist.

Methods

The APHA manual is presented in a stylised manner with diseases and groups of diseases presented alphabetically. Within each of the listed diseases or groups of diseases are given their WHO ICD 9 and ICD 10 categorisations, their names with some of the synonyms are given followed by eight sets of basic information labelled, respectively, Identification, Infectious agent, Occurrence, Reservoir, Mode of Transmission, Incubation period, Period of communicability and Susceptibility and Resistance. There follows what is often a more extensive ninth section on Methods of Control aimed primarily at Public Health workers in relation to diseases with major social impact that can be epidemic or even pandemic. The present author elected to draw out, largely from information given in sections one to eight of the diseases in the manual, a categorisation based primarily on the causal infective organisms, i.e. Bacteria, Viruses, Fungi, Protoctista/Protozoa, Trematodes, Nematodes and a Miscellaneous group with such causal 'organisms' as arachnids, prions and diseases in some instances where the taxonomic classification of the causal agency is not certain. For each class of infective organism tables were constructed with a matrix listing each disease in relation to the Identity of the causal organism, the Geographical location of the disease occurrence(s), the Class of Disease on the WHOICD lists of diseases, an indication of its Impact, Susceptibility, Special risk factors, Immunity, Vaccines where used, primary Reservoir, Vectors and general Comments with in some instances a brief indication of the Treatments available.

Each of the Tables 1-7 is accompanied by a short summarising statement drawing attention to items of special interest. Table 8 labelled Reconciliation, aims to enable immunologists, to gain a better outline of the scale and range of the infective diseases which, ideally, are the targets of activity their immunological discipline aspires to understand and learn how to regulate. Sheep red cells, which have been a common feature of immunological investigations in mice, do not, usually, cause disease neither do they grow exponentially in the organism to which they have been placed.

Results

Bacteria

There are sixty or so diseases written about which are associated with bacterial infection. This number does not include the often-numerous related species of bacteria that cause disease in the category mainly dealt with but for all that it is clear that, although there are millions of bacterial spp. known, only very few of them are pathogenic. Perhaps more importantly it should be noted that the microbiome array in man of several thousand species often includes only very few that become pathogenic. Selected information derived from the Manual concerning bacteria is given in Table 1.

About one third of bacterial diseases are labelled chronic. Clearly there are problems of definition with this epithet. It is evident that a considerable number of diseases can either be acute with no persistence of the causal infecting organism or chronic with persistence. The issue of whether when there is no persistence of the infective organism, but retention of an immunological memory will be discussed elsewhere in this paper. Sometimes when a parasite does not persist, perhaps as consequence of treatment, there is no obvious residual immunological memory (for example some Chlamydial infections, Lyme disease, listeriosis). On the other hand, the diseases caused by certain *Rickettsia* spp seem to lead to lifelong immunity even post treatment aimed at the causal organism. Is this a clear example of persistence of immunological memory? If it is, what is the difference between, say, *Listeria* and *Rickettsia* that leads to the differences in *post hoc* immunological memory? In cases of salmonellosis, many of which recover spontaneously albeit with periods of discomfort in between, there seems to be no immunological memory. In fact, there is no evidence given in the manual for any immune response. How was the parasite brought under control? In the instance of *Salmonella* infections it is clear that the initial dose of infection can determine the severity of the disease that arises. With some other bacteria, *Shigella,* for example, only very few organisms are required to initiate an infection the severity of which is not determined by the starting dose but by other factors. It is not clear whether *Shigella* activates the immune response. The manual says only that up to 40% of households show second attacks. On this basis using the standard immunological paradigms if there is immunity it is sometimes transient and relatively ineffective. Later in this paper evidence will be presented that the normal gut flora normally attracts little if any attention from the adaptive immune apparatus and this might be the situation in relation to *Salmonella* and *Shigella* which are primarily infections of the gut.

Table 1: Bacteria.

Disease	Infectious agent.Target organ if any.	Location	ICD 10entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments, treatment
Actinomycosis	*Actinomyces israelii* and others of the same genus Chronic disease located in orocervical facial, thoracic and abdominopelvic regions	Sporadic throughout the world	A42 rare disease small impact	low	Frequency maximal between 20 and 60 years of age. Mucosal barrier disruption caused by surgery or irradiation, and immunocompromising conditions.	Not demonstrated	N/A	humans	Reasonably common component of oral flora. Can cause problems following trauma that allows access. Prolonged administration of penicillin can be effective.No spontaneous recovery.
Anthrax,Woolsorter disease, ragpicker disease.	*Bacillus anthracis.* Three forms depending on route if introduction. Cutaneous, inhalation, gastrointestinal occasionally among drug users.	S and Central America, S and E Europe, Asia and Africa	A22 Primarily a disease of herbivores	Uncertain	A zoonosis. An infrequent or sporadic disease among veterinarians, wild life workers and agricultural workers.	Second attacks rare. Immunisation for individuals at high risk because of their location or occupation. Using a cell free isolate is said to be effective.	For animals and those humans at occupational risk	Animals and viable spores can persist in soil for decades	Widely bruited as a weapon for terrorism though it has probably not yet been deployed. Complex regimens of post exposure prophylaxis are deployed.
Bartonellosis(Oroya fever, Verruga Peruana, Carrion Disease-)	*Bartonella bacilliformis* Either a life threatening febrile anaemia (Oroyo fever) or a benign dermal eruption (Verruga Peruana). There are many spp.Of *Bartonella*with much more complex patterns of infection than shown in the manual. See also Cat Scratch fever and Trench Fever.	Mountain valleys of Peru, Ecuador and Southwest Columbia between altitudes of 2000 and 9,200 feet where sand flies are present	A44.0, A44.1 Mortality with untreated oroya fever can be as high as ninety per cent	General	More severe in adults than in children. Most common in tourists, i.e., immunologically naïve individuals.	Inapparent infections and carriers are known(up to 5% in endemic areas).Recovery from untreated Oroya fever almost invariably leads to permanent immunity though the Verruga stage may recur. Asymptomatic infections and a carrier state are known.	N/A	Humans, no known animal reservoir. Vector sand flies.	Treatment with antibiotics can be partly successful.
Intestinal Botulism, Infant Botulism	*Clostridium botulinum* is the source of botulinum neurotoxin that causes the disease. Other spp of the genus can be involved.Severe neuropathogenic disease. Respiratory failure common cause of death.	Worldwide, sporadic, family, and general outbreaks are associated with imperfect food preparation	A05.1cumulative cases world wide of which 1400 were from the USA. Nevertheless regarded as amajor hazard presumably because of its high lethality.	General	Almost all hospitalised patients were between two weeks and one year of age. 94% were less than six months!. Adults with bowel problems or treated with antibiotics can be at special risk. The use of botulinum toxin has been associated with the development of iatrogenic disease.	?	Antitoxin is administered presumably as a passively given antibody. There seems to have been no attempt at active immunisation.	Spores in soil, ubiquitous	In effect a disease of the food industry. Most problems are caused not by ingestion of preformed toxin but of bacterial spores that germinate to give rise to more organisms that secrete the toxin.Important as a potential bioterrorism tool. I.V. antitoxin
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Brucellosis, undulant fever, Malta fever, Mediterranean fever	*Brucella abortus* in a variety of strains A systemic disease. Very complex pattern of symptoms	Worldwide	A23 Less now than heretofore. Incidence in USA 120 current cases. In other parts of the world probably unreported and undiagnosed.	Severity and duration of clinical illness subject to wide (unexplained) variation.	A disease of those working with farm animals abattoir, vets, or direct contact with animals. Persons eating uncooked meat are at higher risk.	Unknown	None in man but active successful immunisation of cattle is practised.	Cattle, swine, goats and pigs.	It has been suggested that infection with *Brucella* was a negative indication for cancer. Equally several suggestions have been made that brucella antigens could help suppress cancer. The evidence so far is slender. Anti Biotics

Campylobacter enteritis, Vibrionic enteritis	*Campylobacter jejunis* Diarrhea.	Worldwide	A04.514% of diarrhoea worldwide caused by these organisms.	Many infections are asymptomatic	Children under five and young adults are at higher risk. Immunocompromised individuals at higher risk.		None	Poultry and cattle mainly but many other animals. Most raw poultry meat contaminated!	Common disease with considerable impact. Treatment not generally indicated! Rehydration and electrolytes.
Cat Scratch Disease, benign lymphoreticulosis	*Bartonella benselae* Subacute usually self limiting disease. Affecting lymphoid system and often causing fever	Worldwide but uncommon	A28.1 Slight	unknown	Immuno-compromised hosts most infected but some evidence that younger children and younger adults are more affected	Diagnosis sometimes based on serological evidence of anti-*Bartonella*antibody.	None	Domestic cats. There is no evidence of adverse effects on cats even when they are bacteremic	Interesting example though too little is known about it to place much weight on it. The fact that infected cats are asymptomatic is noteworthy. Antibiotics
Chancroid, ulcusmolle, soft chancre	*Haemophilus ducreyi* STD	Sporadic. Less in temperate regions	A57 small	, No natural resistance, the circumcised are at less risk.	Men who frequent prostitutes!	None recorded	None	Humans	Unpleasant condition with too little-known. Antibiotics
Chlamydial infections, Genital (psittacosis and respiratory disease dealt with separately)	*Chlamydia trachomatitis* STD	Common	A56 Nuisance rather than major threat	General, majority of infected women are asymptomatic, up to 25% of infected males the same.	None given	No acquired immunity has been demonstrated. Repeated infections common.	N/A	humans	Common, seems to have little if any impact on immunological mechanisms. Antibiotics can render patients non-infectious.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Vibrio parahemolyticus infection	*Vibrio parahemolyticus* Enteritis	Sporadic in many parts of the world. Marine coastal environments	A05.3 A disease of moderate severity. Rarely systemic or lethal	Various anterior medical conditions such as liver disease, decreased gastric acidity or immunosuppression.	oysters	No indication given	None	Marine silt	Rehydration, antibiotics
Vibrio vulnificus	*Vibrio vulnificus.* Septicaemia commonly but other symptoms encountered.	Marine environments particularly but not exclusively in N. America.	A05.3 Septicaemia fatal in 50% of cases	Characteristically in patients with chronic liver disease, alcoholism, hemochromatosis or immunosuppression.	Oysters. Sea water exposure of open wounds.	No indication given	None	Free living organism in estuarine environments. Uncooked sea food can be source of infection	Rehydration, antibiotics
Cholera(serotypes other than 01 and 0139)	*Vibrio cholera* Enteritis and otitis media, and cellulitis.	2-3% of cases of diarrhoea (including travellers)in tropical countries	A05.81Small relative to the pathogenic 01 and 0139 serotypes	All humans said to be susceptible	Wound infections, malnutrition and immunosuppression	NK	N/A	brackish waters where they are part of the normal flora	associated with outbreaks of enteritis. Fluid replacement used.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Bacterial conjunctivitis, pink eye, sticky eye, and Brazilian purpuric fever.	Many organisms can be involved the most important are *Hemophilus influenzae* and *Streptococcus pneumoniae.* Viral causes dealt with under Viral Disease heading. Eyes.	Widespread and common	A48.4 Warmer climates seasonal epidemics in the main non-fatal but systemic fatal disease has been reported (Brazilian purpuric fever)	Probably general	Children under five most affected. The debilitated and the aged are particularly susceptible to staph. Infection.	Low grade after infection and varies with the infectious agentClearly lack of knowledge here	N/A	Humans	Sulfacetamide plus or minus antibiotics

Chlamydial conjunctivitis, inclusion conjunctivitis, paratrachoma	*Chlamydia trachomatis* Eyes. An STD	Sporadic throughout the world.	A74.0	?	Affects new born infants otherwise a complication of genital infection in adults	No evidence of resistance to reinfection though severity of disease is variable	N/A	Humans	Often acquired by infants during birth process. Antibiotics
Diarrhoea caused by *E.coli*, Enterohaemorrhagic strains. Shiga toxin producing strains. complex of pathogens	STEC initially Intestine but can create massive renal and other potentially lethal problems.	Important problems in N America, Europe, S Africa, Japan Australia.	A04.3 Outbreaks associated with a variety of poorly cooked foods	infectious dose is low. Little is known about susceptibility or immunity	Old age, achlorhydria and infants under five. Diabetics and infants of infected mothers.	None reported	none	Cattle and perhaps deer, more rarely humans	Fluid and electrolyte replacement. Antibiotic treatment uncertain and potentially dangerous.
Diarrhoea caused by *E.coli*, Enterotoxigenic strains.	ETEC	Primarily in developing countries	A04.1A major cause of traveller's diarrhoea. In developing countries multiple infections of infants occur	Probably universal though it is not so stated	Less frequent in adults. Children <4years of age in developing countries can have up to 32% mortality. WHO reports up to 380,000 deaths of such children annually. Contaminated food particular risk factor.	Serotype specific immunity is acquired following infection. Problem is that there are so many serotypes	none	humans	Fluid replacement, rehydration salts. Anti-microbial agents often deemed dangerous.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Diarrhoea caused by *E.coli*, Entero-invasive strains	EIEC	Endemic in developing countries	A04.2 Causes about 1-5% of cases at visiting treatment centres	NK	Visitors and children in endemic regions	NK	None	Humans	Fluid replacement. Few centres treat this somewhat rarer disease.
Diarrhoea caused by E.coli, enteropathogenic strains	EPEC	Oldest recognized form of largely infant diarrhoea, largely disappeared from the Western world..	A04.0 Still a major problem in many other places in the developing world where fatality rates can be high	Susceptibility is confined to young infants but why is not known. It could be immunity that is not established. Experiments on adults suggest that immunity is the answer.	Disease uncommon in breast fed infants. Often associated with contaminated infant formula. Outbreaks due to contaminated water or rice have been reported.	Likely but not certain	None	Humans	Fluid replacement
Intestinal *E.coli* infections and others	EAEC, DAEC	Cause of sporadic out breaks associated with acute and persistent diarrhoea in infants. In developing and developed countries.	A04.4 EAEC can bea cause of traveller's diarrhoeain as many as 20% o cases in some reports.	DAEC in some reports more pathogenic in children but information is sparse.	Contaminated food and drink.	Infants are susceptible.	NK	Likely humans possibly animals	Rehydration treatment and anti-microbials are said to be useful.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Diphtheria	*Corynebacterium diphtheria* Mucous membranes of upper respiratory tract, more rarely other mucous membranes. A potent exotoxin causes the problems. Carried by some strains of *Corynebacteria*themselves infected with the toxin generating phage.	A disease of colder months in temperate climes	A36 Major outbreaks have occurred in a number of areas of the world in recent years in unvaccinated individuals	Not stated	Infants born to immune mothers are protected for up to six months by passively acquired antibody.	Lifelong immunity is usually but not always acquired after infection. Immunisation with toxoid also produces lifelong immunity (non toxigenic bacteria rarely cause disease)	Very effective	Humans	Presence of a phage as is true for some other bacterial spp. dictates capacity to produce a toxin that is the main cause of pathogenesis. Anti toxin + sometimes antibiotics

helicobacter pylori infection	*Helicobacter pylori* Causes acute and chronic gastritis.	WorldwideSaid to be present in 50% of the human population	K29 usually no symptoms but for some gastritis and gastric Carcinoma can follow infection	Universal it is supposed. Increasing prevalence with increasing age.	Not identified but supposed that there must be identifiable risk factors. Lower socioeconomic status appears to be associated with higher prevalence.	None recognized	None presently available	Humans probably though it has been found in other primates	Treatment with antibiotics can be successful in reducing gastritis stopping continuation to malignancy. Controversial antibiotics
Ehrlichiosis, Anaplasmosis, Senetsu Fever, Neoehrlichosis	*Ehrlichiasennetsu* *Anaplasmacytophylum* *Neorickettsiasenesu,* *Neoehrlichiamisurensis* Acute febrile illnesses with small intracellular bacteria that survive inside a variety of phagocytic white blood cells.	Four diseases here one Sennetsu fever the other threedifferent forms of ehrlichiosis. Distribution mainly in north and south America, Europe, Western Japan and Malaysia	A79.8 Range from mild illnesses to severe life-threatening disease. Diagnosis tricky to differentiate it from other viral illnesses.	General	Older, debilitated, or immunosuppressed people more susceptible	NK	Re-infection rare. implication is derived adaptive immunity. Consumption of raw fish suspected cause with Senetsu fever	Not certain but a variety of vertebrate hosts are involved. Ticks can be vectors.	Doxycycline
Disease	**Infectious agent.** **Target organ if any.**	**Location**	**ICD 10 entry.** **Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Gonococcal infection, (a separate category of gonococcal conjunctivitis is here ignored), clap, strain, gleet, dose, G.C.	*Neisseria gonorrhoeae* STD particularly in the commercial sector.	Common worldwide	A54.0 A54.2, Rarely lethal but with many unpleasant symptoms	General	Not given	Humoral and secretoryantibodieshave been demonstrated but the bacterium is antigenically heterogeneous and reinfection is common	none	Strictly a human disease	Major STD. Antibiotics but many resistant plasmids exist.
Granuloma inguinale (Donovan osis)	*Calymmactobacteri-umgranulomatis* Genitalia in 90% of cases	Rare in industrialised countries but even there small occasional epidemics are recorded.	A58 Slight fortunately, but cluster outbreaks have been recorded in tropical and semi-tropical countries	Most common in 20-30 year old males but known also in 1-4 year old children and it is suggested that non-sexual transmission can occur.	Bought sexual activity	None it appears, i.e., second attacks occur (presumably after treatment of the first attack)	none	Humans	Horrid condition not easily brought under control that essentially erodes the genital regions. We are clearly short of information on the disease. Antibiotics
Legionellosis (there is also non pneumonic legionellosis, Pontiac fever, which is here ignored). Legionnaires disease	Various legionellae	Widespread but sporadic more common in summer and autumn	A48/1 Regarded as dangerous case fatality rate can be 15%.	Age related	Males more than females usually in patients over 50 years of age. Patients who smoke or who have diabetes mellitus are at special risk. immunocompromised people especially those on corticosteroids. Infected cooling towers and warm but not hot water	Implication is that there is an immune response in that in a few locations antibodies have been detected in 1-20% of the general population.	None stated	Aqueous primarily, hot water systems not properly maintained.	Why is it called legionnaires disease? Some antibiotics are effective.Disinfection of suspected water supplies is effective.

