The main symptoms associated with *G. lamblia* infestation were changes in defecation habits, abdominal pain, diarrhoea, and a feeling of bloatedness. The diarrhoea was continuous or intermittent, sometimes frequent—up to five or more daily—and mucoid but not bloody. Three weeks after their disease started most of the patients still had these gastrointestinal disturbances, often combined with nausea, anorexia, and weight loss (Fig. 2).

Spontaneous cure of *G. lamblia* infestation may occur²⁸ but it is well known that many patients with such infestation may have symptoms for months or years.^{1 14 17 20} It is also known that spread of *G. lamblia* may occur in nurseries^{8 9} and in families.^{5 6 7 10} Hence we believe that all patients affected with *G. lamblia* living in a community where such infestation is uncommon should be given an antitrypanosomal drug. To date metronidazole has been the drug of choice.^{29 30 31} In the present study we used a new antitrypanosomal drug, tinidazole, which has been found to be eight times more effective than metronidazole in treating *Trichomonas foetus* infection in mice.^{25 27} Tinidazole has also been reported to be free from side effects involving the blood, kidney, and liver in animals and man.^{25 26 32 33}

Immediately after stopping the tinidazole therapy (150 mg twice daily for one week) 90% of the students with giardiasis were free from gastrointestinal symptoms, and at follow-up after one and two months all were fully recovered and none harboured *G. lamblia* in their stools. For comparison we¹⁷ found that metronidazole 200 mg three times daily for one week given to a similar group of students infested with *G. lamblia* (see above) could eradicate the parasites from the stools of only 71% of the cases. A cure rate of 67% was reported by Petersen¹² when he used the same dose of metronidazole in the treatment of patients with *G. lamblia* in the duodenal contents.

The effectiveness of tinidazole in eradicating *G. lamblia*, the absence of side effects, the low doses required, and administration only twice daily, seems to us to favour tinidazole over metronidazole in treating *G. lamblia* infestations. Further clinical trials with tinidazole and metronidazole may give a definitive answer to the question whether this opinion is well-founded. Finally, it should be mentioned that neither tinidazole nor metronidazole was given to pregnant women.

References

- Belding, D. L., *Textbook of Parasitology*, 3rd edn. New York, Appleton Century Crofts, 1965.
- Faust, C. E., and Russell, P. F., *Craig and Faust's Clinical Parasitology*, 7th edn. Philadelphia, Lea and Febiger, 1964.
- Moore, G. T., et al., *New England Journal of Medicine*, 1969, 281, 402.
- Rendtorff, R. C., and Holt, C. J., *American Journal of Hygiene*, 1954, 60, 320.
- Stern, G., Lantorp, K., and Lidman, K., *Nordisk Medicin*, 1971, 86, 1343.
- Thoren, G., and Aust Kettis, A., *Scottish-Scandinavian Conference on Infectious Diseases*, Copenhagen, 1971.
- Wahlén, S., *Läkartidningen*, 1971, 68, 125.
- Akimova, R. F., *Meditsinskaya Parazitologiya i Parazitarnye Bolezni*, 1969, 38, 272.
- Ormistoun, G., Taylor, J., and Wilson, G. S., *British Medical Journal*, 1942, 2, 151.
- Kidney, W., and Holland, P. D. J., *Journal of the Irish Medical Association*, 1967, 60, 375.
- Uthman, S. M., and Norton, R. A., *Lahey Clinic Bulletin*, 1969, 18, 51.
- Petersen, H., *Scandinavian Journal of Gastroenterology*, 1972, 7, Suppl. No. 14.
- Svensson, R., *Acta Medica Scandinavica*, 1935, Suppl. No. 70.
- Wester, P. O., Molin, L., and Bengtsson, E., *Nordisk Medicin*, 1963, 69, 670.
- Bengtsson, E., *Läkartidningen*, 1967, 64, 3721.
- Gabinus, O., Thulin, H., and Stigmarker, E., *Förekomsten av Tropiska Sjukdomar inom Området där Svenska Missionärer Arbetar*. Falköping, Gummesson, 1970.
- Forssell, J., Lantorp, K., and Stern, G., *Läkartidningen*, 1972, 69, 1132.
- Magnius, L., and Aust Kettis, A., *Scottish-Scandinavian Conference on Infectious Diseases*, Copenhagen, 1971.
- Morbidity and Mortality Weekly Report*, 1970, 19, 455.
- Petersson, T., and Selroos, O., *Nordisk Medicin*, 1971, 85, 78.
- Cortner, J. A., *American Journal of Diseases of Children*, 1959, 98, 311.
- Barbieri, D., et al., *Archives of Disease in Childhood*, 1970, 45, 466.
- Yardley, J. H., and Bayless, T. M., *Gastroenterology*, 1967, 52, 301.
- Ridley, D. S., and Hawgood, B. C., *Journal of Clinical Pathology*, 1956, 9, 74.
- Howes, H. L., jun., Lynch, J. E., and Kivlin, J. L., *Antimicrobial Agents and Chemotherapy*, 1969, 9, 261.
- Miller, M. W., Howes, H. L., jun., and English, A. R., *Antimicrobial Agents and Chemotherapy*, 1969, 9, 257.
- Taylor, J. A., jun., Migliardi, J. R., and Schach von Wittennau, M., *Antimicrobial Agents and Chemotherapy*, 1969, 9, 267.
- Rendtorff, R. C., *American Journal of Hygiene*, 1954, 59, 209.
- Lancet*, 1963, 2, 673.
- Bassily, S., Farid, Z., Mikhail, J. W., Kent, D. C., and Lehman, J. S., jun., *Journal of Tropical Medicine and Hygiene*, 1970, 73, 15.
- Council of Drugs, *Journal of the American Medical Association*, 1963, 183, 952.
- Diwald, J., *Wiener medizinische Wochenschrift*, 1971, 124, 492.
- Frick, J., and Decristoforo, A., *Therapiewoche*, 1971, 21, 472.

