Recent Advances in CLINICAL VIROLOGY

EDITED BY

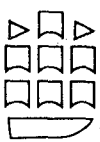
A. P. WATERSON

Recent Advances in CLINICAL VIROLOGY

EDITED BY

A. P. WATERSON MD(Cantab) FRCP(Lond) FRCPath
Professor of Virology, Royal Postgraduate Medical School, University of London;
Consultant Virologist, Hammersmith Hospital

NUMBER TWO



CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1980

CHURCHILL LIVINGSTONE
Medical Division of the Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world.

First published 1980

ISBN 0 443 02094 9
ISSN 0143 6775

British Library Cataloguing in Publication Data

Recent advances in clinical virology.
No. 2
1. Virus diseases
I. Waterson, Anthony Peter
616.01'94 RC114.5 80-49993

Printed in Great Britain at The Pitman Press, Bath

Preface

Approximately four years have elapsed since the publication of Volume One of *Recent Advances in Clinical Virology*. The contents of that first volume could be described as distinctly neurotropic, since, more by accident than by design, about half the contributions concerned viral disorders of the central nervous system. This volume is, if anything, hepatotropic, in that four of the twelve contributions are about viral hepatitis. Research on hepatitis viruses of man has forged ahead, at least in terms of published work, in several directions. Testing for antibodies to hepatitis A has become a routine rather than a research activity, at least for the specialist laboratory. The prophylaxis of hepatitis B with specific immunoglobulin is now generally accepted and, in large measure, effective. Besides this, 'non-A, non-B' hepatitis is at last changing from a tantalising epidemiological wraith into a solid microbiological reality. This means, in terms of medical practice, real advances in the diagnosis and prevention of human viral hepatitis of all kinds, and perhaps Volume Three of *Recent Advances in Clinical Virology* will include a chapter on a safe and effective hepatitis B vaccine. The 'cloning' of hepatitis B surface antigen in *E. coli* (Pasek et al, 1979) bodes well for this, even though virologists have learned to be cautious about promised vaccines.

There is, in fact, continuity with Volume One in that Longson and his colleagues have updated their account of herpes encephalitis. It is interesting that attempts to improve the therapy of this disease have widened considerably our knowledge of its natural history. The treatment of herpesvirus infections in general is dealt with by Bauer, and of ocular herpes infections in particular by Darougar and his colleagues. The herpesviruses have emerged from a position of relatively minor importance to loom much more largely in clinical virology because of the growing population in our hospitals of immunosuppressed patients or of patients with deficiencies in cellular immunity who would not previously have survived. The frequency of herpesvirus infections in these patients emphasises their delicate balance between health and disease. This applies in general to those viruses dealt with by cellular immunity rather than by the antibody response. Fortunately, herpes simplex and herpes zoster are, comparatively speaking, very amenable to antiviral chemotherapy. It is unfortunate that cytomegalovirus, which has so many features in common with the herpesviruses, is not at present susceptible to the same approach.

It is salutary to recall some of the many unsolved problems in medical virology. It is, for example, still impossible to culture in vitro the human wart viruses. However, the molecular biological approach to these, viz. the use of restriction enzymes to characterise their DNA, has enabled a precise taxonomic approach. Their taxonomic relatives, the human papovaviruses BK and JC, bring us back to the problems of immuno-compromised patients, and Dulcie Coleman's account of these contains

much new information which supplements the comprehensive account by Sylvia Gardner in Volume One. The problems of clinical infectious transmissible virus disease are exemplified by Jon Coleman's account of sexually transmitted virus diseases, and this brings us full circle back to hepatitis B. The relationship of viruses to the aetiology of multiple sclerosis is fraught with uncertainty, and there is a stringent analysis of the evidence for and against the involvement of measles in the contribution by Fraser.

It is tempting to say that no book on microbiology would be complete today without a chapter on safety, although it is also true that we cannot be 'documented out of disaster' (British Journal of Hospital Medicine, 1979). The account of safety in the virological laboratory, by Flewett, who was a member of the Howie committee on safety in clinical laboratories, is intensely practical, and also delightful in such details (p. 183) as the citation 'Flewett (personal disagreeable experience)'.