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Leprosy (two forms tuberculoid and lepromatous of which the latter is more severe), Hansen's disease.	*Mycobacterium leprae* Cannot be grown in culture. Chronic disease of the skin and peripheral nerves.	Chief endemic areas are S and S Eastern Asia, Indonesia, tropical Africa and parts of Latin America.	A30 Over a million cases worldwide but it should be stressed that probably only a small proportion of those infected develop symptoms.	Rate of lepromin positive tests increases with age but as this can give false positives it is not clear that this represents a build-up of asymptomatic infections.	Inchildhood, rarely seen under three. Incubation time can be anything from nine months to twenty years!	Immunity said to depend on a cell mediated response though antibodies are produced. It is argued that 95% of the population are naturally immune. In the manual this is termed innate immunity, but this terminology is probably incorrect.	BCG may have some use in this context!	Humans and armadillos.	Still a major disease not easily cured. Prolonged treatment with a variety of antibiotics but resistance is a problem.
Leptospirosis, Weil's Disease, Swineherd fever, mud fever, Haemorrhagic jaundiceand other names.	Organisms from the genus *Leptospira* . Large number of serotypes. First phase of infection can be high fever. Second phase coincident in time with development of antibodies Recovery of untreated cases can take several months.	Worldwideexcept polar regions. Most prevalent in tropical and sub-tropical regions.	A27 Asymptomatic or mild infections are common but occasional epidemics have killed many of those infected. In general 5-10% of cases progress to severe illness.	general	Case fatality rate is generally low but can reach twenty percent in those with renal damage. Largely an occupational disease for those working in sugar plantations and rice fields Often a disease of bathers and campers no other predilections given	Serovar specific immunity arises	In both workers at risk and the local domestic animals this has been attempted. The results are either not known or simply not given	Wide variety of wild and domestic animals.	Prompt specific, early treatment with antibiotics can be effective.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Listeriosis	*Listeria monocytogenes* Can present as an invasive disease with septicaemia and meningitis.	Uncommonly diagnosed infection in USA but frequency elsewhere in the world not given. Outbreak cases are reported associated with contaminated food.	A32 Accounts for a small fraction of all blood borne diseases. Despite this it is regarded as an important cause of severe illness.	Most childrenand young adults are resistant	Adults over the age of 40 become more sensitive and Almost all the debilitating and immunosuppressive conditions, (including pregnancy)confer heightened sensitivity	NK	None	Solid forage water mud and silage plus domestic animals and asymptomatic human (faecal) shedders.	Commonly associated with manufacture of soft cheeses of which it is part of the bacterial array. Antibiotics work
Lyme disease, Lyme borreiosis, tickborne meningopoly neuritis	*Boreliaburgdoreferi* and others Distinctive skin lesions and a variety of other systemic manifestations over a long time.	Found in many places particularly well known in USA but also in Europe, China and Japan	A69.2, L90.4Difficult to say on evidence presented. Clearly an uncomfortable and chronic disease that can usually be successfully treated,	Universal apparently	None stated	Re-infection has occurred in those treated early with antibiotics, the implication is either that immunity is not a result of infection or that antibiotic treatment prevents the development of lasting immunity.	Vaccines have been developed and used with up to 76% success, but this is not a clear story.	Disease is maintained in an enzootic transmission cycle that involves ixodid ticks wild rodents and deer.	A zoonosisTreatment with antibiotics

Disease	Infectious agent. Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments, treatment
Lymphogranuloma venereum, climatic or tropical bubo	*Chlamydia trachomatis* genotypes. STD in both sexes. In men who have sex with men proctitis can develop.	Worldwide especially in the tropical and subtropical areas	A55 Disease untreated is debilitating but not usually fatal.	General	Male homosexuals	Not clear	None	Humans often asymptomatic females.	Antibiotics can be effective.
Melioidosis, Whitmore disease Glanders	*Burkholderiapseudomallei*causative agent for Melioiodosis,*Burkholderia mallei* for Glanders. Cutaneous or visceral abscesses with subsequent development of a wide range of potentially lethal systemic symptoms.	A significant cause of community acquired sepsis in the tropics.	A24.1, A24.4, A24.0 In a number of largely tropical places	Problem here of definition. Disease is uncommon even in parts of the world where the infective organism exists and the (rural) population are in frequent contact with the soil in which the bacterium exists. The implication is that infection is common disease is rare	Those with abraded or burned skin who also have intimate contact with soil	Not clear. Change of environment, e.g. development of diabetes mellitus can give recrudescence of what is probably a long term latent infection	None	Soil and water. A saprophyte. Various animals can become infected but there are no known vectors to which they transfer the organism but they canspread it around passively	TMP-SMX iseffective treatment (a mixture of trimethoprim and sulphamethoxazole)
Meningitis, cerebrospinal fever	*Neisseria menigitidis*various strains/ serotypes that define different epidemics Inflammation of the meninges is the defining feature of this disease and here three bacterial causes of the condition will be considered. A petechial rash often present in Europe and N.America but rarely in Africa.	Ubiquitous	A39.0 Nowadays in developed country case-fatality rate is 8-15%. 5-10% of those in endemic countries may be asymptomatic carriers of whom very few progress to disease.	Susceptibility to disease is low and decreases with age. Disease is primarily of young children and young adults. More common in males than in females. Highest burden of diseasein African meningeal belt.	Splenectomy, certain complement components	Group specific immunity of unknown duration follows even sub clinical infection	Dead vaccines are available and have been reasonably successfully applied	Humans	Epidemics tend to crop up in those inhabiting crowded communal quarters. A variety of antibiotics can be effective treatment.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Hemophilus meningitis,	*Hemophilus influenza* In industrialised countries before widespread use of Hib conjugate, vaccines meningitis was the most common presentation,epiglottitis, and bacteremia were the next most common. In developing countries lower respiratory tract infection was the most common first symptom. Pneumonia of this kind has been said to cause 480,000 deaths per year among children under five years of age.	Worldwide	G00.0 Most prevalent among children three months to three years. Vaccine use has cut down the disease in the USA and a higher proportion of cases is now seen in adults	Universal	Age	Immunity usually associated with presence of circulating anti-capsular antibodies acquired transplacentally or by immunisation. Or a prior infection	Yes, with polysaccharides	Humans	Antibiotics but resistance is now a problem.

Disease	Infectious agent. Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments, treatment
Nocardiosis, Actinomycetoma	*Nocardiaasteroids*and others of that ilkPulmonary infection	Occasional sporadic disease in all parts of the world	B47.1 Difficult to say on evidence presented	Unknown	Endogenous or iatrogenic adrenal hypercorticism and probably primary alveolar proteinosis	Opportunistic infection can occur in immunosuppressed individuals. Implication is that there is an immune mechanism.	None	A saprophyte found in soil, water and organic material.	TMP-SMX depending on serotyope specificity.
Pertussis, Whooping cough Parapertussis, a milder version of the disease	*Bordetellapertussis Bordetella parapertussis.* A respiratory disease with occasional systemic complications.	An endemic disease common especially young children everywhere	A37.0, A37.9 A37.1Schemes of immunisation have reduced the prevalence. This disease is still among the most lethal of all the childhood diseases. In recent years it is increasingly recognized in older children and adults even when they have been immunized as infants.	Universal among non-immunised individuals. Milder and atypical cases occur in all groups (the hundred day cough!)	Malnutrition and enteric infections can be predisposing conditions. Interestingly, transplacental transfer of immunity has never been demonstrated. Note comment in Vaccines column.	One attack usually confers prolonged immunity although second attacks can occur.	A killed vaccine is widely used. Maternal antibodies are carried across the placenta which observation has led several countries to adopt immunisation prior to pregnancy but whether this stratagem works is not stated.	Humans	? Erythromycin reduces the period of communicability but does not affect symptoms except when given early.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Pinta, Carate	*Treponema caroteum* a spirochaete. A chronic non venereal skin disease.	Found only among crowded rural populations living in poor conditions in the American tropics	A67 Physical disability does not occur. Organ systems are not involved Not fatal. Said to be on its way to eradication!	Not defined presumably as in other treponematoses (various syphilitic diseases in relation to which immunity can develop)	Mainly a disease of children	Not stated	None	Humans. Various biting flies are suspected of being vectors.	A none-venereal disease. Antibiotics fix it.
Plague, Pestis	*Yersinia pestis* Three presentations, bubonic, pneumonic and septicaemic.	Almost everywhere that there are wild rodents. Foci of infection exist in the Americas particularly in N.Eastern Brazil.	A20 Both bubonic and pneumonic forms can be lethal and in the past have been responsible for major epidemic mortality. Untreated the mortality rate is 50-60% These days it is clearly less of a problem than it was.	General	None given	Some immunity after recovery.	Yes both living and dead. They can be efficient for about three months	Wild Rats with their fleas as the vector.	A potential terrorist weapon. Streptomycin is the drug of choice. The pathogenicity is associated with a mutation. P. Unusual example of a mutation conferring increased pathogenesis.

Disease	Infectious agent. Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments, treatment
Pneumonia, many organisms can cause pneumonia. Here only four will be dealt with 1,pneumococcal pneumonia	*Streptococcus pneumoniae* (twenty-three capsular types account for ninety per cent of the infections that cause bacterial pneumonia in the USA) Often sudden onset high fever with a wide variety of complications.	Essentially worldwide though increasing control was being developed. Now resistance to antibiotics is becoming a problem.	J13 A major cause of death in developing countries among newborn children. The disease can be associated with influenza infection.	General in the sense that I suspect the organism concerned is always present. Not general in the sense that only few get the disease! The definition of susceptibility is here strained.	In young infants the mortality even using antibiotics can be 60%, malnutrition and low birth weight are contributory factors. Any harm to the lower respiratory tract is predisposing. In adults almost any co-morbidity can predispose.	Serotype specific immunity can be long lasting.	A vaccine with all 23 capsular types is available, it is not effective in children under the age of 2 but it can be useful prophylaxis in the elderly	Humans (many normal individuals have the organism concerned as part of their respiratory tract flora.)	Splenectomy is a predisposing factor. Antibiotic resistance now common.
Pneumonia, primary atypical pneumonia	*Mycoplasma pneumoniae* The taxonomic designation of this organism is uncertain being either virus or bacterium. Here it is included among the bacterial causes.	Worldwide sporadic and epidemic	J15.7 Fatalities rare, differential diagnosis difficult there being at least ten other infectious causes of pneumonia! Clinical disease occurs in 3-30% of infections	Susceptibility not mentioned!	None given	Second infections do occur. Immunity correlated with antibodies that can remain for a while	None	Humans	Impression given is of an occasional infection that elicits only little immunity perhaps because the causal organism simply does not really like it in man. There are many species that infect domestic animals but there is no record here of zoonotic infection. Antibiotics work.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Pneumonia, neonatal eosinophilic pneumonia, Congenital pneumonia due to *Chlamydia*	*Chlamydia trachomatis* various immunotypes A sub-acute pulmonary disease	Probably coincides with the worldwide distribution of the causative organism as a genitally transmitted infection	P23.1 Illness usually moderate	?	Infants born to mothers who have chlamydial genital infection.	Unknown. Maternal antibody is not protective	None	Humans	Oral erythromycin.
Pneumonia pneumonia due to *Chlamydia*	*Chlamydia pneumoniae* An acute respiratory disease.	Presumably worldwide	J16.0 Death rare in uncomplicated cases	Universal	Increased likelihood of clinical disease withpre-existing chronic disease.	Some suggestion of immunity after infection however second episodes of pneumonia are not unusual	None	Humans probably	Oral tetracyclines
Psittacosis, Ornithosis, Parrot fever, Avian Chlamydiosis.	*Chlamydophilapsittaci* An acute disease with systemic presentations and respiratory symptoms.	World-wide	A70 Usually, mild	Universal	Exposure to birds and old age	Immunity after infection incomplete and transitory	none	Parakeets, parrots and love birds mainly. Birds that appear healthy can become shedders under conditions of stress.	
Q fever, Query fever.	*Coxiella burnettii* An acute febrile disease. Various complications sometimes involving the liver.	Worldwide, under reported It should be noted that fatality in untreated cases can be as high as 2.4%.	A78	General	A variety of occupations particularly veterinarian and abattoir workers. are associated with this disease.	Immunity probably lifelong after recovery from disease. Cell mediated immunity lasts longer than humoral (does the organismpersist?)	Not commercially available but for those at high-risk vaccines that are effective have been prepared.	Sheep, cattle., goats and dogs.	Tetracyclines for acute disease Antibiotics.

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Relapsing fever,	*Borrelia recurrentis* Fever often recurrent.	Worldwide except Australia and New Zealand	A68 Untreated case fatality canbe 2-10%	general	None stated	Unknown but second attacks are rare.	None	Humans and wild rodent. There are some differences between the tick and louse-borne forms of the disease.	Tetracyclines
Rickettsioses, tick borne, rocky mountain spotted fever. Some twelve fevers are recorded under this heading, from specific geographical locations, here only two will be dealt with	*Rickettsia rickettsii*	Throughout USA andsome S American states	A77 Case fatality 13-25% ifnot recognized and treated	general	Patients older than 40	Immunity not stated in 20th Edition. In earlier editions it is stated that one attack confers life-time immunity.	none	Maintained in nature by ticks can be transferred to for example dogs in which infection is usually subclinical	tetracyclines
Rickettsioses, tick borne, Boutonneuse fever	*Rickettsia conori* and related organisms.	Widely distributed in Africa and India and Eastern Europe	A77.1 Mild to severe febrile illness	General	Travellers!	Immunity not stated in 20th Edition.	None	Ticks and dogs (travellers dogs pick up infected ticks that are taken home with the owners who subsequently acquire the infection.	Tetracyclines
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Salmonellosis,	*Salmonella bongori*and *S enterica* More than 2000 serotypes are recorded. Severe enteritis	Worldwide, can occur in massive epidemics	AA02 A million cases reported annually in the USA alone! Not usually fatal	General, severity of condition related to 'dosage' of infection.	The young, achlorhydria, AIDS patients, malnutrition and other debilitating conditions.	None recorded	None available	Predominantly an infection of food but commonly carried by a wide variety of animals.	A major disease that only causes problems in high concentrationsNo treatment generally indicated except rehydration. In the young and very old antibiotics can be given. Patients with AIDS may require lifelong therapy
Shigellosis, bacillary dysentery	*Shigella* various spp. Distal small intestine and colon.	Worldwide	A03 Estimated that shigellosis causes14,000 deaths annually but mild and asymptomatic infections occur and the illness is usually self-limiting	General, infection can follow ingestion of a small no of bacteria.	young and elderly and debilitated patients of many kinds. Breast feeding is protective for young infants. Homosexual men where conditions are poor such as in jails.	Not recorded. Secondary attack rates can be up to 40% in specific households.	Vaccines with some short-term efficacy have been deployed. There is a clear need for an effective long-term vaccine.	Humans	A major disease with far too little said about it. Particularly the issue of immunity is not addressed perhaps because there is not any although the experimental vaccines have had some success. Symptomatic treatment except in severe cases. Antibiotics can then work but there are major and complex problems with resistance.
Staphylococcal diseases in the community, boils, carbuncles, sepsis, infected lacerations.	*Staphyllococcus aureus* various coagulase positive strains are involved,identified Skin	Worldwide, highest incidence of disease where standards of hygiene are lowest.	L02, B95.6, B 95.8 A41.0, A 41.2	Universal. 20-30% of general population are nasal carriers of the relevant organisms. Auto-infection responsible for at least two thirds of infection with disease.	New-born and all sorts of generally debilitated patients	Immune mechanisms said to depend on the instruments of innate immunity.	None recorded	Humans more rarely animals	Local disease does not warrant treatment. Treatment of systematized infection with antibiotics is undertaken.

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Staphylococcal diseases in the community, boils, carbuncles sepsis, infected lacerations.	*Staphyllococcus aureus* various coagulase positive strains are identified. Skin	Worldwide, highest incidence of disease where standards of hygiene are lowest.	L02, B95.6, B 95.8 A41.0A 41.2	Universal 20-30% of general population are nasal carriers of the relevant organisms. Auto-infection responsible for at least two thirds of infection with disease.	New-born and all sorts of generally debilitated patients	Immune mechanisms said to depend on the instruments ofinnate immunity i.e., not adaptive.	None recorded	Humans more rarely animals	Local disease does not warrant treatment. Treatment of systematized infection with antibiotics is undertaken.
Staphylococcal diseases, in hospital nurseries, impetigo neonatorum, scaled skin syndrome, abscess of the breast	As above Impetigo Skin.	Worldwide exacerbated by laxity in hygiene precautions and emergence of antibiotic resistance.	L 01 Big problem	In the new-born susceptibility seems to be universal	Infected infants remain at risk for the duration of infection with a pathogenic strain.	?	None	As above	Antibiotics for both local and systemic infections can be effective.
Staphylococcal diseases, in medical and surgical wards.	As above plus the problem that 90% of the strains causing problems are antibiotic resistant (MRSA). Awide variety of conditions including endocarditis, osteomyelitis, pneumonia, meningitis,		J15.2, M86, M00.0, 133.0. Probably the most serious problem of hospitals that have surgery, implants and so on.	Universal?	Any sick people	?	None	As above	The organism concerned is essentially ubiquitous and seems on the face of it to elicit little or no immune response Appropriate antimicrobials with great problems of resistance.
Streptococcal infection, caused by group A haemolytic streps, a large no of diseases including scarlet fever, sore throat, erysipelas, puerperal fever, rheumatic fever necrotising fasciitis and so on.	*Streptococcus pyogenes* group A A wide variety of conditions mimicking sometimes the conditions caused by *Staphylococci.*	The diseases concerned need separate treatment as they differ in distribution across the world.	Again treatment of the diseases as one category is not easy, for example rheumatic fever is much less than it was but in 1985 there were outbreaks in the USA. The highest incidence of impetigo occurs in young children in the late fall and so on.	General	None quoted	For some of the diseases long lasting type specific immunity follows infection for others it does not. For example, rheumatic disease has a significant risk of recurrence. It seems that although we are dealing with the same basic organism its many disease manifestations are relatively ill understood	None	Humans	It seems extraordinary that such a common set of diseases should be lumped together despite clear differences between them in terms of mechanisms of disease. Antibiotics.

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Streptococcal infection, caused by group B, streptococcal sepsis of the new born. (and dental caries of the new born), baby bottle tooth decay.	*Streptococcus agalactiae* Serious invasive diseases of the newborn. Same as above except group B		P36.0 Thought to occur worldwide. Information here lacking.. Most studies from N.America and Europe		Babies born prematurely, particularly when there is rupture of the membranes more than 18 hours prior to delivery.		A vaccine for pregnant women to stimulate antibody production to restrict invasive disease is said to be under production.	Humans. Commonly found in GI and urinary tracts.	Anti microbial preparations. Given particularly to infected pregnant women prior to labour.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Syphilis.	*Treponema pallidum* STD. Extremely complex disease with three distinct phases.	Widespread among sexually active individuals	A50-52 Extremely nasty consequences can arises inuntreated chronic disease although latency is known.	Universal although only 30% of exposures result in disease.	Immunosuppression, particularly HIV	Immunity to re- or further- infection usually develops in time but paradoxically it often fails to develop because of early treatment..	None available	Humans	Complex treatment protocols often involving penicillin
Tetanus, lockjaw, Obstretrical tetanus, tetanus neonatorum.	*Clostridium tetani* Acute disease caused by an exotoxin. A variety of disease forms can emerge after contact with the causal organism.	Worldwide	A35, A 33. A.34. Relatively uncommon in industrialised countries case fatality 2.3% for those aged under 20-39 and 18% for those over 60. Case fatality can up to 80% depending on quality of care.	General	Infants and elderly at higher risk. Members of service groups such as armed forces and police and those in contact with sewage.	Paradoxically recovery from infection does not guarantee immunity and there is no detectable antibody (this is somewhat of a paradox in that anti-toxin immunisation is effective for long periods of time).	Active long-lasting immunity is elicited by toxoid	Intestines of cattle and soil in which human and or animal faeces are found. The organism is essentially everywhere.	Prophylactic antibiotics in those by culture felt to be at risk
Trachoma,	*Chlamydia trachomatis,* specific serovars. Initially conjunctivitis, Can resolve spontaneously but repeated reinfection can lead to blindness.	Worldwide occurring as an endemic disease largely in poorer communities	A71 A major cause of development of blindness over a long period of time.	General. Active disease tends not to be seen in older children andadults	Poor living conditions, Dust and fine sand may exacerbate the condition.	No evidence for immunity	None successful	Humans	A major disease but seemingly curable. Topical tetracylines can be effective. Repositioning of eyelashes so they no longer abrade the cornea can be effective.

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Trench fever, Quintana fever	*Bartonella quintana* A typically febrile non fatalsepticaemia.	Scattered but in many places	A79 Particularly prevalent in world war one trenches	General	Immunocompromised patients have a variety of severe symptoms	unknown	None recorded	Humans but vector is the body louse.	Tetracyclines
Tuberculosis, TB	*Mycobacterium tuberculosis* and to far lesser extent *M.bovis.* It is estimated that 1/3 of the world population is presently infected. Active disease can be pulmonary or extra pulmonary. There is given in the manual a brief account of non-tuberculous mycobacterial disease. Here it is not considered.	Worldwide	AA15-19 Probably the biggest single cause of mortality and disability associated with infection. Despite this it is likely that the majority (90%) ofthose infected enter a latent condition from which there is always a danger of reactivation.	Ostensibly risk of infection is related to degree of exposure. The first six to twelve months after infection are the most dangerous for development of full blown disease.	Risk of developing disease highest under the age of 3, lowest in later childhood and high again among young adults the aged and the immunosuppressed with HIV. Other debilitating diseases can contribute to the likelihood of reactivation.	The utility in some circumstances of BCG vaccination suggests that there is a degree of immunological control but one wonders if this is niche occupation rather than immunity per se. There is little in the text about immunity except in relation to the PPD skin testing that is usually positive in infected people. This is a very complex story	BCG has been deployed but in some circumstances it seems not to work in terms of avoiding disease. The whole issue is complicated by the differences in frequency of wild type challenge in some of the regions that are being compared.	Humans primarily. The argument in relation to badgers and cattle still rages.	Antimicrobials. Whether latent TB should be treated seems not to have been addressed. Also the latent status seems to be little understood
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Tularaemia, Rabbit fever, Deer-fly fever, Ohara disease, Francis disease.	*Francisellatularensis* Skin and lymphadenopathy, or the latter without the former.	N America, former Soviet Union China and Japan	A21 Complex set of diseases with a wide variety of symptoms.	All ages susceptible, and presumably all people	Closely linked to occupational and recreational activities.	Long term immunity follows recovery from infection.	None	Numerous wild animals, with a tick vectorusually or, less commonly, deer fly	Streptomycin.
Typhoid, paratyphoid fever, enteric fever, typhus abdominalis.	*Salmonella typhi*	Worldwide major diseases of which paratyphoid is the milder.	A01.0 A01.4 No of cases annually estimated at 17 million cases annually with estimated 600,000!Deaths. Many mild and inapparent infections occur	General	Achlorhydria, HIV infection, IN endemic areas disease is most common in children up to 19 years of age.	Relative specific immunity follows infection with disease, unapparent infection, or active immunisation	A double vaccine is available, one part live and the other a coat polysaccharide (from paratyphus). They are not uniformly successful.	Humans for typhoid, andparatyphoid. More rarely animals for paratyphoid. Some chronic carriers.	Antibiotics but resistance is becoming an increasingly difficult problem.
Typhus fever, epidemic louse borne typhus fever	*Rickettsia prowazekii* A wide variety of systemic symptoms with a specifically recognized(Brill-Zinser) disease occurring year after the primary attack.	In colder areas where people may live in unsanitary conditions and are infested with lice.	A75, case fatality untreated varies from 10-40%.Mild infections can occur without eruptions especially in children and those partially immunized	General	None stated	One attack gives lifelong immunity This is stated in earlier editions of the manual but not repeated in the 20thedition.	None	Humans and to a limited extent flying squirrels. The vector is the body louse.	Antibiotic treatment, doxycycline, usually effective.