Scientific Basis of Clinical Practice

Viral Epidemiology: The Hidden Universality of Infection

J. E. M. WHITEHEAD

British Medical Journal, 1972, 2, 451-456

A leading investigator of the epidemiology of viral diseases, the late Prof. J. R. Paul of Yale University, used the phrase "the hidden universality of infection" as a succinct description of the concept that clinically apparent infections are far outnumbered by those in which the viral infection produces no sign or symptom of disease. In *A History of Poliomyelitis*¹ he reminds us that in its origins this idea owed nothing to laboratory investigations, but derived from the close clinical and epidemio-

logical observations made by Wickman on the behaviour of the disease in small rural communities during the Swedish epidemic of 1905. Wickman had deduced that the mode of spread of the infection could be explained satisfactorily only if he included as cases of infection not only those suffering from paralytic poliomyelitis but also those with the non-paralytic and minor illnesses, and, by extension, those who remained well but who nevertheless were incriminated on epidemiological grounds.

That a virus so manifestly pathogenic for the central nervous system in reality infected most people without causing them to become ill was a notion over which controversy persisted for a generation until, with the accumulation of evidence from the field and the laboratory, its truth eventually came to be accepted. So intensively have the virology and epidemiology of

Public Health Laboratory, Coventry and Warwickshire Hospital, Coventry

J. E. M. WHITEHEAD, M.B., F.R.C.PATH., Consultant Microbiologist

this potentially crippling infection been studied that more information has been gained about inapparent infections in this than in other viral diseases. It thus forms a useful prototype in which to analyse the relevant epidemiological factors—viral, host, and environmental—which appear to contribute, singly or together, to the clinical outcome in individuals infected by a particular virus for the first time. The insight so gained is not confined to infections by polioviruses, but appertains in varying degrees to infections by various other viruses as well. But the true dimensions of a specific virus infection in the human herd cannot be established by clinical and epidemiological observations alone: laboratory investigations are also needed, and this article outlines their scope.

Detection of Silent Infection

Infections which give rise neither to signs nor to symptoms of disease may be recognized either by isolation of the virus from the infected individual or by detection of the serological response which its silent presence has evoked in its host.

VIRUS ISOLATION

Methods corresponding to those used in clinical virology are employed, whereby virus is isolated by inoculation of tissue cultures, animals, or chick embryos. Much of the success in isolating viruses—and thus the apparent prevalence or otherwise of subclinical infection—turns on the selection of the most sensitive cell systems and the proper collection and transmission of suitable specimens. These are especially relevant in subclinical infections, for virus may not be shed as abundantly as in disease. Also important when infection rates are being compared is the inevitable variation among laboratories in the efficiency of virus isolation, even when using ostensibly similar methods. Information obtained from multicentre surveys has an advantage in not only minimizing the effect of geographical variations in incidence, but also of local, unrecognized variations in technique.

An example of such a cross-sectional survey was one which covered 110 local authority areas of England and Wales and was made to discover the incidence of silent infections by enteroviruses and adenoviruses in children under 5 years, by testing over a period of a year a sample of healthy children selected at random from the birth registers each week. Over 8% of the 25,600 children, though outwardly healthy, were nevertheless found to be excreting viruses; 5.1% were excretors of Coxsackie A, 0.8% Coxsackie B, 1.1% echoviruses, 0.9% polioviruses, and 0.5% adenoviruses.²

In the case of enteroviruses an additional means exists whereby their ebb and flow in a community may be gauged, for they may be isolated from its sewage. Serial sampling by the gauze pad sewer swab technique—originally devised for tracing typhoid carriers—may disclose epidemics of infection unrecognized clinically.

