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Epidemiology in general practice

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INTRODUCTION

Epidemiology in Country Practice by William N. Pickles, published in 1939, has been a source of continuing interest and challenge especially to general practitioners (Watson, 1982; Booth, 1987). Pickles worked for over 50 years as a general practitioner (GP) in rural Wensleydale where there were many isolated villages in which natural immunity against various infections was often lacking. And so the source of infection could usually be traced, and, with little or no immunity, spread was often rapid.

The epidemiological studies carried out by Pickles were mainly based on observation; in those days there was no laboratory diagnosis for virus disease and only limited bacteriological facilities. His research technique was simple but methodical. On his rounds he jotted down in a pocket diary the name of the patient, village, and date of onset of disease. Later in the evening the data was transferred to a large foolscap book, each epidemic in each village being kept on separate pages. From these lists, with the aid of his wife or daughter, charts covering a 3-monthly period were made using different coloured squares for each disease, on the ordinate the villages in their natural social grouping and on the abscissa the dates on which each illness occurred. He was thus able to establish the incubation period and period of infectivity of each disease. He studied influenza, measles, Sonne dysentery, varicella (chickenpox) and herpes zoster (shingles), and epidemic myalgia. But his most important contributions to epidemiology were his original studies of hepatitis A infection (infectious hepatitis), then known as epidemic catarrhal jaundice; he established that the incubation period varied between 26 and 35 days and that it was indeed an infectious disease (Pickles, 1930, 1939).

During the past 50 years there has been a marked change in the pattern of infectious diseases (Galbraith, Forbes & Mayon-White, 1980). Along with the disappearance or decline of some infections, new infections have been recognized. Some of these have been due to technical advances in laboratory methods for identification of causal pathogens, e.g. for bacterial infections such as Legionnaire's disease and campylobacter enteritis. The development of virological methods of diagnosis has resulted not only in more precise epidemiological studies of clinically recognized infections such as influenza, measles, varicella and zoster but also has revealed a wide range of unsuspected virus diseases such as those associated with enteroviruses, rotaviruses and adenoviruses. Other pathogens such as human immunodeficiency virus (HIV) the cause of acquired immune

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deficiency syndrome (AIDS) seem to be new arrivals in Britain. Again, some agents formerly considered as commensals have now been recognized as pathogens, e.g. *Giardia intestinalis* as a cause of diarrhoea and Group B streptococci which have become the leading cause of serious infection in the newborn.

The GP has still many opportunities for epidemiological studies, although inevitably such studies are now more complex often requiring teamwork and co-ordination of information from many departments. However, there are nowadays many facilities which were lacking in the past. With practice nurses and attached health visitors he is better able to promote preventive measures. In the UK virtually every person in the population is registered with his/her own GP. Also, more age–sex registers and computerization of records allow age-sex incidence rates of various diseases to be readily calculated. In addition, systems of surveillance of morbidity in the community have been developed. GPs play a key role in these systems as they are usually the first medical contact of the patient.

In the UK since 1966, the Royal College of General Practitioners (RCGP) has had a Weekly Return Service whereby volunteer practitioners record and classify all diagnoses made using the RCGP diagnostic index. A further stimulus to research was the establishment of the first independent department of General Practice in Edinburgh in 1956; now over 20 universities have such departments.

This review will consider some of the epidemiological studies of infections and their prevention during the past 50 years in which general practitioners have played and are playing an important role.

IMMUNIZATION

Since 1940 mass immunization has produced a marked reduction in several infectious diseases which were formerly important causes of morbidity and mortality, e.g. diphtheria and poliomyelitis. With other infections such as measles, mumps, whooping cough and rubella, vaccination campaigns have been less successful and still require assessment. In the past the efficacy of immunization against a specific infection has been studied mainly by cross-sectional analyses of large numbers of children. However, the GP is often in an ideal position to carry out longitudinal studies of the effectiveness of some vaccines over long periods of time.