Disease	Infectious agent. Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments, treatment
Typhus fever, epidemic flea borne typhus, murine typhus, shop typhus.	*Rickettsia typhi* Manifestations of disease like those associated with louse borne disease.	Worldwide	A75.22 Milder than the louse borne equivalent	General	None given	One attack confers immunity.	None	Rats mice and probably other small mammals, vector infected rat fleas.	Tetracyclines
Scrub typhus, tsutsugamushi disease. Miteborne typhus fever	*Orientia tsutsugamushi* with many serotypes. and a wide variety of symptoms often dermal initially.	Central and South East Asia	A75.3 Case fatality rate untreated as high as 60%	General	Bigger problems with older people, occupational particularly militarytroops	Prolonged immunity against the homologous strain. Unpredictable for heterologous challenge	None successful	Thrombiculid mites are the reservoir	Tetracyclines
Yaws, Frambesiatropica.	*Treponema pallidum* Highly unpleasant skin disorders.	A disease of children in moist tropical regions	A66Rarely fatal but can be very disfiguring and maiming.	No evidence of natural or racial resistance	More frequent in male children	Infection results in immunity and sometimes resistance to other pathogenic treponemes	None	Humans	Pencillin
Yersiniosis,	*Yersinia enterocolitica, Y. pseudotuberculosis* Typically manifest as acute febrile diarrhoea with abdominal pain.	World wide	A04.6Complex pattern of susceptibility, post infection arthritis is more severe in adolescents and young adults	No statement but inference is that susceptibility is universal	HLa-B27 positive patients more susceptible to reactive arthritis and Reiter's syndrome. Septicaemia occurs more often in those with an iron overload or with underlying immunosuppression.	Nothing stated	None	Animals particularly the pig, i.e., a zoonosis	Organisms are sensitive to many antibiotics but not to penicillin.

Table 2: Viruses.

Disease	Infectious agent. Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments and Treatment
Arenoviral, Haemorrhagic fevers, Junin, Matupo, Guanarito, Sabia, chapare.(this last not ICD listed). New world.	Tachibe tribe of arenoviruses Acute febrile illnesses typically lasting for up to 14 days	South America particularly Bolivia, Argentina, Venezuela and Brazil	A96.0,A96.1, A96.2,A96.8, Occasional epidemics with lethality up to 30%. Variable according to location and causal agent	All ages susceptible	Largely occupational with reference to laboratory workers.	Protective immunity of unknown duration follows infection.	A live virus for the Argentinian disease	Various wild rodents	Sub-clinical infections occur. Immune plasma only remedybut it is effective in some instances in the Argentine form of the diseases. Ribavirin also useful across the board.
ARBOVIRUSESThere are more than 100 arboviruses which constitute the biggest single common category of disease causing organisms. Their common feature is their transmission to humans by arthropod vectors, mosquitos, ticks, sandflies and biting midges. Arbovirusesare variously RNA viruses largely of the families *Bunyaviridae, Flaviviridae, Roeviridae,* and *Togaviridae*Here four categories of disease willbriefly be considered., Arboviral arthritis and rash., Arboviral encephalitidies, Arboviral fevers and Arboviral hemorrhagic fevers. Most arboviruses are maintained in zoonotic cycles between birds or small mammals and insect vectors. Humans tend to be infected incidentally.In many but not all instances infected individuals do not develop or sustain a high enough viraemia to infect arthropod vectors. Recovery with immunity is usual but does not always occur. No vaccines mentioned. Birds and small mammals more rarely infected humans.									
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Arbo-virus encephalitides; Mosquito borne – at least 25 separate diseases with similar features but occurring in different localities and associated with different local strains of virus. Japanese encephalitis virus and West Nile virus are listed separately.	Local viruses, alpha viruses, flaviviruses, and Bunya viruses Most infections are asymptomatic or result in undifferentiated febrile illness. Many forms of later complication.	Almost anywhere that has mosquitoes.	A83.8,A83.2, A83.5,A83.4, A83.6, A84.1, A92.2, A83.1. Hugely variable some rarely lethal others with significant mortality.	Many adults have acquired immunity Children, visitors and those new to the area tend to be most diseased.	The young and the old are more susceptible. Various medical conditions predispose to severity of disease.	Infection usually results inlifelong homologous immunity	A variety of live and dead vaccines are used for a few of the diseases in this group.	Birds, small mammals	Inapparent infections usual in younger adults. No treatment available.

Disease	**Infectious agent.** **Target organ if any.**	**Location**	**ICD 10 entry.** **Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Arboviral fevers, vectors, Mosquitos, sand flies and biting midges. 25 listed in the 20th edition. Rift Valley fever listed separately.	Single stranded RNA viruses of various families primarily *Flaviviridae*, and *Bunyaviridae* or double stranded RNA viruses of the family *Reoviridae* Febrile illnesses lasting a week or so rarely fatal	Global but tropical or sub-tropical in the main.	A92.8, A93.8, A 93.2, A93.0, A93.1, B33.8, less than ten per cent were serious in an American outbreak	General, mild infections and subsequent immunity occur frequently in endemic areas	Children at higher risk of CNS infection. Immunocompromised individuals at higher risk of symptomatic infection.	Lifelong immunity after infection is usual	No vaccines mentioned.	Complex patterns of transmission.	No specific treatments
Arboviral haemorrhagic fevers. 4 listed, Yellow fever and Dengue are listed separately.	Causal agents *Flaviviridae* and *Bunyaviridae.*	Specific regions for the different diseases. Often seasonal relating to vector prevalence.	A98.0, A98.1, A98.2. serious diseases with distressing symptoms and very variable mortalities ranging from 1-30-%	Often health care workers, abattoir workers owners of livestock.	Occupational risks.	Lifelong immunity after infection is usual	Some vaccines have been developed but overall use controversial at present.	Wide range of reservoirs which vary according to the specific diseases.	No specific treatments
Corona Virus Respiratory Infections., All enveloped RNA viruses that infect a wide range of mammals and birds. In man they can cause severe and sometimes lethal respiratory disease. Single stranded positive strand RNA viruses, three reported here the first two in the 20th edition of the manual the third in 2020 the cause of a pandemic which will doubtless be reported in the 21st edition of the manual to be published in 2021.									
Corona virus respiratory infections MERS, Middle East respiratory syndrome	MERS –CoV As above	All cases known are linked to the Middle East.	None presently allocated. By mid-2014 699 laboratory confirmed cases were reported to WHO with at least 209 deaths. Sporadic human cases are considered likely to continue.	Not known except for common co-morbidities and contact with infected individuals.	A variety of co-morbidities such as diabetes immunosuppression and heart disease most commonly reported.	?	Use of convalescent plasma has been considered.	Direct contact and fomites recognisedwith camels found to have high titres of neutralising antibodies.	No anti-virals have been deployed but with some patients prophylactic antibiotics have been used.
SARS	Sars corona virus single stranded RNA. Upper respiratory tract	No certainty where it originated but it certainly spread internationally.	U04.9 provisional Up ro 10% mortality in those infected.	Difficult to say as presentation is variable but no information given on asymptomaatic infections.	Originally thought to have been a zoonosis. Those in contact with working with the vectors Are at higher risk. I Without diagrnosis nosocomial infections were common and without doubt most of later infections were consequent upon contagion from infected patients.	None indicated.	Himalayan masked civet and horshoe bats but main problems derives from infected humans	Most measures taken to diminish the dissease involve good health care practice and wearing of mask to restrict transmission by droplets..	

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Corona virus respiratory infections Covid-19	SARS-CoV-2 Huge impact worldwide with many millions of cases and a significant mortality.	Worldwide though major differences have been found between incidences in countries.	Emergency code of U07 allocated. Massive impact on health services and great economic impact as a consequence of the steps enforced by national governments in their attempts to prevent the spread of infection.	Older ages at special risk but cases known in all ages.	Age and prior health conditions. A significant proportion of those hospitalised and dying had prior bad health.	Antibodies are produced in severe cases but it is recorded (27) that asymptomatic cases do not show antibody.	Many presently in preparation as the authorities are wedded to the idea that vaccines are the answer.	The causal agent is said to be new. Arguments rage about where the first cases appeared. In late 2020 we are desperately short of hard information about the biology of the disease and why some 70% of those infected remain asymptomtic.	Declared pandemic by WHO with subsequent enormous attempts to stop it.
Keratoconjunctivitis, adenoviral, shipyard eye.Bacterial conjunctivitis dealt with in bacterial tables.	Adenoviruses types 8, 19 and 37 in the USA Eyes.	Presumably worldwide. Outbreaks have occurred in Asia, Hawaii, North America and Europe	B30.0 Unusually residual scarring appears	Not stated presumably universal	Any trauma can increase the risk of infection	Usually long-lasting type specific immunity after infection.	N/A	Humans	Often associated with eye clinics! Clearly a very contagious agent. No treatment during acute phase.
Adenoviral haemorrhagic conjunctivitis, Pharyngoconjunctival fever	Adenoviruses and picornaviruses	Summer epidemics associated with swimming pools	B30.0 Usually mild but severe chronic cases with residual neurological complications are recorded.	All ages can be affected. Associated with institutional overcrowding.	?	Reinfections and relapses are reported the role and duration of immunity if anyis not clear	N/A	Humans	Swimming pool disease. no specific treatment
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Coxsackievirus diseases, vesicular pharyngitis, vesicular stomatitis with exanthema (hand foot and mouth disease), lymphonodular pharyngitis. Not recorded in 20thedition.	Various coxsackieviruses	Worldwide sporadic particularly the lymphonodular pharyngitis	ICD 9, 074, ICD 10, B34. In general self limiting	Universal	Not stated	Type specific Immunity acquired by clinical or inapparent infection, duration unknown	N/A	Humans	associated with juvenile diabetes No specific treatment
Cytomegalovirus infections adult and congenital,	Human (beta) herpes virus 5 *inter alia.* Febrile illness	*Ubiquitous*	B25, P35.1 Very drastic on affected infants and many of those who are immunosuppressed	Ubiquitous	Immaturity and immunopareses of many kinds. It causes enormous problems in transplant patients.	It produces symptoms relatively rarely. 'it is the classic example of the persistent inapparent infection. As many as 100% of people in developing countries have antibodies and all have the infection!	None generally available	Man. The animal CMVs do not infect humans	Transmission of the disease is by intimate contact with infected mucosal surfaces. CTX ganciclovir

Dengue fever, break bone fever	Flaviviruses of specific serotypes Acute febrile illness	Endemic in most tropical countries	A90. Rarely fatal except in instances of haemorrhagic complications	universal	Children affected less than adults	Serotype specific and effective immunity develops that is lifelong.	None	Human with mosquito vectors	Although rarely lethal it can cause large scale epidemics when the virus and the vector coincide. Supportive treatment aspirin
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Dengue haemorrhagic fever	As above	Outbreaks recorded from many tropical locations	A91. Case fatality rates of up to 50% are reported in which fluid replacement has not been effected.	Universal in that susceptibility tocausal viruses is universal	Antibodies to heterologous infection acquired either passively or as a result of a previous attack are the major risk factor.(see comments)	In this instance stimulation of the immune apparatus has a detrimental effect	None	As above	Heterologous antibody apparently enhances uptake of newly entered virus into mononuclear cells. The consequences seem to be over secretion of cytokines.
Ebola-Marburg virus diseases, African haemorrhagic fever,	Negative stranded Filoviridae. Five Ebola viruses have so far been discovered of which four cause human disease. The fifth can cause fatal haemorrhagic disease in non-human primates. Marburg virus at the moment has only one discovered species High fever is a starting symptom with a variety of detrimental systemicconditions following	Initially recognized as a zoonosis from monkeys in Europe. Subsequently has been recognized in Africa in a number of epidemics with high fatality	A98.4,A98.3 Extremely nasty. With outbreaks in many centres recorded from 1976 for Ebola and from 1967 for Marburg.,	All ages susceptible	Main groups at risk are patients infected with contaminated needles and care givers in affected communities, laboratory workers processing infected specimens. People working with wild life in non-human primates in Central Africa and bats	Antibodies have been found but it is not yet clear what their relationship is to infection by any of the relevant viruses.Watch this space.	None so far	Cynomolgus monkeys, bats, and infected patients. The viruses are highly contagious.	These viruses are highly pathogenic. Seem often apart from monkey bites and contact with direct or indirect contact with infected patients tobe spread by sexual intercourse. Clearly in relation to Ebola and Marburg disease these are early days and we are short of information.
Erythema infectiosum (fifth disease)	Human parvovirus B19 A mild childhood exanthematous disease associated with low grade fever.	worldwide	B08.3 Generally benign	Universal in those with blood group P antigen.	50-80% of adults in the USA have antibodies indicating contact with the organism. Patients with underlying anaemia particularly if they get pregnant are at higher risk, as are immunosuppressed individuals	Anti-B19 virusantibodies seem to confer resistance to disease	One said to be under development	Humans	**Intravenous Ig has been used successful.**
Exantheumsubitum, sixth disease, roseola infantum	Human herpes virus HHV6Usually mildlike glandular fever	Worldwide	B08.2Slight except in immunosuppressed individuals	General	Restricted almost to children under the age of five but over six months	Latent infection with immunity to further infection	Not developed but thought about	Humans with latent infection.	Symptomatic care but nothing given as specific treatment.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Gastroenteritis acute,viral, rotaviral enteritis	Reoviridae, many types involved Vomiting, fever and watery diarrhoea	World wide	A08.0 Huge, one third of all hospitalised cases of diarrhoeal illness in infants and young children due to rotavirus. It is said to be responsible for up to 900,000 deaths of children per year!	Greatest between 6 and 24 months of age beyond that most have acquired antibody.	Immunocompromised individuals at special risk for prolonged rotavirus secretion and intermittent rotaviral diarrhoea	Neonatal rotavirus infections are usual in certain settings, but most are asymptomatic. Immunity in most instances is complete and seems to follow (asymptomatic?) infection.	One being tested presently. Much work has gone into attempt passive immunisation with food containing neutralising antibodies. Result NK.	Humans	One of the major diseases of the world. The virus can survive for long periods on dry surfaces and is resistant to some standard disinfectants. A major cause of nosocomial infection in infants. Symptomatic treatment only – rehydration for example.

Norovirus infection	Norwalk like viruses (small RNA). Commonly known as Norovirus.	Worldwide and common (in parts of the USA 60%of the population had antibodies)	A08.1 Usually a self- limiting mild to moderate disease	widespread	Adults >65 and children < 5year at special risk of developing a severe disease.	Antibody levels did not correlate with resistance or susceptibility. Short lived immunity up to 14 weeks was shown in volunteers butnot always thereafter	none	Humans	Associated particularly with the consumption of raw shellfish. Fluid replacement only. Can be anosocomial infection
Hanta virus disease, haemorrhagic fever with renal syndrome	Hantaviruses of various strains. This and the, pulmonary syndrome are both acute zoonotic diseases with a febrile prodrome, thrombocytopenia. leukocytosis and capillary leakage.	widespread.	A98.5 In its worst manifestation up to 15% mortality	Uniform susceptibility except perhaps those who have evidence of previous infection!	Occupational risks for hospital personnel and animal handlers	Yes, second attacks not documented	None	Field rodents, humans are an accidental host	Obvious zoonosis, fluid management
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Hanta virus disease, pulmonary syndrome	As above	Restricted depends on distribution of carrier rodents	B33.4 Rare but lethality up to 50%	All susceptible without prior infection	None	No second cases identified, mild infections. If immunity exists its duration and strength are not known	None	Deer mouse	Another zoonosis, symptomatic management only.
Hendra and nipah viral diseases	Paramyxoviruses Nipah manifests primarily as a encephalitis, Hendra as a respiratory illness or a prolonged and initially mild encephalitis.	Very restricted	B33.8 Rare but mortality up to 50%, subclinical infections may be common!	All ages suceptible	Those in contact with swine. Or infected horses. Possibly people in contact with palms sap from trees with roosting bats.	Recurrent infection known.	none	Fruit bats and a variety of small wild animals, horses and some companion animals.	Potentially very nasty zoonosis, No specific treatment.
Viral Hepatitis Diseases Some five recognized all affecting the liver but with some different viruses. Collectively they have a huge global impact									
Viral Hepatitis A, infectious hepatitis, Epidemic jaundice.	HAV a picornavirus (RNA) All the hepatidides are hepatropic and in various ways impact on liver function.	Worldwide (33% of adults in industrialised countries are said to have had contact with it.	B15 Usually mild infection which resolves in time Case fatality low. Can reach 1.8% in adults over the age of 50.	General	Number of epidemics among school children particularly. Homosexual males tend to get it. Food handlers. Those with chronic liver disease at higher risk of bad outcome if infection.	Homologous immunity after infection probably life long	Two inactivated vaccines are available and said to be effective	Humans, more rarely chimpanzees and other animals but an animal reservoir in nature has not been recognized.	A major disease but not in the same league as some of its alphabetic colleagues. Passive immunisation with Ig is used.

Viral Hepatitis B, serum hepatitis, homologous serum jaundice, Australia antigen hepatitis	HBV a double stranded DNA virus Fewer than 10%of children and 30-50% of adults having acute infection with HBV show icteric disease. In infants it is usually asymptomatic.	World-wide. It is written that 2 billion people are infected and that approximately 600,000 die each year of the disease with four million new cases a year.	B16	Generalthough only a small proportion of cases are recognized. (by icteric disease usually)	Immunosuppressed individuals tend to get the chronic disease with liver complications. It is the prime cause of hepatocellular carcinoma that is second world-wide to tobacco induced lung cancer.	Vaccination is widespread whether spontaneous immunity develops following a recovered infection is dependent on the quality of antibodies discovered.	Effective vaccines have been available for more than twenty years. One of these is a recombinant yeast which expresses the appropriate antigen.	Humans perhaps occasionally chimpanzees. Closely related viruses from other animals do not affect humans.	The goliath among diseases. Alpha interferon and lamivudine but nothing which is a guaranteed cure.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Viral Hepatitis C, parenterally transmitted nonAnonB hepatitis, tranfusion associated hepatitis.	HCV, an enveloped RNA virus Onset insidious with only 20-30% of active infections being symptomatic. 75-85% of infections become chronic.	Worldwide	B17.1 Limited by the number of people who share injection equipment! For all that about 1% of the world population are infected! (ie 60 million).	General. The enormous problem here is that 90% of infections are asymptomatic. Of those infected a significant number will get cirrhosis of the liver and sometimes hepatocellular carcinoma. Both these conditions are gravely life threatening.	Drug users. Those using non-sterile needles, recipientsof transfused blood, unprotected sex among male homosexuals. Health care workers.	None recognized	None	Humans. In chimpanzees experimental re-infection can be brought about. but there is no evidence that non-human primates act areservoir of. Human infection	An effective treatment with direct acting anti-viral treatment is now available.(not referred to in the 20th editionof the manual but recorded widely on the web.
Viral Hepatitis D, Delta hepatitis	HDV a single stranded RNA virus	Worldwide	B17.1 About 10million people affected worldwide alwaysin conjunction with HBV	General	Severe disease can occur even in children	Not stated	HBV can lead to immunity to HDV.	Humans	None given. For those with established HBV infection there are presently no methods to prevent HDV
Viral Hepatitis E, epidemic, nonA, nonB	HEV a non- enveloped single stranded RNA	worldwide	B17.2 Small in comparison with A and B	Susceptibility unknown	Pregnant women in the third trimester of pregnancy are particularly susceptible	Not stated.	None	?domestic animals including swine	None recorded
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Herpes simplex, anogenital herpesviral infections, Congenital herpes viral infection. In addition, two other herpes infections are listed which will dealt with separately below.	Herpes simplex virus 1and 2(roughly 1 for the top end in kids and 2 for the bottom in adults, it being largely an STD) Neurovirulence, latency and a tendency to local recurrence characterize these infections	Worldwide, 50-90% of adults possess antibodies against HSV 1	A60, B00, P35.2 Many primary infections are inapparent and the symptomatic cases vary a great deal in severity in both instances	Universal	Immunosuppressed individuals	Antibodies are elicited but they seem not to be affected by reactivation of latent infection (or vice versa!)	None quoted	Humans	Remarkably contagious, Acyclovir IV seems to be reasonably effective.