More applicable to the circumstances of general practice is the longitudinal survey of families or households, in which combined clinical and virological surveillance is made over long periods. In this way the mode of entry and spread of infection among the family, whether or not it is clinically apparent, can be investigated, and the type of the infecting virus determined, together with the duration and extent of its shedding by the infected individuals. A two-year survey of two social class III families in Newcastle upon Tyne, comprising nine persons in all, is a recent example of this kind.³ The households were visited each week, cough swabs and specimens of stools were collected for virus isolation, and clinical assessments made. Twenty-two virus infections were associated with illness, but eight were not. Whereas viruses were excreted in the faeces for weeks, they could not be detected in the respiratory tract for longer than one week. Putting more families “under the epide-

miological microscope”⁴ in this way would help to elucidate the real extent of viral infections in domiciliary circumstances.

An obvious advantage of virus isolation procedures in studying subclinical infections lies in the possibilities of determining the antigenic composition and other characteristics of the infecting viruses, on which the occurrence of silent (as opposed to overt) infection may depend.

SEROLOGICAL METHODS

The techniques are similar to those used in diagnostic virology but are adapted for testing sera in batches. Complement-fixation and haemagglutination-inhibition tests are preferred to neutralization tests because they are more quickly and easily performed—an important consideration when many specimens of sera have to be examined. In certain infections antibodies may also be measured by immunofluorescence. In general, neutralization and haemagglutination-inhibition tests tend to be more specific than complement-fixation tests. Some serological tests may, however, be accepted as specific for years until cross-reactions are eventually brought to light, as was the case with the complement-fixation test for herpes simplex and varicella-zoster.⁵ Another discrepancy may result from differences in the initial serum dilution used for the same test in different laboratories. Should this be set too high, disproportionately many sera will appear to lack antibody and this should be borne in mind when comparisons are made.

Serological surveys are a valid means of discovering previous experience of infection, provided the antibody is consistently produced after infection and is specific for the virus in question. The longer the duration of detectable antibody in the circulation, the further into the past it becomes possible to explore. Such “serological archaeology” has pointed to the probability that the influenza pandemic of 1918-9 was due to an influenza A virus closely resembling, if not identical with, the original swine influenza virus, by the discovery that antibody to it existed only in those age groups old enough to have experienced the pandemic.

Antibody surveys may be made in various ways.

Sera from certain categories of persons—for example, age or social groups of various kinds—may be examined and the incidence of antibody determined; this is then related to the individuals' histories. For instance, it was shown that, in women of child-bearing age, 95% of those who gave a history of rubella had antibodies to the virus, as compared with 88% in those who claimed never to have had the disease.⁶ The distribution of antibodies by age groups in different populations, or segments of a population, serves to indicate the prevalence of infections at various ages, whether clinically apparent or not, and these may in turn reflect environmental conditions.

Information of a different kind is provided by longitudinal studies whereby antibody levels before and after exposure to infection are measured. Those in whom no antibody can be detected beforehand, and who develop antibody after exposure, are said to show seroconversion. The histories of those showing seroconversion and those that do not may then be compared. A study of this kind showed that 12% of students who lacked antibody to the Epstein-Barr (E-B) virus on entry to various English universities showed seroconversion during the next seven months. One-third of them had remained well, and about 20% had experienced respiratory and other illnesses, the incidence of which was almost the same as that observed in those who did not acquire antibodies to E-B virus. In about half of them, however, seroconversion was accompanied by the development of Paul-Bunnell-positive infectious mononucleosis.⁷

Serological studies are more economical than virus isolation procedures and subject to the limitations described, also provide information, on past infection. Nevertheless, though circulating antibodies may be regarded as indicating the immune status of the population under study, account also has to be taken of the secretory IgA antibodies, which constitute an “antiseptic slime over the surfaces and passages of the body,”⁸ and provide an important local barrier against reinfection.

OTHER METHODS

In viral hepatitis, subclinical infections may sometimes be disclosed among contacts of frank cases by the use of biochemical tests for evidence of liver damage so slight as to cause no illness. Estimation of the serum aspartate and alanine transaminases may be used for this purpose. In the long incubation form (serum) hepatitis, tests for the hepatitis-associated (Australia) antigen and antibody may bring to light silent infections and can be of value in screening prospective blood donors.