It is my hope that this second number of *Recent Advances in Clinical Virology* will do something towards bridging the gap between advances in knowledge about viruses of medical importance, and the clinical application of these advances to the diagnosis or the containment of disease.

Hammersmith, 1980 A.P.W.

REFERENCES

Pasek M, Goto T, Gilbert W, Zink B, Schaller H, Mackay P, Leadbetter G, Murray K 1979 Nature 282: 575–579

British Journal of Hospital Medicine 1979 Leading Article 22: 537

Contributors

ANDREW S. BAILEY FIMLS
Chief Medical Laboratory Scientific Officer, North Manchester Regional Virus Laboratory, Royal Infirmary, Manchester

D. J. BAUER MB BChir (Cantab) FRCP (London)
Formerly Head, Antiviral Chemotherapy Section, Wellcome Research Laboratories, Beckenham, Kent.

ELIZABETH H. BOXALL BSc (Birmingham)
Principal Virologist, Regional Virus Laboratory, East Birmingham Hospital, Birmingham

DULCIE V. COLEMAN MD (Lond)
Senior Lecturer in Clinical Cytology and Cytogenetics, St. Mary's Hospital, London

J. C. COLEMAN MB BS (Lond) MRCPath
Senior Lecturer in Medical Microbiology, Charing Cross Hospital Medical School, London.

S. DAROUGAR MD (Teheran) DTMH MRCPath
Reader in Public Health Ophthalmology, and Head of Virus Laboratory, Institute of Ophthalmology, University of London. Consultant Virologist, Moorfields Eye Hospital, London.

T. H. FLEWETT MD (Belfast) MRCP (Lond) FRCPath
Consultant Virologist, Regional Virus Laboratory, East Birmingham Hospital, Birmingham; Reader in Virology, University of Birmingham.

K. B. FRASER MD DSc (Aberdeen)
Professor of Microbiology, The Queen's University, Belfast.

PAUL KLAPPER BSc (Trent)
Research Assistant, North Manchester Regional Virus Laboratory, Royal Infirmary, Manchester.

MAURICE LONGSON MD (Manchester)
Consultant Virologist, North Manchester Regional Virus Laboratory, Royal Infirmary, Manchester.

MARJORIE A. MONNICKENDAM PhD (East Anglia)
Lecturer in Virology, Institute of Ophthalmology, University of London.

P. P. MORTIMER MD (Lond) MRCPath.
Consultant Microbiologist, Virus Reference Laboratory, Central Public Health Laboratory, Colindale, London.

SHEILA POLAKOFF MD (Dublin)
Consultant Epidemiologist, Epidemiological Research Laboratory, Central Public Health Laboratory, Colindale, London.

J. D. TREHARNE BSc (Bristol)
Senior Lecturer in Virology, Institute of Ophthalmology, University of London.

ARIE J. ZUCKERMAN MD (Lond) FRCP (Lond) FRCPath.
Professor of Microbiology, London School of Hygiene and Tropical Medicine, University of London.

Contents

1. Hepatitis A and its virus

P. P. Mortimer

Ten years ago it would not have been possible to write a chapter on the clinical virology of hepatitis. There were no specific tests in general use and, though researchers were following promising leads in immunodiffusion, electron microscopic and animal studies, the full potential of the observations on the Australia antigen (hepatitis B surface antigen) by Blumberg and his collaborators had not been recognised. Since then developments in hepatitis B research have been rapid, and they have acted as a catalyst for concurrent work on non-B hepatitis. Using new techniques and experience gained in related fields the essential features of the other common cause of acute hepatitis, hepatitis A virus (HAV), have gradually been established. A notable example of this progress was the observation by Feinstone et al (1973), that virus particles could be seen by electron microscopy in the faeces of volunteers inoculated with MS1, a well-characterised strain of hepatitis A, and that the particles were aggregated by convalescent sera from the volunteers and from patients naturally infected with HAV. This work united two of the three approaches which were being made to the virology of hepatitis A. The first of these was the investigation, by immuno-diffusion and electron microscopy, of faecal antigens associated with infectious hepatitis (Ferris et al, 1970), and the second was the series of studies at the Willowbrook Institution on an agent causing short incubation hepatitis, MS1 (Krugman & Giles, 1970). The third approach, of equal significance, was the inoculation of laboratory primates with HAV (reviewed by Deinhardt, 1976). This work provided an alternative to human volunteer experiments, and pointed the way to sources of antigen and tissue culture cells for current investigations on HAV.