Kaposi's sarcoma	KS associated herpes virus or Herpes virus 8 believed to be causal. STD. though it is argued that non-sexual means of transmission also occur	Where AIDS patients are to be found, i.e. worldwide.	C46.0, C46.9	?	Immunosuppression	Antibodies to the virus are recognised but it is not clear what their relationship is to clinical status.			Associated largely with HIV infections.
Influenza, human diseases and zoonoses are recognised.	Three types of virus some of which are further broken down but a main characteristic of the organism is its capacity to produce new variants. Infection of the respiratory tract	In pandemics in which a variable proportion of the population is affected	J10, J11. as said to have killed up to 50 million in the 1918 outbreak	Complex picture, implication is that all are susceptible except those who have had a previous encounter with the same or similar organism	Again, very variable. In some epidemics more than 80% of those who died were over the age of 65 but in relation to the biggest epidemic (in 1918) young adults were the most affected!	Type specific immunity is strong	Inactivated virus used widely and it does give protection.	Humans primary reservoir but other spp. e.g. aquatic birds have widely been mooted as capable of initiating a pandemic.	A major disease the impact of which can be lessened by vaccination. Oseltamivir and Zanamivir both associated with potential side effects
Other influenza., infections circulating in and causingdiseases in animals	H5N1, avian influenza virus and H9N2, swine influenza virus. Mortality can high among humans infected with the relevant viruses from (diseased?) infected poultry are the main focus in the 20th edition of the manual.	World wide	J09 All potential causes of pandemics. The influenza viruses are highly mutable and always generate antigenically new variants which greatly complicates the invention of prophylactic vaccine preparation.	Initially occupational in that close contact with infected animals is a major risk factor but pandemic spread to the general population is always regarded as a potential hazard.	Potentially all ages can become diseased. Immunity post infection does occur and to a limited extent can be induced either with attenuated live vaccines or non-living vaccines against extracted components of the virus responsible.	Inducible	Some vaccines against H5N1 have been prepared and licensed for use.	Uncertain whether migratory birds are capable of spreading pathogenic viruses either to domestic animals or to man.	As above.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Lymphocytic chorio-meningitis virus, LCM, a viral infection of rodents mainly mice.	An envelopedambisense RNAarena virus closely related to lassa and a number of others Variety of symptoms can be influenza like. Rarely fatal.	Not uncommon in Europe and America	A87.2 Rarely serious, extremely variable in its presentation	Not stated, Implication is that susceptibility is universal	Surprisingly, immunosuppressed patients who become infected may often not show the usual symptoms. Though in them the disease can be fatal. Occupational risk. Human foetuses can acquire the infection vertically.	Recovery leads to lifelong infection. Cell mediated immune responses may play a primary role, antibodies are of lesser importance	none	Mus musculus, the house mouse. The disease in man is a zoonosis	Nude, immunologically incompetent mice become chronic shedders but do not show disease. Ribavirin has been proposedas treatment for humans. A fascinating disease for immunologists.
Measles, rubeola	Measles virus, a member of the genus *Morbillivirus*. A paramyxovirus Prodromal fever and pathognomonic rash. Rarely sub-acute sclerosing panencephalitis develops as late complication.	Complex pattern due to successful vaccination programs. Initially it seemed to be a disease of large metropolitan aggregates with a two to three year cycle. In rural populations it was less frequent butmore severe	B05 Unimmunuized populations can be extremely badly effected with a high case-fatality rate. World-wide it was estimated that prior to global vaccination programs six million measles deaths occurredeach year!. However, it is recorded by WHO that in 2011 157,700 children died. The anti-vaccine activists should look carefully at these figures.	Universal (*pace* immunisation)	More severe in infants and adults than in children Malnutrition, vitamin A deficiency predispose to severe disease.vaccination not recommended in those with immunodeficiency disease.	Lifelong immunity after illness (issue of development of SSPE as a long term outcome of measles infection is not here considered in detail)	Immunisation with a live attenuated virus is very effective.	Humans	In the developed world essentially under control until recently when resistance to vaccination has begun to reduce those who are immune. In days gone by before vaccination more than ninety per cent of people had been infected before the age of twenty. No specific treatment.

Disease	Infectious agent. Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Vaccines	Primary reservoir and vectors	Comments, treatment
Molluscum contagiosum.	Molluscipox virus a member of the *Poxviridae* family. Skin.	Worldwide	B08.1 More nuisance value	General but specially in children	Lesions tend to disseminate in HIV patients	?	none	Humans	No specific treatment
EPSTEIN-BARR INFECTIONS Also associated with infection by this virus are several diseases of which Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease and various non-Hodgkins lymphomas are mentioned in the 20th edition of the manual									
Monoucleosis, infectious, (glandular fever),	EBV, a herpesvirus 4. It affects and transforms B cells.	Worldwide common, in early childhood	B27Usually mild or asymptomatic, about 50% of those infected develop symptoms. All those infected retain the virus in latent (non-lytic) form for life and the possession of the virus is associated with many malignant diseases. This issue will not be dealt with in any detail here	General	May recur or be extremely serious in immunodeficient patients. (particularly X-linked recessive immunoproliferative disorder) Paradoxically, recurrence can be associated with the development of anti EB antibodies but not the array of heterophile antibodies that has been used aspathognomonic for the acute disease.	Infection incurs an immune response, despite which the organism persists in latent form for life.	None yet	Humans	Extraordinary capacity to infect and transform B-lymphocytes (rather as can *Theileria parva*incattle). Also associated with the development of nasopharyngeal carcinoma and Burkitt's lymphoma. NST though the tumours, particularly Burkitt's lymphoma can be successfully treated in most cases.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Mumps, infectious parotitis	A paramyxovirus An acute fever and tenderness of one or more of the salivary glands.	Worldwide, about 85% of unvaccinated people have antibodies by adulthood.	B26 About a third of those infected remain asymptomatic. Under the age of two infections are almost always subclinical.	Not stated but presumably universal	None indicated	Lifelong immunity very often as a result ofinapparent /latent? infection	A live attenuated virus is widely used	Humans	None
Enterovirus Diseases five diseases are considered under this heading, enteroviral vesicular pharyngitis, enteroviral vesicular stomatitis with exanthema, enteroviral lymphonodular pharyngitis, myalgia epidemic and viral carditis. Other symptoms such a conjunctivitis and meningitis are mentioned as associated with the coxsackie virus infections here considered.The issue of immunity to these coxsackie/enterovirus diseases is ignored in the 20th edition of the manual but in the 17th edition there is a powerful statement that immunity to some of these diseases can be powerful either following active infection or as consequence of latent/ inapparent disease. These diseases include poliomyelitis disease which is an extremely serious paralytic condition that can be largely prevented by oral vaccines and it would be surprising if this were not true for the diseases caused by the far less serious enterovirus diseases considered here in the 20th edition. Perhaps the issues is simply a matter of finance it not being worthwhile to consider immunity for the non=-polio virus diseases.									
2 enteroviral vesicular pharyngitis, herpangina	Enterovirus A serotypes CV-A1 to 19, 18, 22 and EV-A71. Herbangina mildly febrile illness with multiple painful mouth ulcers.		B08.5Both this and the following illness have possibility of CNS involvement with a potentially fatal outcome	Young children	Attendance at nursery schools, day care centres, households with many young children.	No mention of immunity and recurrence is stated to be common	None	Humans	Hygienic management
Enteroviral vesicular stomatitis with exanthema, hand foot and mouth disease	Enterovirus A serotypes, CV-A16 and EV71, less frequently with enterovirus B serotype. Skin, lesions usually heal spontaneously without scarring	Worldwide In temperate regions peak incidence is in summer and early autumn but throughout the year in the tropics.	B08.4 Typically, brief and mild disease however see above	Young children	Attendance at nursery schools, day care centres, households with many young children.	No mention of immunity. as recurrence is common	None	Humans	Hygienic management

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
enteroviral lymphonodular pharyngitis	Enterovirus A serotypeCV-A10 skin	Worldwide	B08.8	Young children	The entries for the 17th and 20t edition of the manual differ lymphonodular pharyngitis though mentioned in the latter is not further considered. Whereas in the 17th edition there is come information given Furthermore the accounts ofthree of the diseases mentionedin 20th edition differ greatly in relation to the issue of immunity	?	?	?	
Myalgia, epidemic, devil's grippe, Bornholm's disease	Group B coxsackie virus Pleurodynia with paroxysmal pain in chest and abdomen	uncommon	B33.0 Outbreaks in various parts of the world, Europe, Australia, New Zealand and N Armerica	Probably general	None indicated	Specific immunity presumably results from infection 17th edition, none mentioned in the 020th edition.	None	Humans	None
Poliomyelitis, infantile paralysis	Poliovirus, genus *Enterovirus,* types 1, 2 and 3Paralysis of varying degrees. Can occur. Infection starts in the intestinal tract with spread to regional lymph nodes and more rarely to the CNS.	It was worldwide now it is becoming confined to India and to a lesser extent to parts of Africa	A80 Has been a major cause of partial paralysis. About 90% of infections are unapparent or result in nonspecific fever.	Universal.	. High risk is for those who for various reasons are not immunized. immigrants, refugees, rural, and urban poor for example, and more recently those influencedby the anti-vaccine activists.	Type specific lifelong immunity.	Very effective	Humans with inapparent infections. (also a few chronic shedder)	Nearly eradicated but not quite. The neurotropism demonstrated is extraordinary.No treatment
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Rabies, hydrophobia, Lyssa	Rabies virus a rhabdovirus of the genus *Lyssavirus* Progressive viral encephalitis almost always fatal.	World wide	A82 Estimated 55,000 deaths annually almost all in developing countries. The disease is almost invariably fatal.	All mammals are susceptible though humans are less so than other animal species; in the 17th edition of the manual it is stated that only 40% of Iranians bitten by known rabid animals developed the disease. This statement is not in the 20th edition.?	None recorded	If it is uniformly lethal the issue of immunity does not arise. However it is known that the virus can be carried asymptomatically by a number of animal spp.	Both passive and active immunisation is practised for those at high risk. Human rabies anti immune globulin is administered after bites.	Many wild and domestic canidae. There are also several spp. of insectivorous bats that carry the virus. Their disease status is not stated.	Control over this disease has been maintained in some countries by strict quarantine regulations for imported animals. Nowadays, in some instances, vaccination has allowed movement again under strict control. The lethality of the disease in man is so high that it is almost the most feared of zoonoses. No treatment

Respiratory disease, acute viral rhinitis, the common cold, rhinitis or coryza	Rhinoviruses of which there are more than 100 serotypes account for 20-40% of cases, corona viruses account for 10-15% and influenza accounts for 10-15%. The etiology of common colds has only been identified in 50% of cases!	Worldwide both endemic and epidemic, seasonal	J100 Many people have 1-6 colds annually, incidence highest up to five years of age then declining	Universal, inapparent and abortive infections occur	Nothing indicated apart from age	? with so many known causes and roughly an equal number of unknown ones the issue of immunity is complex	Specific anti-adenovirus vaccination has proved effective but there is nothing available generally	Humans	NST
Respiratory disease, acute febrile respiratory disease (excluding Streptococcal pharyngitis).	Para-influenza virus or, more rarely RSV and a number of other agents.	Worldwide, seasonal	J01-06, J1. Nuisance except in the elderly and young	Universal, reinfection is common	Age, compromised cardiac, pulmonary or immune systems.	Transient immunity in the form of circulating antibodies	None recorded	Humans	Antibiotic treatment is to be avoided! NST
Rubella, German measles	Rubella virus. Usually a mild fever.	Worldwide universally endemic	B06. Usually, a mild febrile disease	Universal after loss of maternal antibodies	Fetuses	Long lasting immunity	Effective	Humans	Important because of its capacity to elicit fetal abnormalities. NST.
Disease	**Infectious agent.** **Target organ if any.**	**Location**	**ICD 10 entry.** **Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Vaccines**	**Primary reservoir and vectors**	**Comments, treatment**
Human Papilloma Virus Infections. There are more than 100 species of HPV with more than 40 types that can infect the human anogenital tract in both males and females. Cancers associated with HPV are of cervix, vulvar, vaginal, penile, anal and oropharyngeal tissues. The 20th edition does not deal with these cancers as communicable diseases and in this document they will not be further considered.									
Warts, viral, common wart, verruca vulgaris	HPV Skin andmucous membranes,	Worldwide	B07A wide variety of conditions most non-fatal	Common	Young children for flat warts, genital warts in sexually active teenagers	Incidence of warts higher in immunosuppressed individuals	None	Humans	NST, cryotherapy effective.
Yellow fever	A flavivirus Variable outcome of infection from mild fever to severe disease with jaundice and haemorrhage.	A complex pattern of disease falling into two categories, sylvatic (jungle)and urban cycles	A95 a sporadic disease with highbut very variable lethality. At worst 50%. The overall fatality rate in endemic regions among native populations is 5%. Mild inapparent infections are common.	Presumably, everybody, it does not say	Young adult males at most occupational risk. Unvaccinated travellers, forest workers in endemic areas. Disease is highly communicable	Single attack can confer lifelong immunity. Antibodies appear in the first week of infection. Transient passive immunity in new born infants.	Extremely effective live vaccine.	Humans and mosquito's in urban areas in forest areas almost anything on four legs.	No treatment cited.

Table 3: Protozoa (Protoctista).

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
In the 20th edition of the manual two amoebic disease patterns are given the first called Amoebiasis, amoebic dysentery and the second rather different group listed below all caused by free living organisms	*Entomoeba histolytica* Initially gut but with chronic infection more commonly and sometimes liver abscess.	Ubiquitous more prevalent in tropical regions with poor sanitation.	A06 Most infections said to be symptomatic. Problems presumably more for none indigenous populations.	General, persons of all ages are susceptible.	. Conditions favouring move to heightened pathogenicity stated to exist but not specified	Reinfection is rare implication is that immunity once acquired is long lasting.	Man, asymptomatic cyst carriers are more frequent than cyst carriers with disease.	Disease unusual in the youngLargely a disease of young adults. Most infectionsasymptomatic, CTX effective.
Naegleriasis, acanthamoebiasis and balamuthiasis	*Naegleria fowleri Acanthamoeba(various spp,)and Balamuthia mandrillari* Brain, encephalitis	Global	B60.2, B60.1	NK both immunocompetent and immunodeficient individuals have been recorded with these diseases.	Swimming in warm fresh water. Individuals with contact lenses	NK. No indication is given of asymptomatic infected individuals	Free living Amoebae in soil and water.	Diseases caused have over 90% lethality but seem to be rare.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Babesiosis, no synonym	*Babesismicroti*sis most common of several spp. involved. Symptoms very variable but non-specific fever common	Worldwide in scattered locations, most in USA.	B60.0 Restricted largely it seems by prevalence or control of tick vectors	universal	Asplenic, immunocompromised and elderly people are at highest risk.	Not written about.	Rodents and cattle., tick vectors.	Recrudescence of symptoms after prolonged asymptomatic parasitaemia can occur. CTX but not always easy
Balantidiasis,balantidialdystentery	*Balantidium coli*Colon with dysentery. Symptoms very variable	Worldwide .Incidence of human disease low.	A07.0	Humans seem to have high natural resistance.	Other medical conditions can predispose to fatal disease.	what is the basis of the resistance.?	Swine and rats laboratory pigs and non-human primates.	Antibiotics of various kinds. Keep away from hog faeces!
Cryptosporidiosis	*Cryptosporidiumhiminis and C. parvum* Epithelial cells of the GI tract. Diarrhoea most usual symptom	Worldwide.	A07.2 Low incidence of disease but occasional epidemics	General but particularly immunodeficientindividuals.	Children younger than 2 years. Animal handlers. Men who have sex with men. Close contacts with infected individuals	None indicated.	Humans and various animals. The organisms infect a large no. of spp.	. Nitazoxanide can be used. For children older than one.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Giardiasis, giardia enteritis	*Giardia lamblia* Mainly of the upper intestine.	Worldwide	A07.1 Not major	Asymptomatic carrier rate is high, and most infections are asymptomatic. Infections are commonly self-limiting. Infected individuals commonly have long asymptomatic periods but reactivation can occur. Inapparentand subclinical infections are common .	Children rather than adults. Persons with AIDS may have a more severe and prolonged infection	Not mentioned! Implication from HIV association is that immunity is involved but no indication that this is adaptive andor innate.	Humans possibly beaver and other wild and domestic animals.	Contaminated water is usual source of primary infections. Metronidazole usually works.
Leishmaniasis, Aleppo evil, Baghdad or Delhi boil	*Leishmania tropica*and others cutaneous mucosal here recognized.	Large number of tropical and semi-tropical locales,	B55.1, B55.2, Reasonably common – about a million new cases per year reported. Not usually dangerous		Factors relating to late development of severe disease not known.	Antibody levels low or non-existent but lifelong immunity can be created that is said to have a powerful cellular component	Many, humans, rodents, hyraxes, sloths. unknown host in many areas	CTX usually effective.
Leishmaniasis, visceral, Kala-Azar	*Leishmania donovanii*and othersFever with a wide variety of subsequent symptoms.	A rural disease occurring in foci in India and Bangladesh	B55.0.Usually fatalif untreated			Infection can predispose to lifelong homologous immunity	Humans and wild and domestic dogs	CTX available but it may require prolonged application.

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Malaria,	*Plasmodium spp* An acute febrile illness with a wide variety of subsequent outcomes depending mainly on the infective sp.of *P.falciparum*thisisparticular is usually lethal if untreated. Disease due to *P.vivaxP.malariae*and*P. ovale*are considered less dangerous.	In all tropical and some subtropical regions	B50-B54 Major cause of disease where it occurs.. in 2010 99 countries report on goingmalaria transmission with an estimated 219m cases and 600,00 deaths mostly in young children in Africa	except in some human beingswith the sickle cell gene, in relation to *P falciparum* or with absence of Duffy factor (*P.vivax*)	None quoted	Tolerance or refractoriness to subsequent clinical disease is present in adults in endemic regions. This could mean they are immune? Are they free from infection? Certainly repeated infections are normal for many of the indigenous population.	Humans, vector mosquitoes	This is a massive disease and the account given leaves many questions unanswered.
Pneumonia, immunodeficient pneumonia	*Pneumocystis carinii* (is it a protozoan or a fungus?) Acute,sub-acute condition which can be fatal	All continents	B59 Persists sub clinically in many instances. Can be lethal in immunosuppressed individuals	Again, there is the question of whether we are talking about susceptibility to infection or disease. The infection is usual the disease is not.	May be endemic and epidemic in debilitated infants. It affected 60% of AIDS patients in the USA before prophylactic measures were instituted.	If immunodeficiency predisposes then it must be supposed that normal control is exercised by the immune response.	Humans. It is found in many animal species, but this is not considered significant in relation to human disease.	It is now believed that the organism is a *fungus. CTX* available.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Toxoplasmosis, and congenital toxoplasmosis.	*Toxoplasma gondii,* a coccidian.	Worldwide in birds and mammals, infection in humans is common.	B 58 congenital versionacquired transplacentally from infected mothers P37.1 Infections frequently asymptomatic	General	Immunosuppression can lead to reactivation of infection.	Immunity is readily acquired, and most infections are asymptomatic. The indication is that the parasite persists	Cats are the definitive host	Treatment for healthy individuals not normally indicated.AIDS patients treated prophylactically.
Trichomoniasis	*Trichomonas vaginalis* STD	Widespread a disease of all continents and races. The most common curable STD	A59 Frequently asymptomatic	Universal	Frequently asymptomatic. Immunocompromised individuals at greater risk.	None written of	Humans	Metronidazole usually effective
Trypanosomiasis, African, sleeping sickness	*Trypanosoma brucei gambiensis*and *T Rhodesiense* Systemic.	Confined to regions of tropical Africa where lurks the tsetse fly	B56 In endemic regions parasitaemia present in 0.1-0.2% of population but during an epidemic the figure can reach 70%. Both forms of the disease are fatal.	General. Though spontaneous recovery has been claimed it has not been validated.	No particular risk factors given. Congenital transmissions can occur.	Various manifestations of activation of the immune apparatus are in evidence but immunity does not seem to arise.	Humans for *gambiense* but wild ungulates for *Rhodesiense*. Vector is various spp. of *Glossinia*	CTX available but relapses can occur. Part of the problem seems to be that the drugs used do not cross the blood brain barrier.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Trypanosomiasis, American, Chagas Disease.	*T cruzi* systemic	S.and Central America	B57No figures are given on prevalence but the disease is potentially very nasty with a whole series of complex essentially autoimmune manifestations.	All ages *susceptible* but the disease is more severe in the young. Proportion clearing the infection not quoted.	Immunosuppressed individuals are said to have greater chance of severe disease	Nothing said about it.	Humans and 150 spp of animals. Vector for man is the cone nosed bug. In the bug the parasite persists for life.	CTX available for acute disease. Nothing indicated for chronic infections.

Table 4: Fungi (no vaccines recorded).