Poliovirus Infections

VIRAL FACTORS

Virulence and Antigenic Type

Among polioviruses three distinct serotypes, with minor degrees of intratypic variation, are recognized. Illness, paralytic or non-paralytic, may result from infection by any one of them, but this happens least often in type 2 infections and most often in type 1 infections. Wild strains of virus, irrespective of serotype, vary strikingly in their virulence for human populations, as is shown by the paralytic attack-rates observed in different outbreaks which may differ by as much as several hundredfold. With polioviruses it is feasible to examine strains for certain characteristics, or "markers"—neurovirulence for monkeys, capacity to grow in low bicarbonate concentrations, capacity to grow at 40°C, and other markers—which together tend to correlate with their apparent virulence for man. But when these tests are applied to viruses isolated in virulent epidemics and to those isolated in communities in which there is little or no overt disease, the differences are not always consistent. Viruses isolated during interepidemic periods from healthy children with no contact with recognized cases of the disease may show various degrees of virulence from high to low. Even in outbreaks where probably almost all of the susceptible population is infected by a strain capable of producing a high incidence of paralysis, most of the infections do not result in paralytic disease.⁹

This suggests that other factors besides the virulence of the infecting virus may be important in determining the outcome of an infection. Though these have more to do with the host and environment than with the virus itself, the size of the infecting dose of virus may also, by analogy with laboratory work, be relevant. Direct evidence in naturally acquired infections is lacking, but features suggestive of a dose-related effect were observed in one unusual outbreak in Nebraska, which appeared to be water-borne.¹⁰

HOST FACTORS

Age

The clinical reaction to infection varies according to age. Estimates of the overall ratio of infections to paralytic cases range from 50 : 1-1000 : 1. For children under 5 in England and Wales during 1957-9 the ratio for type 1 infections was found to be 140 : 1, and for the other types certainly much higher.¹¹ There is general agreement that the ratio is much lower in adult infections, and one calculation based on Swedish experience puts the risk of a paralytic outcome of an infection by type 1 virus in adults over 25 as 20-100 times greater than that in children under 5 years old.¹² Not only is an infection of the adult more likely to result in illness, but the fatality rate of the declared disease is also several times greater than in children.

Sex

A difference is also to be found in the sex incidence, the notified disease being commoner in males than females, especially in

childhood. Nevertheless, when the incidence of silent infections among healthy children under 5 years old in England and Wales was last surveyed no difference between the sexes was apparent.² What predisposes the infected male to a greater risk of developing illness is undertermined.

Other Predisposing Factors

Epidemiological studies have shown several factors which appear to predispose the infected individual to paralysis. These include tonsillectomy or injections with combined vaccines during the month preceding onset, strenuous physical exertion in the prodromal stage, and pregnancy. How far they operate towards the conversion of infections which might otherwise have been inapparent into overt illness has not been measured.

ENVIRONMENTAL FACTORS

The sanitary environment of the population in which poliovirus infection is present has a definite effect on the epidemiological pattern and clinical manifestations of the infection.

Where overcrowding exists—with continuous close contact, poor sanitation, and low standards of living—dissemination of the virus by the faecal-oral and pharyngeal-oral routes is so heavy and widespread that most persons become infected at an early age and so develop protective antibodies. Under such conditions the disease prevails in an endemic form affecting infants and young children with a high ratio of inapparent infections to clinical cases and a low mortality. The disease, being mild, is not readily distinguishable from the generality of febrile illnesses of childhood, unless signs of paralysis attract attention. As standards of hygiene advance and overcrowding lessens with rising socioeconomic conditions, opportunities for spread of the virus are lessened so that infection is progressively postponed until later in childhood or adolescence. The consequent accumulation of susceptibles in the population serves to set epidemics going. Because the infection takes effect at a later age, not only is the illness more severe (and thus more readily identifiable), but also the ratio of silent infections to clinical cases is lower. This change in pattern of incidence of the disease has been the experience of many of the developed countries since the late nineteenth century—until the advent of effective vaccines brought the disease under control—and has latterly been discerned in some newly developing countries.

The occurrence of viral infections is influenced by other epidemiological factors besides those already mentioned—for example, season—but as they do not appear to modify the predominance of subclinical over clinical infections they are not discussed here. Other viral diseases in which inapparent infections greatly outnumber the clinical cases are next considered, to trace how far the same factors as those described for poliomyelitis operate in them.

Other Viral Infections

OTHER ENTEROVIRAL DISEASES

It is perhaps not surprising that infections by the Coxsackie and echoviruses share many of the features of poliovirus infections, for they belong to the same virus group—the enteroviruses. A profusion of antigenic types exists; all may be isolated from healthy and from sick persons on occasion, but some types are found more often in patients suffering from some of the heterogeneous disease syndromes caused by these viruses. So widespread is the occurrence of this group of viruses in healthy persons, particularly children, that the illness they cause is best thought of as "the unusual response of individuals in the midst of an ubiquitous infection of populations."¹³

Evidence of an age-related effect on the severity of the clinical manifestations of infection is less obvious, and if anything the trend is opposite to that in poliomyelitis, as in the instance of the well-authenticated pathogenicity of Coxsackie B viruses for the

myocardium of newborn infants. The mode of spread is the same as that of polioviruses and leads to infection of children mainly below school age, being at its heaviest and earliest in those living under poor socioeconomic conditions.