The fusion of these three strands, technical innovation in the laboratory, clinical observations under controlled conditions, and experiments with primates has, since 1973, brought about a great advance in our knowledge of hepatitis A. This chapter concentrates on the main features of this advance and its implications for the clinical virologist, and suggests how clinical and public health practice might be modified to take account of the new knowledge.

THE VIRUS OF HEPATITIS A

Properties of the virus

The physico-chemical properties of HAV have been studied by Bradley et al (1978). It is a 27 to 30 nm particle with cubic symmetry. Virus isolated from faecal and probably from in vitro material occurs in forms with several densities. The main one bands at a density of 1.34 g/ml in caesium chloride and sediments at 170s in a sucrose gradient. On polyacrylamide gel electrophoresis at least three and probably all four of the major

characteristic enterovirus polypeptides have been found in HAV (Coulepis et al, 1979; Siegl, personal communication). The nucleic acid is sensitive to ribonuclease and sodium hydroxide, and resistant to deoxyribonuclease. The virus is inactivated but retains antigenicity when treated with 1 in 2000 formaldehyde for three days at 37°C. In most of these respects HAV resembles the enteroviruses (Table 1.1), but it is

Table 1.1 Similarities and difference between enteroviruses and hepatitis A virus

	Property	Enteroviruses	Hepatitis A virus
Similarities	Size	27 nm	27–30 nm
	Mean density	1.34 g/ml	1.34 g/ml
	Nucleic acid	RNA	RNA
	Major polypeptides	4	3, ?4
	Inactivated by 1/2000 formaldehyde	Yes	Yes
	Stable at 4°C	Yes	Yes
Differences	Multiple particle densities	Unusual	Usual
	Stable at 60°C for 30 minutes	No	Yes
	Growth in culture in vitro	Prolific	Limited
	Site of replication in vivo	Gut epithelium	Hepatocyte

somewhat more heat-resistant, withstanding 60°C for 30 minutes, and displays obvious biological differences, for instance in its failure to replicate in gut epithelium, its reluctance to grow in vitro and its longer incubation period and hepatotropic behaviour in vivo. It is quite distinct from hepatitis B virus, and from the non-A non-B agents recently described by Shimizu et al (1979).

Experimental infection of man and other primates

Experimental infection of man with material from cases of infectious hepatitis was carried out by several groups during the 1940s (see Cossart, 1977). This work established that acute phase blood and faeces were infectious parenterally and orally and that the incubation period by the latter route was about 28 days. It is fortunate, now that serological methods have been developed, that material from at least one series of volunteer experiments has been available for further study. Decker et al (1979) reported that of 44 volunteers studied in the late 1960s, only 24 were susceptible to HAV and that, of these, 18 were in the group receiving infectious virus. Nine sero-converted following challenge, of whom eight had a clinical illness. The asymptomatic volunteers had a delayed and briefer period of serum enzyme disturbance, and developed a lower titre of anti-HAV in convalescence than the clinical cases. From this, and other studies, typical hepatitis A in man can be defined as an acute viral infection in which jaundice, the most striking feature, develops four weeks after exposure and is preceded by several days of malaise and a slightly longer period during which virus is shed in the faeces. The appearance of jaundice is accompanied by abnormalities in liver enzyme tests, curtailment of virus excretion and a sharp rise in anti-HAV of both IgM and IgG class immunoglobulin. These features are summarised in Figure 1.1. It must be remembered, however, that cases are not