Disease	**Infectious agent.Target organ if any.**	**Location**	**ICD 10entry. Impact**	***Susceptibility***	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Aspergillosis	*Aspergillus fumigatus* and*A. flavus* 40 spp have been reported as infectious. Lungs, initially.	Worldwide though uncommon and sporadic	B44 Naturally, slight.	.The disease is usually secondary to a primary condition. This it is claimed, in conjunction with the ubiquity of the fungal spores indicates that most individuals are resistant	Immunosuppression, particularly prolonged neutropenia. Contact with aflotoxins	Natural immunity claimed. There is no indication of activation of adaptive immune mechanisms.	Aspergillus spp. are ubiquitous in nature	Invasive forms of the disease in immuno-impairedindividualsbecome the problem.. Treatment, of Allergic disease is by prolonged corticosteroid suppression. Treatment far from simple.
Blastomycosis, Gilchrist disease	*Blastomyces dermatidis* lungs	Rare	B40Sporadic in Central and Southern USA, Canada, Africa India, Israel and Saudi Arabia. Untreated chronicinfections often eventually lethal	*Unknown but rarity of the natural disease and of laboratory infections suggests most people are relatively resistant Immunocompromised patients at higher risk of disease.*	Rare in children, more common in males than in females. Disease in dogs is frequent also in such rarities as a horse, a captive African Lion and a sea lion.	In apparentpulmonary infections are probable. There is evidence that CMI plays a role in controlling lung infection	Moist soil.Companion animals susceptible butzoonosis not recorded.	Acute disease often lasts three weeks before resolving.Evolution into a chronic disease is common. CTXavailable
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	***Susceptibility***	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Candidiasis, moniliasis, thrush.	*Candida albicans +other spp.* Skin, mucous membranes	Worldwide. Candida is a part of the normal flora,is this to be called an in apparent infection?	B37Big problems in those with illness of a wide variety of kinds, diabetes mellitus therapy with broad spectrum antibiotics HIV infection and so on.	*Either high immunity or low level pathogenicity!*	Many debilitating diseases can predispose to creating candida problems.	Most adults and older children have delayed type hypersensitivity and humoral antibodies.	humans	Fascinating organism. It clearly occupies a niche probably in balance with other organisms.
Chromomycosis, dermatitis verrucosa.	About ten species involved including P*hialophoraverrucosa* skin	World wide	B43	*Suggestion is that relative rarity indicates a degree of resistance. The absence of laboratory infections is regarded as confirmation.*	Associated with men aged 30-50 only rarely seen in women. Barefoot workers are at higher risk	?	Rotting wood and in general decaying vegetation	A minor problem except for those that get it. CTX available plus sometimes surgery to remove large lesions.
Coccidioidomycosis, valley fever, San Joaquin fever, Desert fever.	*Coccidioides immitis* <1% of symptomatic cases becomedissemi-natedLung probably site of entry	Only in arid regions of Western Hemisphere	B38 Important disease among archaeologists, migrant workers andmilitary personnel from non-endemic areas	Affects all ages, all races and both genders. More than half patients are between 15 and 25 years of age. Susceptibility to dissemination is greater among African Americans, Filipinos and other Asians. Pregnant women are at particular risk. AIDS is a risk factor	Males more frequently affected than females (occupational exposure is suggested). Reactivation of latent infection can occurif immunosuppression arises	High frequency of subclinical infections felt to be the case. Recovery from infection is associated with solid lifelong immunity	Soil especially around Indian middens and rodent burrows.	Infects almost any animal it seems but not transmitted from them to other animals or to man or vice versa. Primary infection usually responds without treatment but in severe cases CTX does exist.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	***Susceptibility***	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Cryptococcosis, Torula.	*Cryptococcus neoformans* Lungs, point of entry. Secondaries in the brain can be lethal.	Sporadic infections in all parts of the world. Classic example of an organism that very rarely causes problems except in impaired individuals	B45 Slight except with immunosuppressed individuals	*Suggestion is that there is resistance. This is based on rarity of the disease and the ubiquity of the organism*	Males more than females, Immunosuppression AIDS is a risk factor. Hodgkins disease and sarcoidosis	No immunity written of in the manual, but there are many papers published that argued both innate and adaptive immune mechanisms are active. Antibodies are however not mentioned.	Pigeons and old pigeon roosts	Secretes poly mannose that presents problems for recognition by macrophages via the mannose receptor. In AIDS patients can be a major problem. Indefinite treatment often the mode.
Derrnatophytosis tinea barbae and tinea capitis (ringworm). This and the following three diseases in the 20th edition are tabulated together as relatively minor fungal diseases of skin hair and nails.	Various spp of *microsporum and Trichophyton*Skin	Endemic in urban areas in Eastern USA, Puerto Rico and Australia	B35.0 Slight	*All ages susceptible*	Children below the age of puberty are particularly susceptible	Reinfections not recordedImmunity NK	Humans and a variety of animal spp.	Treatment can in time give complete recovery

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	***Susceptibility***	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Dermatophytosis, tinea cruris and tinea corporis (groin and body ringworm)	As above with a few other possible spp. Skin	worldwide	B35.6 Inconvenient	*Widespread, all ages affected, hot groins a starting point*	Males more frequently affected than females	None recorded	Soil and humans. The groin infection is almost exclusively male.	CTX
Dermatophytosis, tinea pedis, Athletes foot	*Trichophyton rubrum* and others Foot skin	Worldwide	B35.3 Inconvenient	*Variable, infection may be inapparent*	Males more affected than females.	Repeated attacks are frequent	Humans	CTX initially by local fungicides
Onchomycosis, Tinea unguium (ringworm of the nails)	Various *Trichophyton* spp. Nails usually of the feet	Common	B35.1 Inconvenient	*Variable*	?	Repeated attacks frequent	Humansmore rarely soil	CTX over long periods
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	***Susceptibility***	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Histoplasmosis (two diseases here of which only the more common is considered), number of causal agents but no common names given	*Histoplasma capsulatum* can be a respiratory disease but can also present in a disseminated form. Lungs	Common in particular foci, rare in Europe. In some parts of central and Eastern USA 80% of the population are histoplasmin sensitive indicative of contact with the organism.	B39.5 Of varying severity. Can be lethal	*Infection is common but overt clinical disease is not.*	Possibly opportunistic in immunosuppressed individuals	In apparent infections that are common seem to give increased resistance to (further?)infection	Soil with undisturbed bird or bat droppings	CTX, more difficult in immunosuppressed individuals.
Eumycotic Mycetoma Devil's grippe, Bornholm Disease. See alsonocardiosis in bacterial diseases	*Madurellamycematoma-tis*plus others and a set of bacteria that give comparable lesions. skin	Rare in continental USA but common in Mexico	B47.0 Nasty	*Causal organism's common but disease is relatively rare. Implication is that resistance is usual.*	Barefoot workers, ie infection is secondary to wounding.	None recorded	Soil	CTX and or surgery in extreme cases.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	***Susceptibility***	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Paracoccidiomycosis, South American blastomycosis.	*Paracoccidioides braziliensis* Lungs siteof primary infection	Endemic in tropical and subtropical regions of S. America and to a lesser extent in Central America	B41 A serious and sometimes fatal disease	*Unknown*	?	?	Presumably soil or fungus laden dust	CTX
Sporotrichosis,	*Sporothrixschenckii* Skin.	All parts of the world	B42 An occupational disease of gardeners and horticulturists. Fatalities uncommon	*unknown*	?	?	Soil	CTX
Mucormycosis. Zygomycosis, A complex of diseases with a number of causal organisms.	Various zygomycete fungi including *Rhizopus arrbizus*	Worldwide, incidence may be increasing because of longer survival of various kinds of patient such as those with diabetes mellitus, and certain blood dyscrasias	B46.0 Extraordinary disease that in susceptible patients causes nasty facial problems with erosion of many nasal structures. In the lung it can cause blood clotting and lung infarcts.	*The argument put forward is that as the disease is rare but the fungi concerned are common there must be resistance to the disease.*	A variety of debilitating conditions predispose to the disease. What is not stated is whether it ever occurs in normal individuals. It is certainly rare.	Difficult to say. If immunosuppression predisposes to the disease it could be correctly supposed that the immune response is the basis of the resistance in non-immunosuppressed individuals. This is not the only possible explanation however.	Common saprophytes.	CTX and/or surgery.

Table 5: Flat Worms, Trematodes, Including Tapeworms, Non-Segmented.

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, including treatment**
Liver fluke disease Clonorchiasis, Opisthorchiasis	*Clonorchis sinensis, Opisthorchis felinensis*and*viverrini.* Diseases of the bile ducts, Cholangiocarcinoma can be a late side effect of infection with *O. verrini.*	Endemic in South East China and other parts of SE Asia. Opisthorchiasis is also frequent in the old states of the USSR. It is estimated that globally some 700m people are at risk of infection.	B66.1, B66.0 (C22.1, cholangiocarcinoma)Often completely asymptomatic. Very slow chronic diseases often lasting for 30 or more years only rarely a cause of death but a major risk factor for cholangiocarcinoma	Universal	In endemic areas highest prevalence in adults over age of 30	None cited but fact that infection is often and probably usually asymptomatic is interesting	Humans, cats, dogs, swine, rats and other animals	A danger from raw or undercooked freshwater fish. Treatable with CTX. No person to person transmission
Tapeworms, in the 20th edition of the manual, following the ICD listing, considerssomenine different tapeworm infections. Here only three of the most common will be considered	*Hymenolepis nana*. Dwarf tapeworm Intestinal infection,	Cosmopolitan	B71.0 Rarer in colder climates	Universal	Children more susceptible than adults, immunosuppressed or malnourished people at particular risk	Infection leads to resistance to (?further) infection	Humans and possibly mice (in which it grows well under experimental circumstances)	A very small addition to man!, autoinfection occurs. CTX effective.
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Diphyllothriasis, Broad or fish tapeworm infection	*Diphyllobothrium latum* and several other spp. of the genus. Intestinal infection of long duration symptoms commonly trivial.	Lake regions in N Hemisphere and subarctic regions where eating raw fish is practised	B70.0slight	Universal	None given	Reinfection can occur thus immune resistance does not apparently develop	Humans and a variety of animals including polar bears	Another raw fish problem CTX will work.
Taeniasis (pork and beef tapeworm) and Cysticercosis	*Taenia solium*, porkand *T. saginata* beef. Initially intestinal infections but development and dissemination of cysticerci can create massive later complications	Worldwide wherever pork and beef are eaten insufficiently cooked and sanitary conditions allow cattle access to human faeces	B68 Consequences of infection grave if cysticercosis arises	General	Those living in poor and insanitary circumstances.	No immunity reported though more than one tapeworm per host is rare	Pigs for *T.solium*and cattle for *T.saginata*are the intermediate hosts. Humans are the definitive hosts	CTX or surgery. Treatment complicated by consequences of killing cysticerci.
Echinococcosis, cystic hydatid disease.Three grades or the disease are recognized, cystic, alveolar and polycystic, here only cystic form will be considered.	*Echinococcus granulosus* Slowly developing disease commonly in liver or lungs but can be found elsewhere	All continents except antarctica	B67.0 Not stated although note relatively high grading.	None given presumably universal	Children more likely to be infected but they are also more likely to play with dogs. Really no evidence of greater susceptibility in children	None written of	Dogs and a variety of other animals	Even multiply infected animals are often totally asymptomatic! Problems arise largely because of hydatid cysts Either surgical treatment of cysts or CTX can work
Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Fascioliasis, a zoonotic liver fluke	*Fasciola hepatica* and to a lesser extent *F gigantica* (sheep liver fluke)	Reported in various cattle rearing areas in all continents except antarctica	B66.3 Accidental in man	All ages susceptible, infection persists indefinitely	None given	None written of	Sheep cattle and snails	Transfer to man commonly by consumption of aquatic plants with attached metacercariae. Nasty disease in that there is no sure fire cure!

Fasciolopsiasis, no synonyms	*Fasciolopsisbuski*(a large liver fluke up to 7cm in length)	Rural Southeast Asia	B66.5 Light infections commonly asymptomatic	Universal	In malnourished individuals effects of infection can be more pronounced. Severity of disease determined by number of worms	None indicated	Swine and humans	Another aquatic plant with snail problem especially in the vicinity of pig faeces. CTX.
Disease	**Infectious agent.** **Target organ if any.**	**Location**	**ICD 10 entry.** **Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and Vectors**	**Comments, treatable?**
Paragonimiasis, lung fluke disease	*Paragonimuswestermani* And other spp.of the genus Lungs and elsewhere	Reported from various places particularly far East	B66.4 Said to be 22.3 million people infected in China	General	Infectionmay last for years and the infected person would seem well	None indicated	Humans and various domestic animals, fish become associated with the faeces orsputum that has been spat out	Another uncooked fish disease in which the lung is affected. Often found in snails and edible crustacea. The larvae can even survive pickling! CTX indicated as successful
Schistosomiasis(bilhar-ziasis)	*Schistosoma mansonii*and others A blood fluke.	Various tropical countries, Africa, China and so on. Not indigenous to N America	B65 Primary disease is insignificant the consequences of chronic infection can be serious	General	None given except of course forthose who bath in infected waters	Any immunity is variable and poorly defined	Humans and all sorts of other animals. 'Vector' often snails.	CTX treatable. No direct person to person transmission but indirect contamination can occur via eggs discharged in faeces into water. A major hazard of swimming in tropical fresh water

The trematodes induce a variety of chronic diseases one of which, schistosomiasis, figures on the 'wanted' list ofWHO. No vaccines are quoted as available as is nearly true for all the eukaryotic (and fungal) parasites of man. Effective CTX exists in most circumstances.Most of the transfer of infection arises due to eating habits, usually either raw fish or improperly cooked meat. Immunity if any seems a variable feast. These organisms seem to exist in the host independent of immunity with the severity of infection determined simply by the number of infective organisms that hasgot in. Adverse consequences in some circumstances are due to redistribution of the parasite from an adult form to larval forms that in various encysted conditions can be dangerous as space occupying lesions with the additional problems in some instances of eventual disruption with liberation of a variety of pharmacologically active substances.

Table 6: Nematodes (Non-Segmented Round Worms).

Disease	**Infectious agent.Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Anisakiasis, no synonyms quoted	*Anisakis and Pseudoterranova, larvae* Gastro intestinal mucosa.	Where 'uncooked' fish is eaten Most cases recorded in Japan,	B81.0 slight	universal	NK	NK	Marine mammals various intermediate hosts such as small crustaceans and a variety of fish	On the increase, as eating of raw fish increases in the Western world. Surgical removal is all that is quoted by way of treatment
Ascariasis, roundworm infection	*Ascaris lumbricoides* Intestine but can give rise to symptoms I many parts of the body.	Moist tropical countries	B77Common and worldwide, in many countries prevalence 50%!, complications of chronic infection can be severe,	General	Young children, 3-8 years in whom prevalence and intensity of infection is highest.	NK	Humans, often as a consequence of defaecation in soil. Ascarid eggs in soil can be viable for many years.	CTX that can be complicated.
Capillariasis, intestinal capillariasis	*Capillariaphillipinensis*Variable intestines, liver and respiratory tract	Far East particularly Phillipines and Japan where it is endemic	B81.1Sporadic. On Luzon some 1800 cases have been recorded. Case fatality rates of 10% have been recorded.	General	Perhaps males between the ages of 20 and 45 but this could be an occupational issue.	?	Unknown, perhaps aquatic birds fish are intermediate hosts it is believed.	Associated with eating poorly cooked fish, CTX available
Hepatic capillariasis	*Capillaria hepatica*	Rare only recognized as a human disease in 1924. Worldwide but not common.	B83.8 Occasionally fatal	General	Malnourished children are particularly at risk, 3 years of age in particular.	?	Rats but a wide variety of domestic and other animals.	A liver disease about which because of its rarity little seems to be known. CTX effective.
Capillariasis, Pulmonary capillariasis	*C.aerophila* Larvae from the intestine migrate to the lungs.	Worldwide but rare. Too few cases so far for any sensible generalistions.	B83.8	General	Children	?	Cats, dogs and other carnivorous mammals.	Mebendazole, albendazole and thisbendazole.
Dranunculiasis, Guinea worm infection	*Dranunculus medinensis* Subcutaneous or deeper tissues..often initially on a foot.	Africa and in Asia, particularly in countries with dry climates	B72 Prognosis generally good unless secondary bacterial infection occurs	Universal	In some locales all people are infected, mainly young adults in other areas far fewer carry the organism.	None recorded, multiple infections occur in the same person	Humans	WHO agreed to abolish the disease in 1991 but they have not yet succeeded. CTX not always effective often difficult.
Disease	Infectious agent.Target organ if any.	Location	ICD 10 entry. Impact	Susceptibility	Special risk factors	Immunity	Primary reservoir and vectors	Comments, treatment?
Enterobiasis, (pinworms)	*Enterobius vermicularis* Intestine.	Worldwide	B80 Irritant but rarely with serious consequences	Universal	Differences in severity of infection are due to different levels of exposure. Ranges from asymptomatic to recurrently symptomatic.	None recorded	Humans, none of the animal pinworms communicate to man	One of the most common parasites of school children. Parents occasionally infected and infections in domiciliary institutions can be common. The only nematode disease that shows person to person transmission. Easily treated.
Filariasis, a variety of local or eponymous namings, eg Bancroftian filariasis, Malayan filariasis, Timoreanfilarisis .	*Wucheriabancrofti, Brugiamalayi and Brugiatimori.* All infections of lymphatics	Variously distributed, bancofti wide spreadparticularly in warm humid regions the other two more restricted	B74.0, B74.1, B74.2 Repeated infections in endemic regions can lead to elephantiasis	Universal	?very long persistent condition	None recorded Repeated infections occur	Humans with microfilariae. Mosquitos are the vector	Not easy successfully to treat. Drugs are available and have been used on a mass basis but side effects can be bad. Watch this space.

Disease	**Infectious agent. Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Hookworm disease, ancylostimiasis, uncinariasis, necatoriasis.	*Ancylostoma duodenale, A. ceylanicum, A. braziliensis, A caninum* and *Necator americanus* Intestine.	Widely endemic in tropical and subtropical regions	B76 Variable light infections are often asymptomatic	Universal	None given	No evidence that immunity develops with infection	Humans for one two sppin cats and dogs for two others	Big disease in cattle but no indication that there is any transfer to man. Note also in cattle that an irradiated vaccine was successfully developed, perhaps it was a different kind of hookworm. CTx will usually work.
Loiasis, Loa loa infection, Eye worm disease of Africa, Calabar swelling	*Loa loa*Any body part but Particularly nasty in the eye.	Widely distributed in the African rain forest	B74.3 In some parts of central Africa ninety per cent of the population are infected	Universal	Chronic disease	None apparent	Humans, deer fly vector	Treatment often complicated by hypersensitivity effects. Difficult in many ways.
Disease	**Infectious agent.Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Onchercerciasis, river blindness	*Onchocerca volvulus* Skin and eye.	Restricted distribution in various tropical regions but 97% of cases in sub-saharanAfrica/	B73 Situation now very different in that the Onchocerciasis control program in W Africa has proved effective but previously a major disease causingblindness among many other unpleasant symptoms	Universal	None given	Reinfection can occur	Humans, transmitted by infected black flies of the genus *simulium*	Has been a major disease but the use of ivermectin as a larvicide in patients and black fly control measures are achieving good control it seems. Surgery sometimes used as an adjunct treatment.
Strongyloidiasis	*Strongyloidesstercoralis*and*fulleborni* Skin. And elsewhere.	Throughout tropical and temperate areas more usual in areas of high humidity	B78 Often asymptomatic	Universal	Immunosuppressed patients	Acquired immunity has been demonstrated in experimental animals but not in man.	Humans mainly	Ivermectin, often repeated will be effective.
Creeping eruption Cutaneous larva migrans.	*A. caninum. A braziliensis*Dermatitis, commonly feet and buttocks.	Most tropical and sub-tropical countries world wide	B876.0,B876.9	?	Those who regularly come into contact with soil. Contaminated with dog or cat faeces.	Commonly self limiting but no indication given of how.	Dogs and cats	Freezing infected areas
Disease	**Infectious agent.Target organ if any.**	**Location**	**ICD 10 entry. Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments, treatment?**
Toxocariasis,, visceral larva migrans	*Toxocaracansi*and*T.cati* Eosinophilia a common manifestation of diseasecan affect ceyes.	Worldwide	B83.0 Usually relatively mild, chronic rarely fatal. In some parts of the world the majority of children are infected	Lower incidence in older people largely because of lower exposure	Can be severe in children 4-14 months	Reinfection can occur. Viable larvae can stay asymptomatically in tissues for many years	Dogs and cats but infection often by ingestion of eggs from contaminated soil	A latent infection ina female dog can result in reactivation of infection and its passage to the pups through the milk. CTX but as the text remarks effectiveness of anti-helminthics is questionable at best!
Trichinellosis, trichiniasis, trichinosis	*Trichinella spiralis* And other spp. of the genus	Worldwide but very variable in incidence	B75Varies from inapparent infection to fulminating fatal disease depending on level of intake.	General	Commonly consequent upon eating poorly cooked pork. A major outbreak occurred during the first world war in a army group of whom some 1800 were killed.	Partial immunity is acquired (what does this mean, I suppose that there are no active worms but the encysted organisms in tissues remain intact)	A wide variety of domesticand wild animals, often in arctic regions	Effective treatment is available for both the intestinal and muscle stages In miceT-cell deprivation leads to increase in worm burden and reduction of thickness of cyst walls. (10).