INFECTIOUS HEPATITIS

The short incubation form of viral hepatitis is known from epidemiological observations and volunteer experiments to be transmitted through the faecal-oral route and to exist mainly, but not solely, as an infection of children under 10 years old, with many abortive and subclinical cases. Accurate assessments of the proportion of subclinical infections to overt disease are impossible in the absence of laboratory methods for detection of the virus infection, but it is estimated that they outnumber icteric cases by at least ten to one.¹⁴ Though mild in children, this disease also becomes more severe in adults and the proportion of anicteric to icteric cases falls. Women are more severely and frequently affected than men.

The infection shows similar features to the enteroviruses in being highly endemic among children living in poor environmental conditions, and also in manifesting the upward shift in age incidence in the more developed countries—as, for example, in Sweden, where 60% of notified cases are reported to occur in adults.¹⁵

EPSTEIN-BARR (E-B) VIRUS INFECTIONS

The infections so far described are transmitted mainly by the faecal-oral route, whereas in E-B virus infections probably pharyngeal secretions are responsible.

Recent serological studies have shown that antibodies to this, the virus associated originally with Burkitt's lymphoma, besides being present in 100% of patients bearing these tumours, were also present in other populations throughout the world. The age distribution of antibodies shows that infection is common in childhood and that their frequency is closely related to environmental circumstances which provide close and continuous contact, as exist in poor living conditions. Where these do not apply, as in the more affluent sections of a population, infection may be delayed until adolescence or early adult life. For example, 59% of student teachers aged 18-24 at an English training college possessed antibodies—a proportion comparable to that observed in similar groups elsewhere. The effect of environment of the age of acquisition of antibody is illustrated in the same investigation by the finding that over 70% of 3-5-year-old children in two London day nurseries already possessed antibodies to E-B virus.¹⁶

The studies so far made of childhood infections by E-B virus point to their being largely subclinical; yet when infection by this virus is postponed until adolescence or later a substantial proportion of those infected develop classical, seropositive infectious mononucleosis—a further example of the effect of age on the clinical outcome of encounter with a virus.

Nevertheless, when childhood infections take place in certain circumscribed geographical areas some of them are followed by the development of the unique lymphoblastoid tumour of the face and jaws; and in cells grown from this the virus may be demonstrated. It is current hypothesis that the predisposing factor in the development of the tumours is the heavy and sustained stimulation of the lymphoid tissues by the presence of the malarial parasite, for the geographical distribution of tumour cases corresponds with that of areas in which malaria is hyperendemic.¹⁷

RUBELLA

In outbreaks of rubella the reported ratio of inapparent infections to clinical cases has ranged from 6:1 to 1:1. Serological surveys show that 80-95% of persons reach adulthood having acquired antibodies, the majority during school age, regardless of whether they were known to have had the disease or not. As infection can take place in children with lymphadenopathy but without rash in perhaps 40% of rubella infections with illness,

the disease may easily escape recognition. The virus is transmitted by the respiratory secretions. It has also been detected in faeces and urine, but it seems unlikely that these contribute to the spread of infection—except perhaps in the case of the congenitally infected infant, who may excrete the virus in the urine for months. Socioeconomic circumstances appear to play a smaller part in the acquisition of this infection. Involvement of the joints is a clinical manifestation which could be said to be related to age and sex, for it is encountered mainly in women and rarely in men or children.

CYTOMEGALOVIRUS INFECTION

Studies of the age distribution of antibodies indicate that 10% of children have acquired this infection by the age of 5 years, and by the mid-30s about half the population possess antibodies to it. In children, though the infection may escape clinical notice, enlargement of the liver or biochemical evidence of hepatic dysfunction can be found in many cases.

Most primary infections in adults are also inapparent, but a few cases of cytomegalovirus mononucleosis—with negative tests for heterophil antibody—may occur, mostly in adults over 35.¹⁸ Infection acquired by blood transfusion may result in the postperfusion syndrome and may be encountered at any age. The virus is shed in saliva and urine for long periods—often for months—especially by children, and this may lead to high rates of infection among contacts in institutions.

HERPES SIMPLEX INFECTIONS

It has been known for over 30 years that the incidence of infections by herpes simplex virus correlates with socioeconomic circumstances, being greatest in those who live in poor, overcrowded conditions.