Pickles noted that, in contrast to large towns where measles was biennial, measles epidemics seemed to occur every 9 years in his rural area. In Britain the disease still causes considerable morbidity being particularly severe in young and deprived children (Miller, 1978). GPs have played an important role in helping to establish the superiority in efficacy and safety of live attentuated measles vaccine over killed vaccine (Watson, 1965). Although a safe and effective vaccine has been available since 1968 the overall acceptance rate in Britain is still low (around 60%), in contrast to the USA where measles vaccine uptake has been over 90%. That an enthusiastic GP can do much to improve vaccine uptake is evident from a recent report from a practice in Reading where the immunization rate was raised from 84% to 97% (Anderson, 1987).

Whooping cough was not of concern to Pickles as it was then a mild illness in his area. However, this disease, its complications and whooping cough immunization have raised many problems. Cross-sectional control studies of pertussis vaccines, involving 50000 children and 25 different vaccines over a 10-year period from 1946 showed the comparative efficacy and safety of pertussis immunization (Medical Research Council Report, 1959). But, the different vaccines employed varied greatly in their protective action and toxic reactions were a difficult problem, particularly the occasional association of the vaccine with neurological damage. The anxiety of many GPs about pertussis immunization was partially allayed by the reassuring reports of various national studies (Report, 1981). These reports along with a major outbreak of whooping cough in 1981–2 led to an increase in acceptance rates. However, the balance of risks for each child still requires careful assessment by the GP.

That valuable studies on whooping cough can be carried out in general practice is shown by a recent 10-year longitudinal study in a general practice in Keyworth, Nottingham, where the course of 436 cases of this disease was recorded (Jenkinson, 1988). The results indicated that the efficacy of whooping cough immunization fell gradually from the first year after immunization until it was only 50% effective 5–7 years later. The author therefore suggested that consideration be given to including vaccination against pertussis in the preschool immunization programme. This study has yielded useful information about the duration of immunity unavailable from previous cross-sectional studies.

Rubella vaccine has been licensed in the UK since 1970. However, the national immunization programme to prevent congenital rubella by immunization of schoolgirls and seronegative women of childbearing age has been unsatisfactory (Fry, 1986). This may be due to a confused system of shared responsibility for rubella immunization between schools, general practice and family planning clinics. It has been suggested that more efficient immunization against rubella would be achieved by giving the GP responsibility for vaccination of both sexes in infancy, e.g. by use of a triple vaccine of measles, mumps and rubella (Aylett, 1986; Walker, Carter & Jones, 1986).

HEPATITIS

From the behaviour of 'epidemic catarrhal jaundice' (hepatitis A) in Wensleydale, Pickles (1930, 1939) suggested that it was spread from person to person by droplet infection. However, subsequent workers have shown that the main route of infection is by faecal–oral spread, and that where socio-economic conditions are poor there is a high rate of infection which is acquired at a young age (Christie, 1988). In Britain the infection rate is now comparatively low although outbreaks still occur where hygiene is defective. The GP has an important part to play in educating travellers to areas where the disease is highly endemic, about the hazards of food and water, as well as the advisability of prophylactic immunization with immune serum globulin.

Another form of hepatitis (serum hepatitis) was recognized 50 years ago as a post-transfusion or post-injection hazard. A major advance in the understanding

of this form of hepatitis (hepatitis B) occurred with the detection in 1964 of an antigen in the serum of an Australian aborigine which was called Australian antigen (Blumberg, 1977), now known as surface antigen (HBsAg). Since then it has been shown that blood, saliva, semen and vaginal secretions are infectious, and that hepatitis B may cause not only acute and chronic hepatitis but also cirrhosis and primary liver cancer (Christie, 1988). The knowledge that spread of infection is particularly frequent from contaminated needles and syringes, as seen in drug abusers, has necessitated considerable improvements in the sterilization and hygiene requirements carried out by doctors and dentists, and the general use of disposable needles and syringes. Also, when necessary the GP has to advise patients about the requirements for active and passive immunization against hepatitis B infection (Reid & Grist, 1987).

RESPIRATORY INFECTIONS

Pickles noted that influenza was the commonest and most important infectious disease in his practice and that an 'influenza epidemic could transform a busy but orderly existence into a nightmare'. This statement is almost as valid now as then.