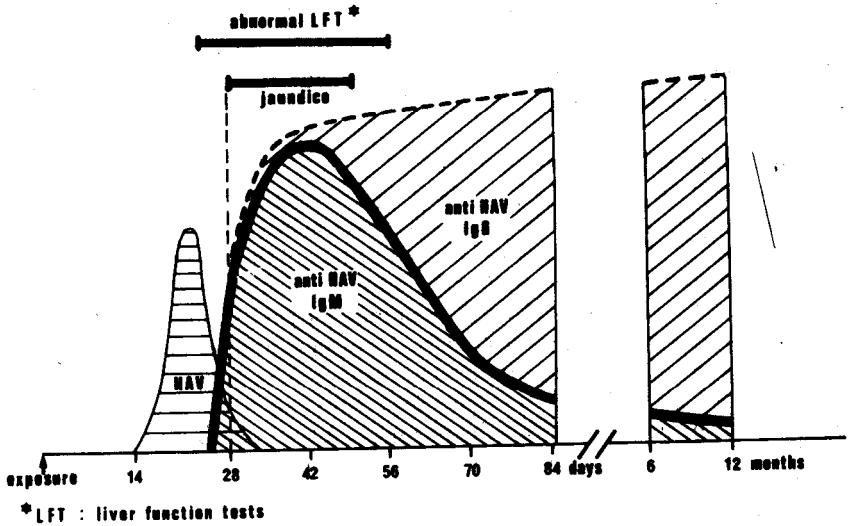


Fig. 1.1 Clinical and laboratory features of hepatitis A.

uniform in severity and, that hepatitis and its associated features are generally milder in childhood.

Transmission of hepatitis A infection between man and other primates such as chimpanzees, can occur in both directions. It is doubtful whether chimpanzees are infected in the wild state, but they are commonly infected soon after capture and in turn often infect their handlers (Ruddy et al, 1967). They were used in some early experimental work on hepatitis A, but this was confused by the inability to recognise the pre-existing immunity of some subjects. Chimpanzees were again used as an animal model as soon as tests for susceptibility to HAV became available. Dienstag et al (1975) fed and inoculated the MS1 strain of HAV into susceptible animals. Clinical, biochemical and histological features of hepatitis appeared in the fourth week and were similar to those of human infection.

The other main primate group susceptible to hepatitis A is marmosets. Evidence for their susceptibility originally came from a survey in which laboratory colonies of white-lipped and cotton-topped marmosets were challenged with a range of human viruses (Deinhardt et al, 1967). It is now known, that, with varying susceptibility, several other species of marmoset can be infected with HAV. There is faecal excretion of virus followed by a mild serum enzyme disturbance four to five weeks after inoculation. In suitable conditions marmosets breed freely in captivity and they are more convenient to handle than chimpanzees. HAV can be recovered both from the faeces and the liver of infected animals.

Although the pattern of these experimental infections in non-human primates is now well established, chimpanzees and marmosets are still needed to provide adequate supplies of antigen for diagnostic tests and primary liver tissue for cell culture, and to allow animal testing during vaccine development. Enlargement of existing facilities or the setting up of new colonies of both primates is needed if we are

to profit fully from current developments in the field of hepatitis A. To achieve this, further stocking of breeding colonies with feral animals is probably necessary, although this is opposed both by some of the countries of origin and by pressure groups in importing countries.

Propagation of HAV in tissue culture

For many years it had seemed that HAV was resistant to conventional cell culture techniques. Now Provost & Hilleman (1979) have shown that HAV can be propagated in at least two in vitro cell systems. Using a battery of fluorescence, radioimmunoassay, immune-electromicroscopical and animal inoculation tests they have demonstrated that strain CR326 of HAV will, after multiple passes in marmosets, replicate in primary cultures of marmoset liver cells. More significantly, they have passed this strain in a semi-continuous line from fetal rhesus monkey kidney (FRhK6). Yields of virus from passage in this line are higher than in primary marmoset liver, and it seems likely that adaptation of the virus by passage to a level that will prove more prolific and less exacting in its choice of cell substrate can be achieved. Although the cell line FRhK6 cannot be carried through more than a dozen passes, the potential, if CR326 can be adapted to better established semi-continuous lines such as those used to prepare viral vaccines, is enormous.

There are now preliminary reports that HAV may also be propagated in African green monkey kidney (AGMK) cells, and in the Alexander hepatoma cell line. This suggests that there are, in fact, a range of cells capable of supporting replication of HAV in vitro, several of which may form suitable substrates for vaccine production. None of these reports describe a visible cytopathic effect of HAV: neither has a direct isolation from a human faecal specimen in tissue culture been reported.