Most infections take place in the first two or three years of life and about 85% of them are estimated to be subclinical,¹⁹ though this may be an overestimate owing to the difficulty of distinguishing the initial illness from other childhood complaints.²⁰ Serological surveys show that, depending on their environmental upbringing, 30-90% of adults have acquired antibody. It also appears that, in Britain at least, the proportion of young adults with antibody may be diminishing,²¹ in which case primary infections may be encountered more frequently in older age groups than at present. Whether the ratio of silent to overt infections will alter with the upward trend in age of primary infections remains to be established. By contrast, antibodies to the genital, or type 2, herpesvirus appear first in the 13-year age group and reach a maximum incidence at about 30—in keeping with its venereal mode of transmission.

ADENOVIRUS INFECTIONS

Though this group of viruses could justifiably be included with those already considered—on the grounds that inapparent infections by them outnumber the cases of illness they cause—their detailed study is complicated by the existence of at least 30 different antigenic types. Some occur more commonly in certain age groups, giving rise to clinical or subclinical infections whereas others tend to be associated with certain disease syndromes, usually of the respiratory tract. Their analysis is further complicated by the tendency of adenovirus to persist as latent infections of lymphoid tissues. Whereas herpes simplex and cytomegalovirus also possess an intrinsic ability to persist as latent infections, they lack the complication of antigenic diversity possessed by the adenoviruses.

OTHER VIRUS INFECTIONS

Laboratory investigations have established that infections by other viruses are sometimes inapparent, but not to the extent that they outnumber clinical cases as in the examples so far con-

sidered. In mumps, for example, the ratio is reversed and is about one silent infection to every two clinical cases; in influenza the ratio varies, the antigenic plasticity of the virus impeding accurate assessment.

By contrast, other virus infections exist which almost invariably result in overt disease and in which primary subclinical infections are rare or unknown. Measles is one, variola is another.

It can thus be seen that in those virus infections in which inapparent infections exceed clinical cases it is usually possible to trace the operation of one or more factors analogous to those which predispose to subclinical infection rather than overt illness in poliomyelitis.

Consequences of Inapparent Infection

IN PREVENTIVE MEDICINE

The individual and collective immunizing effect of these infections under natural conditions is self-evident. Moreover, it is implicit in the current practice of oral poliomyelitis vaccination, whereby the deficiency of naturally occurring subclinical infections of infants by wild strains of virus is made good by the administration of vaccine strains of attenuated virulence in controlled doses to produce subclinical infection by the natural route. The reinforcement of immunity which occurs on reinfection under natural conditions finds its counterpart in the booster doses of vaccine given at school entry.

The establishment of an infection by one virus may exclude infection by another, by the process of interference. This effect of a silent infection by one virus in excluding more virulent viral infection is used to bring outbreaks of poliomyelitis under control by mass (blanket) vaccination of a community with oral vaccine. Silent infections contribute as much, if not more, than overt infections to the spread of virus by reason of the more numerous contacts made by the infected individual in the course of everyday activities unhampered by illness. Though their role as links in the chain of infection between clinically apparent cases of disease was evident to Wickman more than half a century ago, it has only recently become apparent that in certain circumstances silent infections by particular viruses may be the cause of much concern to the clinician.

IN CLINICAL PRACTICE

Congenital Infections

Rubella infections of the expectant mother are now so well known—both to the patient and to her doctor—as a cause of congenital malformations as to require no further emphasis, but it is less widely recognized that the extent of the rubella syndrome resulting from subclinical infection during pregnancy may be just as great as that which results when the maternal rubella infection is overt.²²

It is not safe to assume that failure of a pregnant woman to develop the disease after exposure indicates that infection has not taken place and therefore that the fetus is not at risk, for studies show that in these circumstances a small proportion of silent infections occur.²³ In such cases sera collected within a day or two after exposure and three weeks later show evidence of seroconversion when examined for rubella antibodies.

Cytomegalovirus infections are more sinister, for their occurrence is almost always inapparent and hence cannot alert the clinician. They may occur during pregnancy in up to 6% of cases as gauged by serological studies,²⁴ and about 3% of women may excrete the virus during pregnancy or at term.²⁵ Though fetal infection does not always follow, 0.5–2% of the newborn are found to excrete the virus,¹⁸ of whom at least 10% may be expected to show some degree of mental retardation, often accompanied by microcephaly. It has been calculated that this (silent) infection adds not fewer than 800 mentally retarded individuals to the population of England and Wales each year.²⁶ For this reason, a reliable means of detecting the infected fetus, adaptable to

large-scale screening, is a prerequisite to preventive measures, together with more certain knowledge concerning the stage of pregnancy at which this silent infection leads to significant damage to the fetal central nervous system.