Since 1940 much epidemiological knowledge has accumulated about influenza following the first isolation of influenza virus in 1933. Many GPs both in rural general practice (Hope-Simpson & Sutherland, 1954; Watson, 1982) and in urban practice (Breen, 1958; Fry, 1958) have contributed much valuable information about the clinical epidemiology of influenza. Hope-Simpson & Sutherland (1954) were the first to question whether direct spread from person to person could explain all the epidemiology of influenza A, but there are still many conflicting theories on this subject (Oxford, 1987).

From such studies it is now known that infections with both A and B virus types occur characteristically in epidemics. However, virus A unlike virus B is subject to antigenic change. Early warning of the emergence of a new influenza strain and of its effect in the community requires active surveillance in which GPs play an important part. For this surveillance 'spotter' GPs throughout the United Kingdom provide weekly information about changes in the occurrence of influenza in their practices (Grist & Reid, 1987). It has been shown that figures obtained form 'spotter' general practices follow similar curves to those obtained from other indices of influenza (Fig. 1). By surveillance and dissemination of information the harmful effects of influenza may be lessened by various health planning procedures such as immunization of 'at risk' groups.

Although the periodicity of outbreaks of influenza is characteristic, the clinical and epidemiological picture is blurred by the existence of infections with other viruses unrecognized before 1940. These include parainfluenza viruses, adenoviruses and rhinoviruses. Illness with respiratory syncytial virus is more distinct as it mainly affects infants and occurs in Britain in epidemics during the winter months with a peak incidence in February or March; GPs have come to realise that it is the most important cause of acute bronchitis and bronchiolitis in infants (MRC Report, 1978) but are often undecided on the advisability of treating the illness with antibiotics to prevent secondary bacterial infection.