Table 7: Diseases That Do Not Readily Fall Into The Categories Already Considered.

Disease	**Infectious agent, target if any**	**Location**	**ICD entry, Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments and Treatment?**
transmissiblespongiform Encephalopathies, Four examples are given in the 20th edition of the manualCreuzfeld-Jakob disease. Variant CJD Gerstmann-Straussler-Scheinker syndrome Fatal Familial insomnia	Prions Nervous system	Worldwide	A81.0 . A81.01 A81.09 Potentially enormous	Genetic differences in susceptibility exist in families that resemble autosomal dominants	NK except the genetic factors. All the ones quoted here are sporadic and not believed to be exogenously acquired though KURU and Iatrogenic CJD are of exogenous origin.. Sometimes long incubation times.	None demonstrable either in relation to adaptive or innate immune processes.		An extraordinary collection of diseases that has created great controversy particularly in relation to the human consumption of prions contained in bovine products.
Disease	**Infectious agent, target if any**	**Location**	**ICD entry, Impact**	**Susceptibility**	**Special risk factors**	**Immunity**	**Primary reservoir and vectors**	**Comments and Treatment?**
Pediculosis and phthiriasis	*Pediculus humanus capitis*(head louse)	Worldwide	B85Common infestation among schoolchildren everywhere	Universal	None given	None given	Humans	Tends to spread in families all of whom require CTX treatment.
Scabies, sarcoptic itch.	*Sarcoptesscabiei* a mite	Widespread, endemic in many developing countries but recent epidemics in the 'developed' world.	B86 Irritant wih intense itching	Universal	In immunodeficient andsenile patients can present as a general dermatitis	Fewer mites succeed in establishing themselves on previously infected individuals. Hyperinfestation tends to occur in immunosuppressed individuals.	Humans	Usually treatable

Table 8: Approximate Percentage of Diseases in Various Categories.

		Miscellaneous	**Trematodes**	**Nematodes**	**Fungi**	**Protozoans**	**Viruses**	**Bacteria**
Approximate Number of diseases in the various categories according to the taxonomic classification of the causal organisms		4	9	14	15	14	160	65
		Miscellaneous	**Trematodes**	**Nematodes**	**Fungi**	**Protozoans**	**Viruses**	**Bacteria**
Distribution	Worldwide	100	34	28	53	64	56	57
	Regional		66	72	47	36	44	43
The old classes given here relate to the issue of whether an outbreak of disease must be reported to WHO. The old classification is described in detail on pp XXJV-XXIX of the 17th edition.The new insertion of ICD listing in the 20thedition gives no indication of the severity of the diseases which to get some idea of what proportion are major threats is helpful. The severity classifications have in some instances changed over the years.								
Class.1 is most most serious, 5 least harmful. The classifications relate largely to reporting requirements.	1						2	3
	1A					7	4	3
	2A			7			22	12
	2B			7	6		2	31
	3A						6	2
	3B		11	7	6	7	26	12
	3C		33	7	6	50	4	
	4				18	7	16	21
	5	100	55	72	60	28	18	8

Impact	Large	25				7	20	11
		Miscellaneous	**Trematodes**	**Nematodes**	**Fungi**	**Protozoans**	**Viruses**	**Bacteria**
	Medium		22	50	26	50	44	57
	Small	75	77	50	74	43	36	32
Primary Target organ if any.	Intestine		66	57		36	8	20
	Lung				20	7	8	17
	Liver		22	7		7	10	2
	Lymphatics and Lymph nodes			7			2	6
	Lymphocytes						4	
	Nervous system	25				7	26	9
	Skin	50		7	66	7	8	31
	Eyes			14			6	6
	Others including sex organs							11
	Urinary tract					7		
	systemic	25		7	33	36	32	34
Susceptibility	Universal	75	100	100	60	64	100	95
	Resistance	25			40	14		5
Special risk factors	Malnutrition		11	7		14	2	6
		Miscellaneous	**Trematodes**	**Nematodes**	**Fungi**	**Protozoans**	**Viruses**	**Bacteria**
Immunity	Immuno-Suppression	25	11	7	27	50	14	15
	Pregnancy						4	
	Gender							8
	Embryos						4	
	Achlorhydria							6
	neonates							9
	young children	25	11	14		7	18	28
	Older children						4	9
	Adults			7			8	14
	Old people					7	4	12
	Occupational				13		6	9
	Other, such as diabetes general illness				7	7	2	18
	Trauma						2	12

Immunity	Prior antibiotic treatment							2
		Miscellaneous	**Trematodes**	**Nematodes**	**Fungi**	**Protozoans**	**Viruses**	**Bacteria**
	N/k			64		7	44	5
	N/k	25	22	57		64	16	34
	Cell mediated						2	8
	General immunity	25	11	14	20	36	80	38
	None or adverse effect	50	66	28			2	18
Vaccines	+						44	25
	--		100	100	100	100	56	75
Point of access	Skin		12	14	80	43	24	17
	Anus			7				
	Mouth		88	78	20	50	16	25
	STD				7	7	8	12
Transmission	Vector to man			21		21	24	17
	Animal to man					7	10	15
	Man to man	75			33	36	6	20
	Autoinfection			14		7		2
	Food	25	88	78		7	6	23
		Miscellaneous	**Trematodes**	**Nematodes**	**Fungi**	**Protozoans**	**Viruses**	**Bacteria**
	Air				20		28	8
	Soil							3
	Secretions, mucosal contact except sexual, but including respiratory droplets						28	17
	Water				7	21		11
	Inanimate penetration				7			
	Syringes						2	
Inapparent infection	+	25	100	50	20	86	34	14
	-	75		50		14	66	
Recrudescence of latent infection.	+	25	N/A	N/A	7	57	6	2
	-	75	N/A	N/A	93	43	94	

In some instances, as with Meloidosis, there is no evidence of immune mechanisms, but it does seem that the infecting organism persists in patients infected years previously who, subsequently, have recrudescence of infection on becoming diabetic. The Streptococcal, Pneumococcal and Staphylococcal organisms are all common components of the normal flora associated with skin and upper respiratory tract. All are associated with a variety of unpleasant diseases, but we are not sure in mechanistic terms why what was ostensibly a balanced equilibrium (13) between host and parasite becomes unbalanced, in favour, as it were, of the parasite and active disease ensues. All the organisms concerned are numerous in relation to the varieties they display and for none of them is there a clear immunological controlling mechanism. If, for example, illness leads to alteration of the equilibrium between host and parasite what aspect of the various immune mechanisms is affected and is there any way we can identify this and perhaps intervene purposefully?

Direct zoonotic infections are found particularly among those who, as part of their occupation or as carers of companion animals, frequently encounter animals. In other instances, a non-human vertebrate or non-vertebrate reservoirs of infection can be the source of transfer to humans by vector organisms. The disease status or not of the vectors is of considerable interest but not often considered. Invertebrate vectors, for example, do not possess the adaptive immune mechanisms which the vertebrates do possess as a class. If the transferred organisms capable of causing disease, which is sometimes controlled by adaptive immune mechanisms, what if any is the control mechanism for the invertebrate vectors? Also, the immune status of non-human vertebrate organisms that serve as reservoirs of infection after transfer to humans is worth exploration. It does seem that many organisms which can potentially cause disease in man exist in an asymptomatic state in the reservoir host animals. Could it be that the symptoms of disease in the vertebrate organisms are attributable to some facet of the adaptive immune response rather than being necessarily prevented by it?

Clearly in relation to bacterial infection there are many strategies of interaction. Rather little has been done with vaccines with bacterial infections largely because the majority, though not all, of dangerous bacterial infections can readily be controlled by antibiotics. Where vaccination against a bacterial infection has been deployed it has sometimes been against a toxoid liberated by the infecting bacterium, cholera for example, or sometimes derived from phage in the bacterium rather than a product of the parasite genome, *vide* diphtheria. It looks as if each organism as an infection and as a cause of disease must be explored in detail if what is referred to as evidence-based medicine is properly to be practised.

Viruses

The absolute number of viral infections in man is of the order of two hundred the majority of which are arboviruses which reach human hosts *via* an arthropod vector. Taxonomically viruses are diverse, and it could be advantageous to group them according to the taxon they belong to. This has not been done consistently in the Table 2 which in the main lists them alphabetically by the name of the disease or group of diseases they are responsible for.

Of the viruses, of which account has been taken here roughly one third lead to chronic often asymptomatic infection. The remainder generate acute infections in many instances with life-long immunity to further infection by homologous organisms. As to whether this immunity is built upon a germ-free immunological memory is a matter for discussion. There are few treatments for viruses that are effective and those tend to have adverse side effects. On the other hand, some vaccines have been deployed successfully and, in some instances, attenuated live organisms have proved superior to dead vaccines. It is interesting to speculate how, where there is long term immunity but no evidence of persistence in intact form of the infective organism concerned, the immunity is maintained. The gut bacterial flora has something of the order of one hundred times more genes than are present in the human genome and there are in addition an unknown but probably large numbers of species of viruses. It could be that material detached from the organisms in the alimentary canal does gain access to the main body of the host and offers a massive library of cross-reacting antigens that can mimic antigens on the offending parasite. Such material could serve to maintain a low level of active immunity it is not certain whether food constituents stimulate immune responses in the gut but evidence will be presented later that this is likely. If it happens regularly this in another way, aside from persistence of a parasite, that a state low level active immunity could be maintained. Whether this speculation in time proves to have a factual basis it could be that the vaccinologists could tailor their efforts to include the maintenance of active immunity based on materials from introduced genetically manipulated micro-organisms rather than entirely on what could be a fiction that long lasting memory cells maintain long lasting adaptive immune response.

The arboviruses constitute the biggest single group of infective organisms and probably overall the least known scientifically. They are transmitted by vector through skin puncture and the great majority of them can engender disease free infections with lasting immunity against superinfection and the development of active disease. In evolutionary terms these organisms must surely collectively be the most important in influencing the human condition during the millions of years that our remote ancestors were hunter-gatherers with no urbanisation. At a guess it is from the ranks of the arboviruses that the 8% of the human genome that is thought to be of viral origin was recruited [2]. The significance of this is not immediately apparent except perhaps in relation to HIV that is possibly in the process in time of being established with less pathology than is now apparently the case in the human species [3].

AIDS is regarded at present as one of the most dangerous of pathogens though in fact presently it annually kills fewer individuals than does, for example, hepatitis B virus or *Mycobacterium tuberculosis*. The menace of HIV derives probably from its relative newness and initially its apparent inexorability. One facet of this virus which needs attention is its presently demonstrated capacity for mutability leading to switches of antigenicity that enrage those seeking appropriate vaccines. It is tempting to wonder whether, from the viral viewpoint, switching antigenicity is not an attempt to evade what seems to be an ineffective host immune response but part of a strategy to seek rapprochement with a host that has not, presently, got the capacity

to make an accommodation response that would lead to a relatively peaceful co-existence. This is not particularly helpful to those presently infected with HIV who may die before the rapprochement formula is achieved but there is little in Nature to suggest that survival of all individuals by right, a view driven partly by the remarkable successes of our medical profession, is what happens in what could be termed the wild world.

When the myxomatosis virus was introduced into Australia in the 1950s, after a first failed trial, it began to kill the offending rabbits on such a massive scale that it would have been predictable that there would soon be no rabbits in Australia. In fact, this is not what emerged. Although it might seem likely that the surviving rabbits had been selected for resistance to the relevant virus, those who have investigated the phenomenon have shown that it is certain that the virus that changed. It is not as pathogenic as the form that was introduced into the continent [4]. Thus, in host/parasite interactions it has perhaps to be recognized that there are two life strategies involved of which mutability of the parasite is perhaps the more rapid in achieving co-existence. The immune response of the hosts in these circumstances could be orchestrated by the parasite as part of an overall accommodation system between host and potential parasite rather than the development, selectively, of genetically based resistance to the virus by the host.

CMV is a rather different example of viral infection from HIV or the arboviruses. In developing countries, it is usual for all the adult human population to be infected. It can cause problems in immunosuppressed individuals and one wonders why infants *in utero* who ostensibly, before the age of say twelve weeks of gestational age are immunologically incompetent, are not all killed by the viruses of their mothers. As it is a small proportion of infants are infected *in utero* and of them only a small proportion (10-15%) develop disease caused by the virus. What are the factors that lead to the harm done to an exceedingly small proportion of perinatal infants? It is likely that the mother transmits anti CMV antibodies across the placenta and that these are passively effective in preventing infection of the developing foetus. Presumably, the protective effect of such antibodies in inhibiting the establishment of infection is lost as maternal antibody declines during the six months post-partum. Alternatively, the relationship with CMV may under normal circumstances in the mother be such that infectious viral particles are rare. In terms of the Topley and Wilson 'equation' (see the text below the reconciliation document) the dynamic equilibrium in this instance usually favours the host. Whatever the answer to these conundrums it is clear that there seems to be an immune response to CMV, but it is not associated with rejection of the parasite. It is intriguing to note that related CMV organisms found in animals simply are not found in man. Is it that human beings have learned how to reject these potential invaders or more simply those animal viruses simply do not have the capacity, perhaps lacking appropriate receptors to enable them to enter human cells? A comparable example would be the total incapacity of diphtheria toxin to kill mouse cells to which it cannot bind whereas human cells are acutely sensitive to the same material. It is important to consider these issues of host predilection in coming to an understanding of the interface between man and those organisms that can invade him with potentially detrimental effect. The immune response has been created by immunologists as an all-purpose reaction system capable of responding to any foreign intruders which it probably is not. But, more importantly, most 'foreigners' almost certainly simply do not have the capability of living in the human body. This is not an example of a host defence system but rather more a demonstration of what is self- evident that not all organisms are able to react with all other organisms.

Hepatitis C virus is an extraordinary example of menace to humans. Firstly, it is said by WHO to infect at least 60 millions or so of all living humans *cf* HIV with 40 millions. Secondly, few (less than 10%) of those infected realise they are infected. Thirdly, a high proportion of those infected (80% perhaps) become chronically infected essentially for the duration of their natural lives. Fourthly, a major problems is that a proportion (roughly 30%) of those chronically infected takes between ten and forty years to become clinically apparent. Fifthly, we know virtually nothing about the immunological interface between man and HCV. Antiviral antibodies are produced but, in the present state of our knowledge they have no significance in relation to the staging of the disease. This raises an intriguing issue as far as intervention is concerned. Most vaccines are developed in order the better to prevent infection. Whether infection is in fact prevented or whether what happens is that disease, because of infection, is prevented is an issue that needs to be argued out in relation to each host/vaccine combination. We simply have little idea how to vary an ongoing immune response. In this age of molecular biology when almost any conceivable vaccine can be produced there are, nevertheless, presently few positive leads on so called therapeutic vaccination. In terms of the Topley and Wilson 'equation' (see the text below the reconciliation Table 8) we have a long way to go to balance the equilibrium in favour of the host as far as HCV infections are concerned. Prevention is a possibility as HCV infections is closely correlated with poor parenteral practices in hospitals and in the back streets, essentially reuse of poorly sterilised needles. It is thus a modern and preventable disease, recognized only twenty-five years ago (after a long period as non-A, non-B hepatitis virus). HCV is also, paradoxically, one of the few viral infections which is 'cleared' by the host for reasons that are far from apparent. Recently effective treatments for the condition using sofosbuvir or simeprevir have been applied and thus the issue of their immune status from a practical point of view is less pressing.

Before leaving the hepatitis viruses, that have no taxonomic affinities, it should be noted that before successful vaccination against HAV and HBV was started they infected roughly half the population of the world and the proportion even now will not be much less. Collectively the viral hepatitides constitute what is one of the biggest single health hazards to our global populations. A point that emerges from an overall look at viruses is that relatively few of them kill the majority of those infected. HIV presently is an example of a slow viral infection that is lethal in many instances though commonly many years after initial infection. Rabies virus is thought always to be lethal but, according to the (17th edition of) the manual, only forty per cent of those bitten by rabid dogs in Iran died consequently. Was the majority immune? If they were immune was this an active process involving

activation of the host immune response or was it failure of the virus to grow in an environment with which it has little experience. In many animals' rabies viruses exist in an asymptomatic state. Did this happen in the lucky Iranians?

Along the same lines Lassa fever viruses were likely to cause the most enormous havoc when the first American cases were taken to the States. There seemed no way of stopping the virus [5]. And yet it did stop and, when those parts of the world in which the virus is endemic were looked at more carefully, it was discovered that some ninety per cent of those infected remained asymptomatic. Again, the question arises as to whether the population of people concerned have been genetically selected for resistance to the virus. To my jaundiced eye this seems unlikely but, clearly, the resistance of the human populations to the viruses concerned in certain parts of Africa is greater than that of those few unfortunate Americans who initially met the virus in the USA. The mechanisms involved would merit investigation.

Protozoa

The protozoa offer a very mixed bag of chronic infections including malaria that is one of the major killers in those countries with infected mosquitoes. All the diseases seem to be treatable by chemotherapeutic attack upon the parasite though clearly those with a higher parasite burden and more complex invasion patterns are more difficult than the more superficial infections. (Leishmania, dermal and visceral indicates the contrast though there is also the issue of different species of infection being involved.). In a few instances immunity that is solid and long lasting seems to be acquired, i.e. the patients are disease free. As to whether they are chronically infected seems not actually to have been seriously addressed. In the instance of such a disease as malaria it seems likely that chronic persistent and asymptomatic infection is the usual condition among the indigenous population. Infection, it is assumed, from the prevalent sp. of malaria occurs in almost all infants soon after birth and in perhaps 15% of instances proves fatal without intervention. The great majority who survive these early infections probably remain chronically infected for the remainder of their lives or are perhaps continually re-infected without usually adverse effects. Is this state held at bay or maintained by the immunological apparatus? It depends how you think about it. Is anything known about the precipitating factors in an episode of malaria among the indigenous population most of whom will be demonstrably parasitaemic throughout their lives? This seems to be the kind of question like trying to find out why individuals in more temperate climates suffer quite often from the so-called common colds. It is not that there are no answers but there are many reputed risk factors often based on totally fallacious thinking (Table 3).

Trypanosomiasis attributable to the transfer of an infectious flagellate organism from another human or animal by means of various invertebrate vectors can be a most unpleasant disease but an interesting characteristic of the organisms concerned is that many of them can vary their antigenicity [6]. The usual interpretation of this fascinating property is that the invading organism is trying to avoid the immune responses of the host and of course this is a possibility. It can however be argued that the parasite if trying to persuade the host that it can produce an immune response capable of sustaining the relationship between the host and the parasite and incidentally providing edible and nutritious antibody for the parasite to take in. Such a notion does not fit with the standard paradigm of many immunologists and clinicians who commonly suppose that the parasite is trying to harm the host rather than to seek an accommodation slip. It is worthy of note that for example *T. musculi* which can ostensibly live in perfect harmony with its natural host mice [7] shows no capacity for antigenic variation but it might if transferred to a host where neither of the two components of the interaction had experience of each other.

Is disease potentially an immunopathological event and, if it is, should we better target the immunological apparatus rather than the parasite? It depends perhaps on a comparison with side effects and what if any are the collateral effects of interference with the immunological processes. In Ian Clark's experiments in mice [8] in which he successfully converted a potentially lethal plasmodial infection into an asymptomatic inapparent interaction by simple prior reduction in the capacity of the host to make TNF, there seemed, in the short term, to be no adverse effects. If immunopathology constitutes the major mechanism of the symptoms of diseases, as will be urged later, these tables contain interesting clues as to how inapparent infections are created and or maintained. For example, in relation to amoebiasis the very young seem only rarely to be affected by disease. Do they acquire the parasite without immunopathology or can the parasite for some reason not prosper in young organisms? Whatever the answer, there is, perhaps, a clue here to symptomless host/parasite interactions.

In eight of fourteen of the protozoan diseases immunosuppression is a major risk factor in rendering disease more severe. This suggests that immunity is a major defence mechanism but this conclusion, unalloyed, must be regarded carefully. In almost all circumstances that immunosuppression occurs there are many collateral effects any one of which can have major physiological consequences that could affect host/parasite interfaces. It is intriguing to note that so far there are no vaccines available for any human protozoan disease despite the strong evidence that immune mechanisms are important in relation to most protozoan parasite/host interfaces. Surely those indigenous human host populations in Africa who live with malaria all their lives are essentially 'vaccinated' and there only arise major problems (idiopathic tropical splenomegaly, for example) in relatively small numbers of those concerned. Of course the problem is made more complex in relation to malaria by the existence of at least three major pathogenic species but is it beyond our wit genetically to tailor a parasite having epitopes common to all three that could serve as components of a live 'attenuated' vaccine? The fancy methods that are being proposed to vaccinate against malaria (point of entry molecules and so on) perhaps will not succeed against such a complex organism as are protozoans with a very reactive plasma membrane capable of many changes when attacked or indeed ingestion and digestion of attached antibody molecules. Antibody can of course inactivate and kill parasites but it is not difficult to imagine scenarios where the rate of production of antibody and parasite is in balance or, as has been shown in mice infected with *T. musculi*, the parasite is restricted by antibody to a particular region of the body [7].