The genital, or type 2, herpes virus may establish itself in the pregnant woman as an inapparent infection of the cervix. In this case the risk to the infant of acquiring neonatal herpetic infection—often systemic in character and frequently fatal—has been estimated as 60%.²⁷ Serum hepatitis is another virus infection which may occur silently in the mother, as judged by the presence of Australia antigen in her blood, and which may be transmitted at or after birth to her offspring. Such infants may appear normal, though some may show biochemical evidence of liver damage—yet the antigen persists in the circulation for months or even years. Their eventual outcome remains to be determined by prospective studies.

Although the foregoing represent established instances of the contribution of inapparent infections during pregnancy to congenital disease, there have been suggestions that other viral infections may occasionally be implicated. Closer and more detailed study of events during pregnancy may bring to light further instances of untoward effects of the fetus.

Persistent Infections

The viruses so far considered include some—in particular the *Herpesvirus* group—which have a tendency to establish themselves as persistent, latent infections. Though the primary infection is often inapparent, the recurrence may not be. External herpetic lesions which recur are commonplace, but reactivation of latent virus may be the underlying mechanism in the development of herpes encephalitis, other than in the newborn. Inapparent infection of the uterine cervix by type 2 (genital) herpes virus which persists in a latent form may eventually be shown to play an aetiological part in the development of cervical carcinoma,²⁸ and would provide a further instance of a clinical outcome to an initially subclinical infection.

Cytomegalovirus is another herpesvirus in which reactivation of persisting, latent infection is a likely explanation for its prevalence, in various clinical guises, in patients suffering from debilitating diseases or undergoing immunosuppressive therapy. E-B virus, another herpesvirus, may be detected in cultured leucocytes many years after infectious mononucleosis, and also in persons with no history of the disease but who possess antibodies to the virus—but the long-term results of this persisting infection are as yet undetermined.

Hence it is unwise in clinical practice to discount entirely these ubiquitous virus infections solely because they lack immediate clinical manifestations.

References

- 1 Paul, J. R., *A History of Poliomyelitis*. New Haven, Yale University Press, 1971.
- 2 Galbraith, N. A., *Journal of Hygiene*, 1965, **63**, 441.
- 3 Hurrell, G. D., Sturdy, P., Frood, J. D. L., and Gardner, P. S., *Lancet*, 1971, **1**, 769.
- 4 *Lancet*, 1971, **1**, 791.
- 5 Ross, C. A. C., Subak Sharpe, J. H., and Ferry, P., *Lancet*, 1965, **2**, 708.
- 6 Report of the Public Health Laboratory Service Working Party on Rubella, *British Medical Journal*, 1968, **2**, 203.
- 7 Joint Investigation by University Health Physicians and P.H.L.S. Laboratories, *British Medical Journal*, 1971, **4**, 643.
- 8 Hobbs, J. R., *British Journal of Hospital Medicine*, 1970, **3**, 669.
- 9 Evans, C. A., *Bacteriological Reviews*, 1960, **24**, 341.
- 10 Bancroft, P. M., Engelhard, W. E., and Evans, C. A., *Journal of the American Medical Association*, 1957, **164**, 836.
- 11 Spicer, C. C., *Journal of Hygiene*, London, 1961, **59**, 143.
- 12 Olin, G., cited by Gard, S., in *Live Poliovirus Vaccines, 1st International Conference on Live Poliovirus Vaccines, Washington, 1959*, p. 228. Washington, Pan American Sanitary Bureau, Regional Office of W.H.O., 1960.
- 13 Gelfand, H. M., *Progress in Medical Virology*, 1961, **3**, 193.
- 14 Zuckermann, A. J., *Virus Diseases of the Liver*, London, Butterworth, 1970.
- 15 Ström, J., *Acta Medica Scandinavica*, 1959, **165**, 49.
- 16 Pereira, M. S., Blake, J. M., and Macrae, A. D., *British Medical Journal*, 1969, **4**, 526.

- ¹⁷ Burkitt, D. P., in *Burkitt's Lymphoma*, ed. Burkitt, D. P., and Wright, D. H. p. 213. Edinburgh, Livingstone, 1970.
- ¹⁸ Stern, H., *British Medical Journal*, 1968, 1, 665.
- ¹⁹ Scott, T. F., McN., *American Journal of Ophthalmology*, 1957, 43, Part 2, 134.
- ²⁰ Knox, J. D. E., *Journal of the Royal College of General Practitioners*, 1968, 16, 23.
- ²¹ Smith, I. W., Peutherer, J. F., MacCallum, F. O., *Journal of Hygiene*, 1967, 65, 395.
- ²² Avery, G. B., Monif, G. G. R., Sever, J. L., and Liekin, S. L., *American Journal of Diseases of Children*, 1965, 110, 444.
- ²³ Report of the Public Health Laboratory Service Working Party on Rubella, *British Medical Journal*, 1970, 2, 497.
- ²⁴ Sever, J. L., Huebner, R. J., Castellano, G. A., and Bell, J. A., *American Review of Respiratory Diseases*, 1963, 88, Suppl. 342.
- ²⁵ Hildbrandt, R. J., Sever, J. L., Margileth, A. M., and Callagan, D. A., *American Journal of Obstetrics and Gynecology*, 1967, 98, 1125.
- ²⁶ Stern, H., Elek, S. D., Booth, J. C., and Fleck, D. G., *Lancet*, 1969, 2, 443.
- ²⁷ Nahmias, A. J., Alford, C. A., and Korones, S. B., *Advances in Paediatrics*, 1970, 17, 185.
- ²⁸ Nahmias, A. J., Josey, W. E., Naib, Z. M., Luce, C. F., and Guest, B. A., *American Journal of Epidemiology*, 1970, 91, 547.