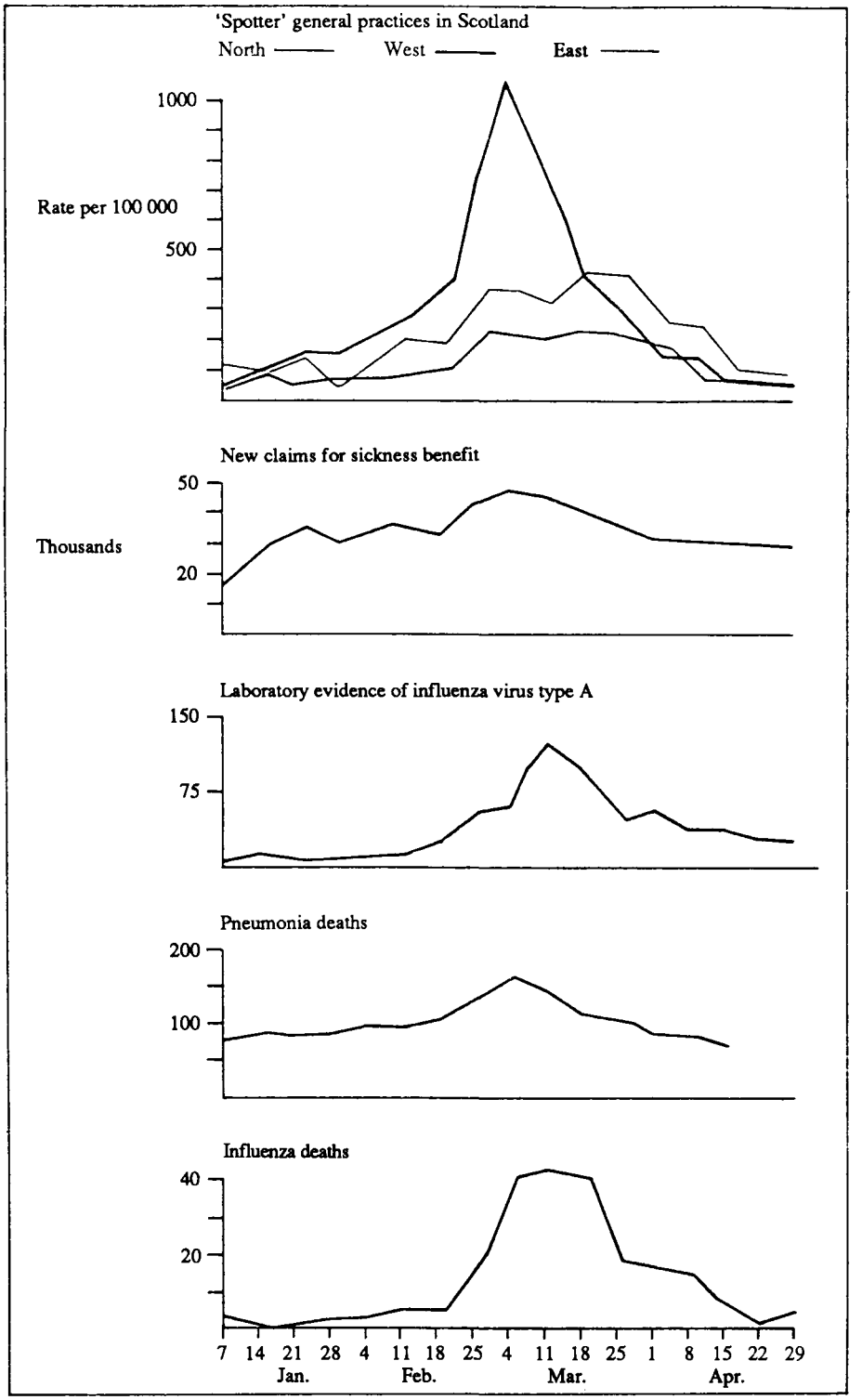

Fig. 1. Some indices used in the surveillance of influenza in Scotland in 1978 (from Grist & Reid, 1987).

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However, there is little evidence to support the efficacy of antibiotics in prophylaxis (Christie, 1988). It would seem that more consideration is required on the potentially harmful effects of unnecessary antibiotics not only on the patient but in relation to the development of bacterial resistance.

The picture of pneumonia in general practice has changed dramatically since 1940. With the decline in severity of pneumococcal pneumonia a group of pneumonic illnesses emerged which did not respond to penicillin – the atypical pneumonias, caused by *Mycoplasma pneumoniae*, *Chlamydia psittaci* (psittacosis) and *Coxiella burnetii* (Q fever), but these were rarely fatal. Of these *M. pneumoniae* has been most frequently associated with atypical pneumonia since its isolation by Eaton in 1944. It has been of particular interest to GPs because most patients do not require hospital admission and the disease can be readily confirmed by serological diagnosis. The epidemiological studies by Ian Watson, who was then a GP in the Tillingbourne Valley in south-east England, are particularly important (Watson, 1982). Like Pickles he meticulously recorded the natural history of *M. pneumoniae* infection and considered that a truer picture of the epidemiology of this disease could be obtained from general practice than from hospital cases. He noted an incubation period of 12 days and a mean serial interval of 16·5 days between the primary case and secondary and tertiary cases. He also observed that the highest clinical attack rate (90%) was among children aged 5–9 years, and that a relapse of symptoms occurred in 13% of patients at one or more serial intervals after the onset of their original attack; this suggested that *M. pneumoniae* persisted in spite of antibiotic treatment.

A more dramatic infection (Legionnaires' disease) was first recognized in Philadelphia in 1976. This disease aroused much public interest through the attention of press and media and interest was kept alive when it was shown that the source of infection lay in water distribution systems such as cooling towers and domestic water systems in large buildings such as hotels and hospitals (Bartlett, Macrae & Macfarlane, 1986).

The GP must now be alert to the possibility of legionella infection as a cause of pneumonia. And, since there are no specific clinical features of this disease, laboratory investigations are required for correct diagnosis; this is important as legionella infection, unlike pneumococcal, is resistant to penicillin but sensitive to erythromycin.

VARICELLA AND ZOSTER INFECTIONS

Varicella and zoster have been of special interest and concern to GPs because these illnesses generally present as clear clinical entities, and have also been associated with intriguing and troublesome problems.