Fungi

There are some fifteen main fungal diseases, all chronic with often different presentations and pathogenicity according to the organism responsible. Three of the fungal diseases (candidiasis, aspergillosis and cryptococcosis) almost only occur as secondary to other debilitating conditions all of which could be said to involve immunosuppression. The clear inference is that the immune response normally keeps the relevant invaders out or prevents them creating disease. This needs looking at on a case-by-case basis. For example, contact with cryptococcal spores occurs almost daily in those crossing Time Square in New York but cryptococcosis, the disease, is only seen in few already sick individuals. The 'resistance' to infection is almost certainly primarily the physical barrier of the lung mucosa that is capable of capture and exclusion, perhaps by ciliary action, of considerable numbers of the spores. Is this equivalent to resistance based on a particular capacity of the adaptive immune system? In my view it is not largely because, in normal mice, if the physical barrier is circumvented by giving very few spores as an intravenous injection, death is likely. A similar argument could be applied to the entry of *Aspergillus* conidia though experimental evidence in support is not, as far as I know available. A rather similar argument could be used for apparent resistance (so-called) of humans to the infective agencies of Chromomycosis and Mycetoma, ie if the physical barrier to entry is disrupted or defective by for example cuts on the feet then the fungi concerned can occasionally get a toehold and cause harm (Table 4).

For the other disease that occurs as secondary to a pre-existing disease condition, Candidiasis, it is less easy to point to a particular portal of entry or specific weakness related to allowing fungal proliferation. The adaptive immune response may be the main defence against *Candida* but the argument for any significant adaptive immunological controlling mechanism is not strong. *Candida* infections for example are ubiquitous and, as is related in the manual, the organism is regarded as part of the normal skin and mucosal surfaces which any way are presumably the portal of entry of the organism. Is this normality imposed by the immune responses of the host or more simply due to failure of the infecting yeast particles to gain entry to the body except when it is in various ways debilitated? Whatever the answer there is a point of dispute on the present evidence as to whether the adaptive immune responses maintain the normal symptom free condition.

For only one of the fungal infections, Coccidioidomycosis, is it evident that there is a powerful and long lasting immune response capable of rejecting systemic infection. In Blastomycosis the case is not made, as the evidence is incomplete as presented in the manual. In Coccidioidomycosis, infections that have no clinical consequences are common but pathological disease is rare. Further some disease arises because of reactivation of latent infection consequent upon acquired immunosuppression. Here it can be argued that the adaptive immune response is an important regulatory mechanism at the interface between the fungus and its host. But it also must be considered that, under normal circumstances, the immune response comes to an accommodation with the invading fungus that can be stable and maintained over long periods of time. There is no evidence that the quoted long-lasting immunity is associated with the rejection of the parasite. It simply betokens resistance to the development of the disease. It would be intriguing to investigate this fungus/host relationship to see exactly how the putative accommodation is achieved, what element of the fungus is recognized by the adaptive immune system of the host and what exactly goes wrong with it when overt disease erupts? It at least must be considered that the fault lies not with the parasite itself, as it is difficult to see why it should have changed, but with the development of immunopathological changes consequent upon alteration of the physiological controlling mechanisms of the immunological apparatus of the host. If this is the case attack upon the fungus may not necessarily be the only or even the most satisfactory way of reducing the disease condition.

Dermatophytoses seem to cause inconvenient conditions which are not life threatening. The implication is that the potential invaders are common and that repeated contact with them often in circumstances of slight abrasion can lead to the development of largely minor infections in which it may be that the adaptive immune response is in no way implicated. The barrier to entry to the skin is keratin and under most circumstances this is enough to prevent access to any deeper tissues. In such circumstances attack upon the fungus to reduce the irritation would seem to be the right strategy. Mucormycosis is perhaps a different case. There the attack upon underlying tissues almost seems to be directly due to erosion by the fungal hyphae rather than consequent upon any immunopathology. The details given in the manual of the lesions are insufficient to make any proper comment. The evidence for any immunological control of the fungal/host interface is, as presented, weak. Attack on the fungus would nevertheless seem *a priori* to be reasonable and probably the only way of control of the disease

Histoplasmosis is a relatively common condition with evidence that there is recognition by the adaptive immune response of the causal organism (80% of some individuals in endemic areas can be histoplasmin positive on testing). In the manual the phrase 'inapparent infections are common and usually give increased resistance to infection' is somewhat ambiguous. It could mean that there arises a state of immunity from inapparent infections that involve the adaptive immune response, and this immunity inhibits the development of disease because of (further?) infection. It could perhaps mean that the mucosal surfaces are protected by, say, secreted IgA antibodies that reduce or inhibit entry to the various organs systems that can be harmfully affected by the fungus. If this is the case a specific mechanism can be postulated and searched for and, if found used to monitor susceptibility to disease or indeed used as a target for maintaining resistance, by for example transmucosal vaccination. Clearly here, as is true for paracoccidiomycosis, coccidiomycosis and sporotrichosis - we are too short of information to make any satisfactory conclusions about mechanisms of resistance.

Reasonably effective fungicides exist for most but not all the infective fungi. What is however to be noted is that whereas with the fungal infections the word resistance is used in many instances in relation to the fungal/ host interface this is not so for most other host/parasite interfaces. It should be noted that the scientific

literature presently contains many papers arguing that both innate and adaptive immune mechanism are active against fungal invaders and it may be that they contain significant truths nevertheless in experiments conducted by the present author and colleagues expert with the organisms in question, many years ago, it was possible to show that overall T-cell deficiency affected neither the speed nor final result of experimental infection of mice with either *Candidaalbicans* or *Cryptococcus neoformans*. Since those times (mid 1970s) the sophistication of immunological experiments has much improved and it may be that the more simple experimental models we adopted at the time are no longer useful. A recent review summarises what are regarded as presently tried methods of manipulating the immune response to offset the consequences of fungal invasion [9]. Having read the review, which is thorough, it gives many indications of improvement of immunological status in sick patients which in a variety of ways have been incapable of exercise of immune functions as found in normal individuals. It is not easy in the patients considered to define exactly how the complex immune functions are impaired and, perhaps for this reason, there areeven now no clear strategies put forward for the evidence-based amelioration of the immunodeficient immune states involved. It would nevertheless be useful for those who write the Manual to look carefully at the evidence presented by Loreto and his colleagues.

Trematodes

The trematodes induce a variety of chronic diseases one of which, schistosomiasis, figures on the 'wanted' list of WHO. No vaccines are quoted as available as is nearly true for all the eukaryotic (and fungal) parasites of man. Effective CTX exists in most circumstances. The transfer of infection often arises due to eating habits, usually either raw fish or improperly cooked meat. Immunity if any seems a variable feast. These organisms seem to exist in the host independent of immunity with the severity of infection determined simply by the number of infective organisms that have got in. Adverse consequences in some circumstances are due to redistribution of the parasite from an adult to larval forms that, in various encysted conditions, can be dangerous as space occupying lesions with the additional problems in some instances of eventual disruption with liberation of a variety of pharmacologically active substances (Table 5).

Nematodes

All the infections included are chronic a few of which are nasty. Most are to be found in tropical countries, a few worldwide. Universal susceptibility seems to be the rule. In no instance is immunity recognized and quantified. Our own work on *Trichinella spiralis* indicated clearly that in experimental mice a T-cell dependent immune response could regulate both the number of muscle encapsulated larvae and the thickness of the capsule wall – it was much thinner without T-cells [10]. My guess is that vaccination could influence some of those organisms that gain entry but that for others, such as pin worms that are relatively benign and remain outside the body, it would be of no significance. There are some five quite serious diseases among this collection on several of which the WHO has declared war. The Onchocerciasis efforts seem to have been reasonably successful. In general, there exist successful chemotherapeutic strategies of elimination. Except of pin worms, no person to person transmission, *pace* strongyloidiasis in relation to which auto-infection is common. For all, except anisakiasis, reasonably effective anti-helminthic drugs are available. There seems not to exist any information on immunity or otherwise in treated patients (Table 6).

Miscellaneous

There is little to be said about this miscellaneous category except that it includes a disease that in cattle and in man has led in parts of the world, particularly in the UK to huge losses of money and some loss of life, largely in cattle. The disease concerned is one of four recognized prion diseases that are, ostensibly caused by accumulation of deformed protein molecules that in some way or for some reason have evaded or overwhelmed the standard mechanisms that exist for shaping proteins in a specific and appropriate way [11]. The reason for the infectiousness of the prions is not clear although a Nobel prize has been awarded for their discovery. Prions in the sense of deformed protein molecules are common occurrences. What is less clear is why under certain, ill-defined circumstances things 'go wrong'. The issue of immunity in relation to prions seems on the face of it sensible as deformed proteins can elicit immune responses that relate to the deformity but, so far, immunity to BSE seems not to be on the cards (Table 7).

Reconciliation

As far as distribution is concerned about half of all recognized disease-causing organisms are worldwide in their distribution. In these days, when travelling between continents is common, this proportion may increase in time. The restrictions on distribution in part relate to differences in distribution of vectors such as mosquitoes, ticks and sand flies of particular kinds. It is also clear that many diseases are more common and rampant in tropical developing countries than in the temperate regions. The class of organism was put in for the sake of completeness and will not comment further on here except to point out the obvious fact that the more severe and dangerous diseases are largely caused by viruses or bacteria. If we were to look at domestic animals that in the tropics are ravaged by a wide variety of protozoan parasites a different story would emerge. Diseases in cattle in Africa include, on a potentially enormous scale, Trypanosome and Theilerial infections. For this table the old WHO classification which gave an indication of the reporting category to both local and global health authorities has been retained (Table 8).

The impact classification indicates roughly how important a disease was but the one plus, two plus, three plus categories adopted are too crude and of necessity applied arbitrarily. In some instances, the numbers of people dying annually are recorded but in some instances this is not stated in the Manual. The various diseases in addition to their lethality and morbidity, that impose strains on the health care services, have economic consequences on for example the labour force. There are other sources of information dealing with these issues, but overall figures of economic impact would perhaps be useful for PH officials to get some idea of the import of the diseases in question. These things are not written in criticism of the Manual,

that clearly is written for American practitioners primarily but, faut de mieux, there seems little else enabling a global look at communicable diseases and the Manual does not confine its approach to diseases that are only significant in N America.

The target organ category looks at in broad terms what seem to be the primary disease sites. Clearly with many of the diseases in their worst and later manifestations major organ failure will be common often starting with the lung and heart. There are one or two things that stand out, ie the neurotropicity of some viruses emerges as does the predilection of bacteria to cause skin disease. Many of the diseases are recorded as systemic in relation to protozoa, bacteria and viruses. One of the most striking things that emerged is the high frequency with which it is recorded that susceptibility is universal or widespread. With the exception of the fungi and to some extent protozoan infections almost all human hosts, as far as we know, are susceptible to invasion by all the disease-causing organisms. There are very few exceptions. All the organisms to which attention is drawn cause disease in the broad sense the human species is, *ipso facto,* susceptible to the diseases in question. What the manual shows many times is that susceptibility to invasion is in many instances not a good indication of whether disease will develop. Nor, if disease does develop, what will be the outcome. Rabies virus, for example, in Iran it is written in the 17th edition, only caused disease in 40% of those known to have been bitten by rabid dogs. On the other hand, the statement that when the disease caused by rabies virus develops it is always lethal indicates clearly the difference between being infected and developing disease. It should also be noted that a comparable statement does not exist in the 20th edition. In foxes epidemiological studies [12] showed that disease was more rampant when the fox population density was highest. Is it ridiculous to see such organisms as rabies being part of the strategy for population density control at least in some wild animals!? There are many organisms with which we come in contact that live within us without causing disease or which do cause disease relatively rarely but not in a manner that leads suspicion to fall on a named organism. CMV is not far off such an organism nor, perhaps, is EBV. Both the organisms in question are essentially ubiquitous but only rarely cause disease.

There is a lovely statement in the 1964 Topley and Wilson, Vol 11 [13] as follows:

'The scientist shares with Humpty Dumpty the privilege of making words mean what he/(she) likes. But if we are to avoid confusion, we must at least give our words definite orders and see that they are obeyed. It happens that the state suggested by the word that we have chosen as a generic label for the phenomenon we wish to study is one about which we know extraordinarily little; because the study of true immunity, in the sense of complete natural insusceptibility to infection, does little to illuminate the relations of host and parasite that are our chief concern'.

It is a minor paradox that since 1964 our understanding of the genetic basis of susceptibility to infection on the one hand and development of disease once infection has occurred seems to have evolved relatively little. (*pace* the nice work that has been done largely in experimental systems on the genetic basis of the quantity of immune response to certain defined antigens. As far as I know this kind of work has not been extended to the more earthy fields of parasitic disease). Perhaps the genes we are looking for are for susceptibility to infection that really does seem ubiquitous. Perhaps we should be looking for other genes or other environmental factors that make this susceptibility to infection at least occasionally hazardous because of the development of disease. In standard thinking for susceptibility to infection to be a genetic characteristic it would seem sensible to suppose that there are advantages to the organisms that will become infected. Is this an outrageous suggestion? Man, for example, is a huge conglomerate of organisms with bacterial genes in all the mitochondria and 8% of the whole genome initially of extrinsic retro-viral origin. As Todaro [2] suggested many years ago the possession of viral genetic material may be highly advantageous particularly in enabling constant replacement of epithelia, even if it carries the occasional disadvantage of making development of cancer, usually in old age, more likely. Surely, we did not acquire all these other organisms that are an integral part of our make up without susceptibility to infection being genetically determined? Can it seriously be suggested that infectious disease does not have an evolutionary impact? The hackles of all the immunologists and parasitologists will rise with such an idea as the war game within which they plot their experiments and house their thinking is itself attacked as not necessarily the natural way of thinking about host/parasite interactions.

Nevertheless, as Topley and Wilson in the same introductory context go on to write, '*Our main business is with those interactions between host and parasite that are characterised by a fluctuating equilibrium, and with the factors that shift this equilibrium, so that sometimes the parasite, sometimes the host, gains the upper hand*'. Special risk factor analysysis, reveal some of the mechanisms that shift the Topley Wilson equilibrium referred to above.

As far as immunity is concerned in some instances there are no known immune mechanisms afoot. This corresponds to what I, to my surprise, found in the experimental systems which my colleagues and I developed in the '70s. I also note that most but not all viruses seem to elicit immune responses. The view among many immunologists is that the adaptive immune response is all purpose and designed to respond to any antigen, but this seems not to be entirely true. Not all infective organisms elicit immune responses. Perhaps the most evocative experience which justifies such an alarming statement derives from some studies fifty or so years ago which gave what we thought at the time was a totally negative result and would therefore be unlikely to be accepted for publication. In retrospect the study provides much information which is fascinating. My colleagues and I had conducted a reasonably systematic study of the histopathological consequences of stimulating, or not as the case turned out, the adaptive immune response. We used sheep red cells as tried and tested means of eliciting a response in mice and with a slightly different intent, oxazolone a powerful inducer of delayed type hypersensivity. We used pneumococcal polysaccharide as a third material as the response of T-cells to that was probably negligible. These T-cells, which we had played a large part in discovering, were, not surprisingly, a main interest for us. We discovered that there was a regular repeatable sequence of histopathologically perceptible stimulation of cells in responding lymphoid organs. Mitotic activity involving T-cells was

followed by the development of germinal centres and the appearance of antibody forming cells (ref 23 leads to the published versions of this work). The picture was clear and being ambitious we elected to look at what happened when gnotobiotic mice were taken out of their bacteria proof containers and exposed to bacteria for the first time. It there was an adaptive immune response to such a huge influx of antigenic material we felt it would have spectacular consequences putting what we had found with sheep red blood cells and oxazolone to shame. We found that when put into clean boxes the retrieved gnotobiotic animals died overnight. Our microbiologist said it was due to opportunistic infection by *Clostridium difficile* or a similar organism. This finding offers another obvious lesson which will not be spelled out here. We then took out the gnotobiotic mice and put them into boxes that had been used by mice and which were festooned with mouse faeces. They all lived and seemed incredibly happy in their new environment. We culled five off these mice each day for ten days using gnotobiotic and normal mice as negative and positive controls. From each mouse we retrieved the Peyer's patches, the mesenteric lymph nodes, and the spleen all of which were prepared for histopathological examination. The 450 or so sets of slides were coded and read blind by an expert in the histopathological consequences of elicitation of an adaptive immune response. The result was to us, at the time, felt to have been a total waste of effort. Aside from a few metamyelocytes in the spleens of the 'contaminated' mice there was not the slightest sign of any immune activity. As a slight bonus, of which we thought nothing at the time, the germinal centres in the Peyer's patches of gnotobiotic mice were the same in number as those from normal (laboratory bred) mice, We seemed to have an answer to a conundrum which had puzzled us for some time – does a mouse, or a human being for that matter, make a vigorous adaptive immune response to and keep control by such means of its gut flora. As far as we could see from our massive, properly controlled and blindly read study the answer was no. The humble earth worm that, along with the other triploblastic invertebrates, does not have an adaptive immune response, must be grateful, nevertheless, for being able to ingest, every day, a diet largely consisting of microorganisms without adverse consequences. Huge contemporary interest in the microbiome is illuminated in part from the negative outcome of our study. The signs of adaptive immunity in the gut associated lymphoid aggregates of gnotobiotic mice suggests perhaps that standard feed components play a role in the lymphoid activity in the normal GALT (gut associated lymphoid tissue). There are other indications that the immune response to introduced biochemically complex living organisms is only a pale imitation of what might have happened if responses to all the potential epitopes capable of eliciting an adaptive response had been enabled but, sadly, this is not the place to pursue such a line of thought.

As far as vaccines are concerned the lack of some of these in relation to disease is related to the fact that it is has not been a commercial proposition to produce them. I have not seriously addressed the issue of whether live or dead vaccines are to be preferred. This is an argument that needs more space than is available here. There is however something that needs to be written. Some dead vaccines lead to lifelong immunity, for example diphtheria toxoid and to a great extent tetanus toxoid. The immunologists are in the main happy with this as they suppose perhaps rightly, that the immunological orchestra (Lancet leader 1967, 185-186) has a clear memory of the music it has played in the past. If that is true then, all the various categories of memory T and memory B cells with which the immunologists play games are secure and reasonably part of the mantras with which they punctuate their days. Also, it could seem quite ridiculous to suppose that there is an ongoing response to the injected toxoid when it was administered sixty years previously.

There are nevertheless various possibilities other than the immune response, like the nervous system, possessing a long memory. For example, after administration of the toxoid the immunised individual might have encountered the relevant bacterium (carrying the relevant phage that codes for the toxin) and taken it on board as a chronic asymptomatic infection in relation to which there is a continuous ongoing immune response that, under normal circumstances is stable; the fluctuating equilibrium that Topley and Wilson allude to but with no significant amplitude to the fluctuations. There is another explanation Corynebacteria are not uncommon neither are bacterial toxins. Also, the host organism has an enormous library of bacterial species with which it is in continuous intimate contact. Is it impossible that, given the initial priming injection with toxoid, the response is maintained as an ongoing affair by epitopes that are found in the host but which without the priming injection will not elicit sufficient immunity to negate any marauding toxins? If this is the case can vaccinologists, as suggested previously in this document, tailor the gut microbiota to deliver the required trickle of cross reacting antigenic material? In veterinary practice the concept of trickle infections, particularly in relation to multicellular parasites, is thought to play a role in maintaining resistance to further infection.

The design of vaccines could perhaps be influenced by such considerations as these. Now it seems largely to be determined by the classic view of the immunologists that sterile immunity is an achievable state. The evidence in the manual suggests that it is not common nor one to which is it necessarily reasonable to aspire. As far as the point of access category it is not particularly helpful. In many instances in a parasite gains access through the skin and that at the site of introduction there is an inflammatory lesion. If I were a parasite and I wanted to creep into the host in the dead of night and kill him or her stone dead and quickly I would not advertise my presence. I would not be antigenic. I would hide my light under a bushel (or whatever is handy). I would certainly not alert the host to my presence by bringing all his various inflammatory foot soldiers to the shore on which I had landed. Have we got it wrong? Is the parasite quite deliberately trying to persuade the host to produce a reaction that if it is successful will lead to a state, as Topley and Wilson put it, of (safe?) fluctuating equilibrium?