LABORATORY DIAGNOSIS OF HAV INFECTION IN MAN

Detection of HAV

Although serological tests, not tests for viral antigen, are now the mainstay of laboratory diagnosis, it is important to be able to detect HAV, particularly in faeces. Faecal HAV is the earliest marker of infection and a valuable source of reagent. Two techniques are in general use. The first, immune electron microscopy, is based on the aggregation of faecal particles by an immune serum (Locarnini et al, 1974). To control this procedure, a non-immune serum, preferably a pre-infection specimen from the same source as the immune serum, should be shown not to clump the particles. In the second technique the faecal suspension is 'sandwiched' between a solid phase coated with an immune serum and a labelled antiserum. While these two techniques are of comparable sensitivity the second is rather more useful, partly because it gives a better indication of the quantity of antigen present and therefore its potential as a reagent, and partly because it is more readily available to diagnostic laboratories. Labelled anti-HAV, commercially obtainable in anti-HAV test kits, can be used for sandwich tests on faecal specimens.

Because of difficulties with the supply of susceptible primates and inability to prepare antigen in reagent quantities in vitro there is now an urgent need to identify

positive human faecal specimens. Screening of faeces in the prodromal phase of hepatitis A can easily be done by the sandwich method, and it would be of mutual benefit to offer this test to clinical colleagues who frequently see cases of infectious hepatitis.

From the diagnostic point of view tests for faecal HAV have not, however, been of as much practical value as the serological tests described below. The maximum excretion of virus precedes the early symptoms of hepatitis. Collecting serial faecal specimens is not a popular task, and once the anorexia of the early illness sets in there is a paucity of faecal material. Often, unless previous cases have been recognised, the diagnosis of hepatitis A is not considered until jaundice has developed and faecal particles have gone. When cases are recognised the contacts are usually given immunoglobulin and this probably suppresses faecal excretion of virus. For these reasons and because hepatitis A is now uncommon in developed countries most workers have found it difficult to obtain HAV in reagent quantities from human sources.

Detection of anti-HAV

Because there are no abundant sources of HAV antigen, tests for anti-HAV have not proved easy to establish. The earliest effective method, immune adherence haemagglutination (IAHA) (Moritsugo et al, 1976), has now largely been abandoned: apart from inherent difficulties in the technique, it uses antigen relatively extravagantly. It does, however, have one useful feature, that the antibody rise is slow, and therefore a diagnostic change in titre between an acute and convalescent serum is usually demonstrable (Gust et al, 1977).

As a routine diagnostic test, anti-HAV determination is now mainly done by solid phase radio and enzyme immunoassay (SPRIA, SPEIA). At the present time most laboratories depend on a SPRIA kit (*HAVAB*, Abbott Laboratories). The basis of this assay is an antigen-coated bead which is added to a mixture of the serum under test and a radio-labelled IgG fraction of an immune human serum. The amount of the radio-label taken up by the bead is diminished by competition from any anti-HAV that may be present in the specimen. Although the test is simple it has disadvantages. The anti-HAV response is usually well developed by the time a serum specimen is collected from a case of acute hepatitis, and even a low titre of anti-HAV prevents the uptake of most of the radio-label onto the antigen sites on the bead. Therefore no clear difference between the reactivity of an early and a late serum can be shown unless successive dilutions of each are tested to establish an endpoint. Up to ten tests on two sera may be required. This greatly increases costs as well as involving delay while waiting for a convalescent serum. For these reasons HAVAB and similar competitive methods are not very convenient for diagnostic work.

For determining immunity to HAV, on the other hand, the competitive tests are ideal. They are easy to set up and rarely give equivocal results, except on sera from patients who are actually in the incubation period of hepatitis A. They are more sensitive than IAHA, which fails to detect anti-HAV in some patients (Drucker et al, 1979). As more laboratories undertake serum surveys the anti-HAV test will provide a broad indication of the prevalence of immunity in different communities. It also promises to be the basis for more rational prophylaxis with immunoglobulin and, in the future, with vaccine.