Pickles (1939) mentioned the known association of clinical cases of varicella with cases of zoster, first observed by Bokay in 1888 and confirmed by many workers since then. Pickles himself observed 177 patients with chickenpox in 7 years and noted that in all these patients the illness was no more than an inconvenient infectious rash, and that in two villages, in 1937, the varicella epidemics started with a case of zoster. However, a more precise relationship between the two illnesses was established by Hope-Simpson, who was then a GP

in Cirencester (Hope-Simpson, 1965). During a period of 16 years (1947–62), in a practice of some 35000 persons, he studied 192 patients with zoster, giving a rate of 3·4 per 1000 per annum. This was lower than the 4·8 per 1000 per annum previously reported in general practice study in and around Hawick (McGregor, 1957), perhaps because it was a more thinly populated area than Cirencester.

Hope-Simpson found that, unlike varicella which occurred in epidemics, zoster was present throughout the year, and that it showed no perceptible seasonal effect. From his observations he made a new hypothesis, namely, that contact with zoster in susceptible individuals, e.g. young children, may cause varicella, but that varicella does not cause zoster. He suggested that zoster is generally due to a reactivation of the latent virus and not acquired from external infection, although he admitted that in rare cases external infection might occur.

The isolation of the virus in 1952 and the demonstration by several workers (Christie, 1988) that virus isolated from cases of varicella appeared to be the same as from cases of zoster made virological diagnosis possible. Virological studies of clinically diagnosed zoster infections carried out with the co-operation of several GPs in Glasgow showed that demonstration of a rising antibody titre to varicella–zoster virus by complement fixation technique was a practical and reliable test despite occasional cross-antigenic responses to herpes simplex virus (Ross, Subak Sharpe & Ferry, 1965). In a subsequent study, involving eight practices in Glasgow, 87 patients with zoster were seen, giving a rate of approximately 2·4 per 1000 practice population; of these 78 (90%) had serological evidence of active infection with varicella–zoster (Ross *et al.* 1975*a*). The anatomical location of skin lesions was most common in the areas of the fifth cranial nerve, middle and lower trunk and thigh, i.e. similar to Hope-Simpson's findings. Post-herpetic neuralgia was the most troublesome complication, found in 44% of 64 patients revisited 3–18 months after the acute illness.

Hope-Simpson had observed that, although varicella was a very common infection, only half the number of people living to 85 years old had an attack of zoster; he suggested that there might be factors interfering with the decline of antibody and so prolonging the latent interval. With the demonstration of a possible antigenic relationship between varicella–zoster virus and herpes simplex virus (Ross, Subak Sharpe & Ferry, 1965), it seemed possible that recurrent attacks of herpes simplex might boost immunity to varicella–zoster. However, in the study carried out with the help of Glasgow GPs it was found that recurrent herpes simplex infections did not seem to prevent herpes zoster nor modify the severity of zoster (Ross *et al.* 1975*b*).

Recently GPs have taken part in a study on the epidemiology of varicella in England and Wales, during the period 1967–85, based on a sample of 40 general practices serving a population of about 220000 (Joseph & Noah, 1985). This study showed that the age distribution of varicella appears to be changing, with more cases now being reported in children aged 0–4 years who have, however, a lower case fatality rate than adults, and that the number of deaths in adults has increased especially when associated with pneumonia and immunosuppression. The authors of this study concluded that at present, in England and Wales, more deaths are attributed to chickenpox than to whooping cough and mumps.

It has now been repeatedly shown that zoster is particularly frequent and serious in immunocompromised patients and that the problem is of growing importance (Mandal, 1987). Although there is little evidence of an increased frequency of zoster in patients who are on low doses of long-term corticosteroid therapy (Dale, Fauci & Wolff, 1974) longitudinal studies are required to clarify this; such studies would be best carried out in general practice.