Clinical Endocrinology

Gynaecological Symptoms

ALISTAIR W. F. MILLER

British Medical Journal, 1972, 2, 456-458

Gynaecological symptoms such as menstrual disorders are a common feature of endocrine diseases. They may not be the most striking clinical manifestation of the condition, however, and the patient may not be seen by a gynaecologist. In this article the emphasis is on those conditions whose main symptom might be described as "gynaecological." Several symptoms, mainly menstrual upsets, will be considered, their endocrine causes indicated, and brief reference made to other possible explanations where this seems desirable.

Amenorrhoea

The terms primary and secondary amenorrhoea are often used, the first to describe the situation when a patient has never menstruated and the latter the development of amenorrhoea after menstruation has previously occurred. The terms have a useful descriptive value, though the possible causes of both types overlap to a considerable degree.

It should not be forgotten that amenorrhoea is physiological before the menarche, after the menopause, and during pregnancy and lactation. The age at the onset of menstruation is very variable and in the presence of apparently normal physical and sexual development special investigation before the age of 18 is not indicated. Before this, reassurance is all that is necessary, provided cryptomenorrhoea has been excluded. This is false amenorrhoea due to an imperforate hymen. The girl may experience lower abdominal discomfort each month when the endometrium is shed. The menstrual blood collects in the vagina and may eventually distend the uterus making it palpable abdominally. On inspection of the introitus the hymen may be distended by the retained blood. Treatment is by surgical incision of the hymen. Similarly there is a wide variation of the time of occurrence of the menopause. Though most women stop menstruating between the ages of 45 and 50, in 25% this occurs before the age of 45.

The most important cause of amenorrhoea to consider is, of course, pregnancy, the commonest cause of amenorrhoea in any practice. Only by thinking of it first in any woman in the reproductive age group who complains of amenorrhoea will

embarrassing mistakes be avoided. Denials of the possibility of pregnancy because the patient is on the pill, has not missed a period, has been bleeding continuously, or for a variety of other reasons are to be treated with reserve until pregnancy has been positively excluded. The return of menstruation after childbirth or abortion is also variable, though the first period will usually be at about six weeks. If the patient is lactating, however, the interval will be greater, usually three to four months.

HYPOTHALAMIC AMENORRHOEA

It is well known that emotional disturbances of various kinds can lead to amenorrhoea, owing to the influence of the cerebral cortex on the hypothalamus. Common examples of this are worries about examinations, living away from home for the first time, marital upsets, and nervous tension. Such factors should be specifically investigated in a patient who develops secondary amenorrhoea. Recognition of the relevant background factors and reassurance or help with them are the only appropriate therapeutic measures.

Pseudocyesis

The not uncommon condition of pseudocyesis or false pregnancy, which usually results from a great desire for or a fear of pregnancy, is also a hypothalamic disorder. The patient may develop all the signs and symptoms of pregnancy including abdominal swelling; fetal parts cannot, of course, be felt and the abdominal wall is held tense. Examination under anesthesia will lead to disappearance of the swelling when the muscles of the abdominal wall are relaxed, but x-ray or ultrasonic examination of the abdomen should make this unnecessary.

Froehlich's Syndrome

Froehlich's Syndrome (dystrophia adiposogenitalis) is a hypothalamic disturbance in which primary amenorrhoea is a main feature, together with genital hypoplasia and obesity. Vigorous attempts at weight reduction may result in menstruation occurring. The Chiari-Frommel Syndrome, in which galactorrhoea (continuous secretion of milk) and amenorrhoea persist after pregnancy, is also believed to be of hypothalamic origin. It may be treated by stimulation of ovulation by clomiphene citrate.

University Department of Obstetrics and Gynaecology, Royal Maternity Hospital, Glasgow

ALISTAIR W. F. MILLER, M.B., M.R.C.O.G., Senior Lecturer