As an experimentalist I was much influenced by some experiments we undertook with mice some of which were variously immunologically impaired. Basically, the animals concerned were prepared to have either a normal or a deprived complement of T-cells with all the relevant controls that I will ignore as they did not detract from our conclusions. I want to draw particular attention to some work we [7] did with *Trypanosoma musculi*. This is a parasite that is

found in various species of small rodent. As far as I know in the wild it does little harm. In the laboratory in normal mice injection of as few as one live tryps would give substantial otherwise asymptomatic parasitaemia evident from twelve days or so and declining quite quickly twelve days later. The infected animals gained weight at the normal rate and, as far as we could tell were hale and hearty. Their spleens, unusually for laboratory mice, were replete with very healthy-looking germinal centres indicative of an ongoing systemic immune response. The infected animals were solidly resistant to further challenge. For the parasitologists, with whom I was working, this was an indication that the parasite had been exterminated and that the immune response was doing what it should do. In T-cell deprived mice a different story pertained. The parasitaemia developed at the same rate but continued to grow often over many months with eventually a fulminant condition arising and death following soon afterwards. This clearly shows that without T-cells control over the growth of the parasite cannot be achieved. 'Cell-mediated immunity in action' mutter the immunologists sagely. But was it?

I persuaded my parasitological colleagues to look at recovered normal mice for live parasites as we had a sensitive infectivity test. Eventually they found them in the kidney in an extremely healthy condition and ostensibly doing no damage. The tryps would be spending their days bathed in antibody (dare it be said that this was probably their main food?). Thus, in the absence of T-cells the infection eventually led to disease and death. In the presence of T-cells antibody was produced in buckets full and the parasite, albeit on a restricted scale, lived on. I found it difficult, with this example, not to suppose that the immune response functioning properly was responsible for safe retention not rejection of the parasite. It was in fact probably the most important factor in maintaining the equilibrium between host and parasite [13] without, in this instance, any obvious pathology. My hard-working parasitological colleagues, for whom I should say I had and still have the greatest respect, went on to try to persuade the parasite to 'come out' from the kidney otherwise there would not be, *pace* predation, any continuity of infection. In 'hyperimmune' mice with infected kidneys they tried steroids and, post-thymectomy, total body irradiation and restorative implantation of fresh syngeneic bone marrow to produce animals with few T-cells but nothing disturbed the equilibrium until, one day, in a burst of genius, they discovered that pregnancy in long term infected normal mice led to parasitaemia (personal communication). There were no adverse consequences noted of this disturbance of the equilibrium which could anyway be designed to pass the parasite to the foetuses. Sadly, we did not look for this. This small example coupled with much other evidence inadvertently provided by APHA began to push me to the view that the war paradigm of sterile immunity in relation to parasites was not totally satisfactory.

The last categories in the reconciliation table show that many infections can be asymptomatic and that some can recrudesce after long periods probably of equilibrium. The immune status of organisms with latent infections is not adequately researched but such research could be helpful in enabling us to decide which patients are likely to be stable with their latent infections. It is already known in AIDS patients in which latent infections, often of *Pneumocystis carini* or *Mycobacterium tuberculosis,* are thought to become active but the exact reasons why, except to show that in the broad sense the immune mechanisms probably regulate the equilibrium, is obscure. Also, as far as *Mycobacteria* are concerned, it may also be that a different sp. to that of the original infection causes the later problems. The main diseases that kill many humans globally of which, incidentally, there are very few, all show more infected individuals have few if any symptoms. Particularly for tuberculosis the statement that 90% of those in regions of the world where the disease is indigenous show no symptoms when first encountering the organism but are nevertheless probably carrying the *Mycobacterium* which causes the disease for life illustrates what seems to be counter intuitive.

Overall Discussion

Biological Advantage

The most usual method of teaching Biology without evocation of Special Creation, which will not be done here, is to suppose that a process of evolution of living organisms has occurred. The fossil record supports such a way of proceeding and the monumental work of Darwin, on the selection of advantageous forms of life capable of better succeeding in our diverse global climate, provides a framework for the process to occur. The relatively recent discovery of the genetic apparatus in the early days of the last century [14] offered a mechanistic basis for evolution to occur by selection of genetic constructs, point mutations as they are often called, offering survival advantage to their possessors. The role of point mutations in the process of natural selection will not be queried but it will be suggested, based on the survey of the APHA handbook, that it is far from the only method of genetic selection that exists. Most recent biological teaching, to make sense of the tremendous morphological diversity of living organisms particularly the multicellular eukaryotes of which the human species is an example, has continually posed the questions involved in deciding on the possession of properties of biological advantage. For example, the fins of fish facilitate their movement in a liquid environment, the wings of birds enable them to move in air, the possession of chlorophyll by many plants enables them to fix solar energy, a process on which humans are presently totally reliant, and the hair of mammals helps to keep an homoiothermic organism such as *Homo sapiens* warm in cold climates. Students of biology have laboured over such issues ever since Darwin published his groundbreaking study on diversity as the basis of biological evolution but it will be suggested that the concept of monophyletic evolution of single species should be queried and replaced by an alternative with many species of organisms working together to constitute the units for evolutionary advancement.

Communicable Diseases and Vaccination

It is about such studies, exploring the biological advantage of possession of an immune response, that the present review of communicable diseases in man has been conducted. On the face of it, organisms that can invade and clearly in some instances harm humans seem to constitute a selective disadvantage and the immune response seems tailored to overcome this disadvantage. The contemporary social, disruption following the emergence and depredations made on the human species of the SARS-CoV-2 virus which can give rise

to the Covid-19 severe respiratory disease, and the apparent failure of the immune mechanisms always to act protectively, underlines the importance of this manner of thinking. The standard way of getting round the problem is to evoke prophylactic vaccination, a process known in outline for centuries. Edward Jenner is often given great credit for showing, in 1798, that vaccination, in humans, using a form of smallpox 'vaccinia' virus derived from cattle, could offer protection from the great harm that the wild type human pox virus could wreak [15]. That it took till October 1977 to extirpate the disease from human populations [16], by a combination of vaccination and contact identification using the immunisation technology invented by Jenner, *inter alia,* shows that highly beneficial changes in medical practice can take considerable time to become established but, nevertheless, vaccination worked. The immune response is certainly in part protective, but it will be proposed that there are other aspects of its functioning. It is useful to amplify such a statement by reference to the information given in the American Public Health Association Manual of Control of Communicable Diseases which aims to review nearly all the presently known such diseases with attention to the kind of information needed by Public Health practitioners to reduce their effects when they harm humans.

The Evolutionary Perspective of the Immune Apparatus

Humans live in an increasingly sanitised world in which as far as possible micro-organisms are given short shrift as they are believed to be potentially dangerous and to be capable of causing disease. There is no doubt that there is a sound basis for such a belief in that there are some such organisms that can be pathogenic i.e., capable of causing harm in human populations. It is, nevertheless, worthwhile noting, against an evolutionary perspective, that the selective mechanisms by which the human body effects an immune response were probably put in place more than five hundred million years ago when vertebrates were first found in the fossil record. This is well before the advent of what we now know as the medical profession. The point about the medical profession is that the mores of the present age regard all human life to be valuable and that in those circumstances, where for medical reasons it seems to be threatened, it is the duty of the profession to do their best to reduce harm due to infection and where possible save lives. No such remediable measures were available at the time that *Homo sapiens* or his earlier progenitors first roamed the earth. Life then, for the extant humans, was much as it is now for wild animals and plants. It can reasonably be argued that if we wish to estimate the biological significance of immune mechanisms in an evolutionary perspective it is to the 'wild' situation that we should look. This in no sense to argue that the medical profession are not doing a good job or that their mores are to be changed but simply to assert that the medical profession and the public health experts have moved the demographic structure of human populations massively in the last hundred or so years and that this demographic change can distort the way we think about an ancient interface system, between man and his complex environment, such as that constituted by the various facets of the immune response.

The Adaptive and the Innate Immune Responses

For historical reasons, our thinking about immunity in recent years has been almost totally dominated by our pre-occupation with what immunologists call adaptive immunity. This property is possessed only by vertebrates [17] and its pursuit has largely led us to ignore the fact that the innate immune response is also an integral part of the total mechanisms of immunity. Innate immunity is not only a property of vertebrates but also functions in multicellular invertebrates [18] many of which have, in their adult forms, an exoskeleton, an alimentary canal and three basic blast layers in the early stages of their ontogenesis - so called triploblasts. The innate immune response in all such organisms has a system of cells that can become phagocytic and which, operating inside the body which contains them, in part if not exclusively, using a system of toll receptors [19], can find, ingest, and destroy living invaders and act, in circumstances in which cells have been damaged or killed in the body, not necessarily as consequence of infection, to perform a clean- up operation.

The differences between adaptive and innate immunity in terms of their mechanisms and overall purpose have been dealt with extensively elsewhere [20]. Here it only needs to be said that the adaptive immune response is specific and capable of tailoring an immune response to relate to the inducing antigenic stimulus by the production of antibodies which have specific binding sites for the inducing antigen. In addition, it is widely argued that specifically cytotoxic cells are produced. It must also be noted that adaptive immunity depends to a great extent on the existence and activities of two populations of lymphocytes terms T and B cells, the former of Thymic origin [21] the latter from Bone marrow. In vertebrates T-cells have a variety of ascribed functions of which one of the first to be discovered was to work synergistically to facilitate the production of antibodies by B cells [22]. These two populations of lymphocytes are often credited with a potentially long-term memory of past activities perhaps comparable to memory possessed by organisms with a brain. This notion of immunological memory will be queried not as necessarily wrong but one which should be argued about.

The Adaptive Immune Response, Reject or Acceptor of Invaders

The adaptive immune response is seen by most medical practitioners, by many contemporary immunologists and often by parasitologists as primarily a defensive mechanism ideally capable of rejecting living invaders and dealing with foreign bodies of any kind. This view has been criticised [23-25] and the counter suggestion made that the adaptive immune response in evolutionary terms exists to assist accommodation of invaders. The name adaptive against this background can suggest either rejection or accommodation with, in the views of its protagonists, the latter being commonly possible and the former less often observed. These notions are not in general popular either with immunologists or parasitologists but nevertheless deserve consideration here. Probably the vertebrates appeared later in evolutionary time than the invertebrate organisms which are generally supposed to be their precursors. Accepting this view, it is worth considering briefly why the adaptive immune response,

characteristic of the vertebrates, was added, in response to a selective advantage, to the innate immune response of their precursors. The innate immune response has no specific memory such as is seen as a property of the adaptive response. It could be that the acquisition of a specific memory is a selective advantage. Equally because of the existence of the substantial array of isotypes of immunoglobulin antibody and their even greater array of idiotypic diversity associated with the adaptive immune response it could be seen as providing an all- purpose far more extensive protective reaction to invasion than the innate immune response alone. It seems to make good sense, but it can be argued that if that were the case vertebrates would have been selected for their capacity to reject pathogenic organisms capable of reducing their viability. In fact, a significant finding from the APHA manual is that humans and incidentally their domestic animals very often live for long periods of time asymptomatically with latent disease forming organisms. Also most disease causing organisms are found to be symptom free in species other than the target of interest. For example *Theileria parva* which can cause a disastrous and almost always lethal disease in non-indigenous Zebu cattle in East Africa is to be found asymptomatically in native species of [26] bovids (buffalo). That the great majority of viruses and bacteria do not cause disease in man could be attributed more to the organisms concerned not having a necessary biochemical affinity with hosts that they do not invade. The APHA manual makes it clear that susceptibility to the infections known to be capable of causing disease is almost universal. If such susceptibility were dangerous perhaps the all-purpose apparatus of the adaptive immune response will deal with the consequences of the 'free' entry of invaders. Of course there are many non-immunological barriers to entry such as mucosal membrane secretions with anti-microbial properties and physical barriers such as provided by sturdy keratinised skin but when these barriers, for whatever reason, have been by-passed successfully invasive organisms often do not cause disease symptoms or only those that can readily be dealt with by the various responsive systems possessed by the vertebrates, particularly the elements of the innate immune response which act as very effective sentries in locating and exterminating foreign organisms intent on immigration. Without doubt the adaptive immune response can control the scale of invasion which for various reasons has not been dealt with by the innate system [7] but it is not too difficult to show experimentally that long term persistence can be associated with the presence of circulating antibody specifically capable of binding to and inactivating, though not exterminating invaders [7]. It has even been argued in relation to eukaryotic single celled organisms that antibody bound by specific idiotypic ligands to their target cells could offer a high level nutritious proteinaceous diet [7]. Fie!

Recent studies on Covid-19 patients claimed that high antibody levels were present in seriously ill patients but far less frequently in most infected individuals who were asymptomatic [27]. Is it totally ridiculous to argue that elements of the adaptive immune response contributed in some way to the sickness of the patients with severe disease but, in those who were asymptomatic, no such harmful effects were seen for the simple reason that the adaptive immune response was not so active? Alternatively, the asymptomatic patients, using their adaptive system or their innate immune response, had restricted the prevalence of the invading virus and thus only a minor response in terms of inactivating circulating antibody was observed.

Invertebrate vectors which facilitate the introduction of potentially pathogenic invaders of vertebrates do not themselves seem to suffer disease symptoms or at least do not have sufficient restriction of their movements to prevent them being capable of gaining entry to the vertebrate host usually with the aim of getting a blood meal. Is the apparent general lack of suffering from disease in infected invertebrates because they do not have adaptive immune mechanisms? There are no easy ways of resolving these apparently conflicting interpretations of observations. Theprevailing view is that pathogenic microbes exist to harm their hosts and must be avoided or killed. The terminology adopted by the human protagonists of this kind of approach is that used in waging wars and it is difficult not to be sympathetic but it must be pointed out that the possibility of mutual benefit as a consequence of infection should be considered. The benefit to the potential parasite is that it gets somewhere safe to live. The long-term advantage to the host could be that it gains an indwelling source of genetic material. If this seems bizarre it should be remembered that two major steps in evolution, firstly the formation of eukaryotic organisms from fusion of several species of archaea and bacteria with subsequent simplification of the genomes involved as Lynn Margulis [28] has so elegantly pointed out, led to the emergence of the nucleated cells of which all the living organisms that not microbial are now composed. The mitochondria which are the relics of these long-ago events still retain a small fraction of genetic material known to be of microbial origin. The mitochondria are essential vital energy managing organelles of which the much-simplified genetic material, derived from what were initially free living organisms, enacts the required energy managing function.

Is it too difficult to imagine a protracted evolutionary sequence involving contact between living organisms leading sometimes to invasion, the initial stages of which in evolutionary time could be tempestuous and dangerous, facultative parasitism it could be thought of, followed by period of accommodation, obligate parasitism, and perhaps in time genetic simplification of the invaders and total loss of their independence? The microbial flora which all triploblastic organisms possess, the acquisition of which was a major step in evolution, shows convincingly that organismal relationships can be mutually beneficial despite the massive differences in the life-styles and genetic constitutions of the organisms concerned. Several billion years ago almost the first fossil organisms to be discovered, stromatolites, were complex symbiotic associations. Symbiosis is essentially a universal phenomenon and not one easily predicted by a theory of evolution only advancing by selection of advantageous point mutations. The disadvantage to host of harm or death as consequence of invasion of course exists but it can be argued that this is irrelevant in evolutionary terms however abhorrent it is to a species such as *Homo sapiens* which prides itself on being able to keep all the individuals of its species in good health. The innate immune response is swift and lethal. Impose on this assassin the mechanism for adoption and rehabilitation of immigrants and it can be argued that this potentially accelerates evolution by creating greater gene pools that have the capacity over time for responding to a greater degree of environmental vicissitudes than can be arrived at by monophyletic notions of evolution.

Non-Immunological Consequences of Activation of the Immune Apparatus - Inflammation

Over the years it has become apparent that immune cells of all kinds activated *in vitro* or *in vivo* produce a wide variety of proteins other than the specific antibodies, which are derived from B-cells transformed into plasma cells. The various cytokine products, in addition to antibodies, are exported into the surrounding medium whether this is a tissue culture dish or extracellular spaces. In this way activation can be, in addition to be concerned with the response to an antigenic stimulus, part of a signalling process having consequences on surrounding cells often *in vivo* on adjacent tissues and systemically. The secretions include what are called paracrine and autocrine hormones which act locally. Wikipedia has this to say:

"*When macrophages are exposed to inflammatory stimuli, they secrete cytokines such as tumour necrosis factor (TNF), IL-1, IL-6, IL-8, and IL-12. Although monocytes and macrophages are the main sources of these cytokines, they are also produced by activated lymphocytes, endothelial cells, and fibroblasts.*"

The cytokine secretions from activated cells of the immunological apparatus, whilst they can also act locally in the paracrine sense, can also have systemic endocrine effects. The relationship between these cell products and the rather better-known products of the endocrine organs, the thyroid, the adrenals, the pituitary, and the sex organs, for example, is less well understood. There are other organs which secrete hormones such as the alimentary canal and again the relationship between these and the other secretions which can act hormonally in the sense that they have effects remote from their sites of production is far from clear though in the years to come research will sharpen up our knowledge. The cleaning operation after damage to cells in the previously whole body, referred to above, is an aspect of inflammation executed by elements of the innate immune response operating internally. This mopping up is comparable in some ways with the external debridement of wounds surfaces by the medical profession to expedite the commencement of the healing process. The clean- up operation can involve what are called pro-inflammatory constituents of the innate immune system. All being well they give way in time to anti-inflammatory components associated with the healing process. This transition often goes smoothly but if the pro-inflammatory influences do not give way in time to the next phase symptomatic problems can arise which, to those suffering from them, can be unpleasant, dangerous, and potentially lethal. Presently we are not fully capable of easing the transition process, but it seems likely that we can begin to identify the internal mechanisms involved. It must be made clear that the account given here is an oversimplification in that some of the cytokines identified as pro-inflammatory can be anti-inflammatory and *vice versa.* The whole array of inflammatory molecules is highly complex and perhaps for this reason the general analytic methods which will need to be applied to further its control have not yet been fully discovered but a start has been made.

The Wikipedia entry summarises these issues and points particularly to a phenomenon, the secretion of TNF, tumour necrosis factor, which, as Ian Clark has pointed out for over forty years, [29] is vastly important in relation to disease symptoms including lethality. His argument based on an elegant series of experiments showed initially that the lethality of an infection of a species of *Plasmodium* in mice could be abolished prophylactically by reduction of the capacity of the recipient animals to produce TNF. Clark went on to show that TNF minus mice did not get sick and die, and if he injected normal animals with TNF, he could elicit disease symptoms. The issue is whether such a mechanism relates to the symptoms of some or all infectious diseases and whether it can be predicted which organisms will be most affected by the pathological effects which can derive from immune activation. Clark's work with infection of various strains of mice with *Babesia* points a way forward in this respect. He found that the pathogenesis of *Babesia* could be predicted from a knowledge of the sensitivity of the species or subspecies strain of host animals to LPS, a bacterial product which has powerful physiological consequences due to its capacity to induce massive and dangerous inflammation [30]. Beyond such a finding if we could identify by some clinical biochemical markers those individuals most at risk from what is in fact immunopathology, lies the issue of how we can intervene to reduce such processes which, *ex hypothesi,* can be very harmful and should if possible be controlled.

Some of these issues are considered in a recent paper [31] summarising what I, an immunobiologist, believe is how we should think of infectious disease as a step in the evolution of a greater degree of genetic complexity. Such a message to those who die as a consequence of infection is not helpful and of course the medical profession should continue to strain to keep sick people alive, but it is likely that some of their efforts are not mimicking the ways that over the ages man has emerged from the evolutionary swamp.

In summary:

1. Genetically based resistance to disease is uncommon compared with susceptibility to invasion by potential pathogens.
2. Immune activities are both helpful and potentially harmful to humans we should seek better to understand the mechanisms by which the harm element is brought about in addition to learning more about the general physiological benefits of immune processes.
3. Only to think of attacking and killing invaders is to disregard the immunopathological processes that often and probably always are involved in creating the symptoms of disease.
4. Inflammation arising from activation of immune cells occurs and it could often be better to attempt control of the host response than necessarily waging war on the invading organism. Most interaction between living systems are complex and involve activities which could be thought akin to playing table tennis i.e., the players change their activities according to the way that their partner in the game has played. An organism that can replicate in minutes rather than years and where the process of replication is prone to mutational error has a much better chance of creating advantageous genetic diversity.
5. It should be better recognised that both adaptive and innate immunity exist in humans and the roles that each of these mechanisms both in relation in the broad sense to infection and the maintenance of good health should be considered.

6. There are many problems susceptible to solution by active research by immunologists that arise from perusal of the APHA manual on Control of Communicable diseases in man.

7. The reasons why so many diseases are more severe in those who are said to immunosuppressed or physiologically at a disadvantage , diabetic say, should be better investigated than is presently the case. In balanced ecosystems predation occurs but the loss of life due to it is easily balanced in several ways. Man, is a complex example of a whole series of ecosystems and their structure and maintenance might be facilitated by better recognition of this fact.

8. Particular attention should be given to the role that our microbiome friends play in the maintenance of health and how this property can be augmented and maintained perhaps by pro- and pre-biotics which have defined effects on the gut flora [32-34].

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