Various therapeutic agents have been used in varicella and zoster; of these acyclovir is currently the best for reducing the severity of these infections (Mandal, 1987). A recent report suggests that oral acylovir at a dose of 800 mg five times daily for 7 days may modify acute zoster and reduce pain but it is not yet known whether post-herpetic neuralgia will be modified by this regime (McKendrick *et al.* 1986); this again would seem an ideal study for general practice.

EYE INFECTIONS

Ophthalmia neonatorum remains common in general practice but is now rarely caused by *Neisseria gonorrhoea*. The main bacterial pathogens *Staphylococcus aureus*, *Streptococcus viridans* and *Haemophilus* spp. are sensitive to chloramphenicol (Taylor, 1983). However, if the infection does not respond to this antibiotic, laboratory tests for viral and for chlamydial infections are required. In opthalmia neonatorum *Chlamydia trachomatis* is being detected more frequently and accounts for many of the eye infections resistant to chloramphenicol (Pierce, Wand & Seal, 1982). Since the incubation period of chlamydial infection in the newborn is usually between 5 and 14 days, the eye infection is usually not manifest until the child is at home. The GP now realises that it is important to obtain laboratory confirmation of chlamydial eye infection for two important reasons: firstly, there is almost always concomitant nasopharyngeal infection so that prolonged systemic treatment is required, e.g. 40–50 mg/kg erythromycin daily by mouth for 14–21 days; secondly, since chlamydial eye infection of the newborn is usually acquired at birth from the mother's genital tract, the affected baby may be the first indication of a family with previously unsuspected chlamydial infection and both mother and her sexual partner may require treatment (McMillan, 1987).

Except for the neonate the commonest known viruses affecting the eyes of children and adults are adenoviruses and herpes simplex (Grist *et al.* 1979). Herpes eye infections are of special concern to the GP because if untreated they may result in permanent damage to the eye. Thus when herpes eye infection is suspected, e.g. by the presence of characteristic lesions in or near the eye, the patient must be referred to an ophthalmologist.

The occurrence of outbreaks of adenoviral eye infections in hospitals and eye clinics with spread to family contacts have shown that contaminated instruments and hands of medical attendants spread the infection (Reid *et al.* 1974). It is therefore apparent that good hygiene is all-important in the prevention of eye infections. Paradoxically, some hygienic measures such as careful handwashing after examining a patient and the use of a clean hand-towel were more carefully observed 50 years ago than in recent years when overmuch reliance has been placed on disinfectants and antibiotics. However, with recent knowledge of the

epidemiology of eye infections the general practitioner has had to inculcate the importance of hygienic and aseptic technique both in the consulting room and in the home.

ENTEROVIRAL INFECTIONS

During the past three decades virological studies have revealed an increasing number of enteroviruses associated with a wide range of diseases. Of these, epidemic myalgia, myopericarditis, hand, foot and mouth disease and the postviral syndrome have posed particular problems to general practitioners.

Pickles was the first in Britain to describe epidemic myalgia with its severe intermittent pain and its good prognosis. He recognized that it was similar to 'Bornholm disease' reported from Denmark in 1930 (Pickles, 1933). Since then the disease has been described under other names such as pleurodynia, acute myositis, and devil's grip. Virological studies have shown that Coxsackie B enteroviruses are the agents mainly associated with this disease but occasionally Coxsackie A viruses may be responsible (Christie, 1988). The statement by Pickles that 'unless the syndrome is thoroughly understood it will inevitably come in some instances under the care of the surgeon' is at true today as it was then.

The myotropic properties of coxsackieviruses may also cause myo-pericarditis: mainly myocarditis in young children and pericarditis in older children and adults. This cardiac involvement has been a considerable problem to general practitioners in relation to differential diagnosis from other more serious cardio-vascular diseases. Virological and clinical studies, often in association with GPs, have shown that the main causal agents are Coxsackie B viruses but Coxsackie A viruses may also be causal (Grist & Bell, 1974).

Hand, foot and mouth disease, characterized by stomatitis and a vesicular rash on hands and feet, was first reported in Britain in 1960 by Alsop, Flewett & Foster. In this study GPs played a major role in identifying cases and sending relevant information to the Epidemic Observation Unit of the College of General Practitioners, the causal agent in the outbreak being Coxsackie A16 virus. Since then other epidemics and sporadic infections have been described associated with other coxsackieviruses (Christie, 1988).