Detection of anti-HAV IgM

The humoral response to hepatitis A infection is, as already noted, brisk. Even if a serum has been collected when the patient is first seen there is only an even chance of showing a diagnostic rise in titre of anti-HAV. This difficulty in making a serological diagnosis is best overcome, as it has been in the case of other virus infections, by the use of a specific IgM test. The test can be accomplished either by separating an IgM rich, IgG free fraction of serum by gradient centrifugation or gel filtration and testing it for anti-HAV as described above, or by direct testing of the IgM component in serum. These direct tests are based on an anti-human μ chain serum which is either bound to the solid phase (Flehmig, 1978), or used in a labelled form as the final layer in a sandwich (Locarnini et al, 1979). All three approaches to specific IgM estimation have been compared by Roggendorf et al (in press). For the time being the first is the most convenient for diagnostic laboratories, many of which already use similar methods for the diagnosis of rubella. Sera collected within two months of the onset of hepatitis A usually have anti-HAV IgM detectable by this method (Mortimer et al, 1979). However the separation of IgM from serum is slow and laborious, and the anti-HAV in the IgM fraction competes poorly with the label (an IgG fraction). As a result tests on isolated IgM fractions by *HAVAB* and similar tests are sometimes inconclusive.

For these reasons one of the direct approaches to specific IgM estimation is likely to emerge as the method of choice, and experience so far favours the test in which an anti-μ chain serum is coated to the solid phase. The features of this test are of sufficient general interest to justify description here. Polystyrene tubes, wells or beads are coated with a dilution of an anti-human μ chain serum. They are then incubated with human IgG free of IgM in order to block the non-specific binding of IgG when the specimen is added (serum from cord blood is a convenient source of this blocking IgG). A high dilution (about 10^{-6}) of the specimen is applied to the surface, and, in subsequent steps, HAV antigen, and radio-labelled human IgG with a strong anti-HAV activity are added. This is a sensitive method, and anti-HAV IgM can often be detected for up to six months after the acute phase. The specificity of the method, when applied to the diagnosis of hepatitis A, is also high, though theoretical objections that rheumatoid factor may interfere with the test have not been wholly refuted. This RIA 'anti-μ' method, or a similar one using an enzyme label (Duermeyer et al, 1979), is likely to become the standard diagnostic method for hepatitis A, and commercial kits using both kinds of label are soon to be available. available.

RECENT EPIDEMIOLOGICAL OBSERVATIONS

Serological surveys

Once tests for anti-HAV had been introduced laboratories in many countries carried out surveys to assess the prevalence of infection with hepatitis A. The results have provided a useful overall picture, but it should be noted that the surveys have been small, the groups studied sometimes not representative, and ages of the subjects often not recorded. For instance blood donors from whom patients with a history of jaundice have been excluded do not form a good sample for this purpose. No easily

available sample is, in fact, likely to represent a whole population accurately, particularly because of locally variable socio-economic conditions. These conditions are an important factor influencing the prevalence of anti-HAV. In addition there seem to be greater differences in prevalences between countries and between age groups than can be explained by a stable process of exposure to a virus spread by the faecal-oral route. This suggests recent changes in prevalence in some countries, and these are discussed below.

The first comparisons of immunity levels in various populations and social groups were reviewed by Dienstag et al (1978). They were based mainly on immune adherence tests for anti-HAV whereas, more recently, surveys have used RIA tests (Frösner et al, 1979). The results by each test are probably comparable though there is evidence suggesting that RIA detects more immune patients. Several patterns of prevalence emerge from the surveys so far reported. The first exists in countries with poor sanitation, where transmission by the faecal oral route is unimpeded. In such conditions at least 90 per cent of adults can be expected to be immune to hepatitis A, though, in a capital city for instance, the existence of basic sanitary amenities allows more inhabitants to escape infection. The latter point is underlined by the very many adult cases of hepatitis A seen in New Delhi when the public water supply became contaminated (Viswanathan, 1957). Although few studies have been carried out in the tropics it appears that most children are infected at an early age. The virus is endemic, and susceptible adults, for instance visitors from Europe, are at considerable risk of being infected and suffering clinical hepatitis, especially if they 'go native'. In a few parts of Europe a similar level of endemicity exists. In Sicily, for example, 90 per cent of children aged 1 to 10 years in two towns were immune to hepatitis A, though in the main city, Palermo, where no epidemic had been recognised in recent years, only 28 per cent of the same age group were immune (La Rosa et al, 1978).