POSTVIRAL FATIGUE SYNDROME

A controversial current issue is the place of viral infection in postviral fatigue syndrome, also commonly known as myalgic encephalomyelitis. This condition has received various other names during the past 30 years, including epidemic neuromyasthenia, Icelandic disease, benign myalgic encephalomyelitis and Royal Free disease.

The main difficulty in determining the aetiology of this disease is the lack of a clear clinical definition. In studies from general practice a wide range of symptoms and signs have been described with fatigue and emotional disturbance being most frequent (Fegan, Behan & Bell, 1983; Calder & Warnock, 1984; Behan, Behan & Bell, 1985). Such features are seen in a large number of patients in general practice but it is their persistence over many weeks which has caused much disability and created anxiety. There have been many diverse opinions on whether the disease is

organic, functional or multifactorial (Dawson, 1987; David, Wessely & Pelosi, 1988). In these studies the only consistent laboratory finding was a raised but static titre of Coxsackie B virus neutralizing antibody. Many doctors accepted this as an answer to the problem, but since Coxsackie B viruses are common infections in the community it was soon realised that controlled studies were required to establish a causal relationship.

A recent study carried out in a Dunbartonshire practice found that 46% of 140 patients with postviral syndrome and 25% of 100 controls had raised Coxsackie B neutralizing antibody titres (Calder *et al.*, 1987). However, the selection of controls in this study was questionable as well as case definition (David, Wessely & Pelosi, 1988). More convincing evidence of enteroviral involvement has been obtained by a group of workers, including GPs in Essex, who were searching for hidden virus or viral antigen (Yousef *et al.* 1988). Their findings suggest that chronic infection with enteroviruses may occur in some patients with postviral fatigue syndrome. It would appear that tests for detection of enteroviral antigen in serum may prove valuable in diagnosis of this condition, but further work in co-operation with GPs is still required to substantiate this claim.

SEXUALLY TRANSMITTED DISEASES

The facts available indicate that since the 1970s there has been an increase in promiscuous sexual activity (Welsby, 1988). Up to then gonorrhoea and syphilis were the main recognized sexually transmitted diseases. For the GP the problems associated with more recently recognized genital infections are often more complex.

It is now recognized that *Chlamydia trachomatis* is the commonest cause of non-gonococcal urethritis (NGU) in men in the Western world and the prevalence is increasing. The organism can be isolated from 80% of their female sexual partners, most of whom are symptomless but if untreated may cause pelvic inflammatory disease, sterility, painful intercourse, or ectopic pregnancy (McMillan, 1987). Babies infected from the mother during birth may develop ophthalmitis or pneumonia; this often draws attention to the parents' infection and they also require diagnosis, treatment and much reassurance from their GP.

The association of certain genital virus infections (papilloma, herpes simplex) with carcinoma of the cervix have created new problems for the GP, although this association may be coincidental rather than causal. He must also be aware that primary genital infection with herpes simplex virus at the end of pregnancy may result in serious neonatal infection. The public now realizes some of the dread implications of herpes simplex infections, highlighted by the occasional tragedy of herpes encephalitis, and patients require assurance from the GP that herpes simplex infection is common and usually benign (Christie, 1988).

Acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is now posing increasing problems. Because of the damage done to the immune system by the virus, infections not usually harmful may be fatal. Thus patients suffering from AIDS usually present with frequent infections, many of these caused by unusual agents. It would seem that GPs will

have increasing opportunities for epidemiological studies of AIDS, due to the information they have systematically gathered on an individual and family basis over many years (Robertson, 1987; Hodgkin, 1988). They will also have to play a crucial part in education to prevent spread of AIDS. A recent survey following government advertising campaigns on AIDS found that most people wanted more information and would ask their doctor for advice (Bradley, 1987). This presents GPs with a continuing challenge to keep abreast of current knowledge of AIDS, and to help unravel its epidemiology.

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