The second prevalence pattern is that seen in much of the rest of Southern Europe. Because of variable social conditions and hygienic standards, part of the population is infected, mostly subclinically, in early childhood, and part is infected, mainly with accompanying symptoms of clinical hepatitis, as older children and young adults. This pattern exists in much of Greece, Italy and Spain. In these areas the prevalence of anti-HAV rises steadily to a level of 90 per cent in middle age (Table 1.2).

Table 1.2 Prevalence of anti-HAV in young adults (20–29 years) measured by radioimmunoassay

Country	Centre	Authors	Number examined	Number anti-HAV positive	Percentage positive
Sweden	Gothenburg	Frösner et al (1979)	208	6	3
Norway	Oslo	Frösner et al (1979)	80	4	5
Switzerland	Bern	Frösner et al (1979)	147	18	12
UK	London	Mortimer & Pollock (1979)	220*	28	13
Netherlands	Amsterdam	Frösner et al (1979)	199	62	31
West Germany	Tübingen	Frösner et al (1979)	221	79	36
Belgium	Leuven	De Groote (1979)	224	100	45
France	Paris	Frösner et al (1979)	107	57	53
Italy	Milan	Zanetti et al (1979)	99†	79	80
Greece	Athens	Frösner et al (1979)	92	77	84
Spain	Barcelona	Vargas et al (1978)	?	—	90

* Voluntary Service Overseas personnel
† aged 16–30 years

The third prevalence pattern is one that is probably new to human populations. Studies in developed countries, notably in Scandinavia, suggest that the transmission of hepatitis A is now so inconstant that the disease would disappear were it not for the visits that many of the population make each summer to countries where hepatitis A is endemic. The prevalence of anti-HAV in young adults is now only 10 per cent in Sweden and it is not much higher in London (Table 1.2). It has been estimated that only 10 per cent of newborn Scandinavians will acquire anti-HAV by the age of 40 years (Schenzle et al, 1979).

Of course results from single centres cannot really be regarded as representative of a whole country, and differences probably exist between regions, and between communities in the same locality. For example published figures of prevalence of anti-HAV in Sicily and in Milan show a gross difference; and, while most young adult Germans are without antibody, guest workers of the same age, mostly Turkish, Italian, Greek and Yugoslav, are almost all immune (Flehmig et al, 1978). The children of these workers, however, if born in Germany, are mostly susceptible, and often contract hepatitis when they visit their parents' country of origin.

The prevalence pattern of anti-HAV in England is probably similar to that in West Germany. The results of surveys known to the author can be summarised by saying that the present prevalence of anti-HAV in any English cohort is close to its age expressed as a percentage. A small survey carried out in London in 1978 makes this point (Table 1.3). The rather low figure of 13 per cent prevalence in young British

Table 1.3 Prevalence of anti-HAV at various ages (London, 1978)

Age group (years)	2–4	5	10	15	25	30
Number examined	40	36	40	63	25	58
Number positive	1	2	1	7	6	28
Percentage positive	2.5	5.5	2.5	11.1	24.0	48.3

adults in Table 1.2 may reflect a preponderance of social class I and II among volunteers for service overseas.

Changes in the prevalence of hepatitis A

Both notification data and serological studies point to a remarkable change in the epidemiology of hepatitis A in North West Europe and North America in the last twenty years. The delayed acquisition of anti-HAV in young people almost certainly reflects a recent partial interruption of the natural spread of infection. The alternative explanation, that experience of hepatitis A infection, unlike that of other viruses, is acquired at an even rate throughout life, seems improbable.

Notifications of infectious jaundice in England and Wales over the last ten years are consistent with the view that hepatitis A no longer circulates freely in this country (Table 1.4). There has been a sharp fall in notifications, particularly in the period 1969 to 1974, and the decline has been most pronounced in children. In the period for which tests for hepatitis B surface antigen (HBsAg) have been generally available (1974 to 1978) no such decline has occurred in the incidence of hepatitis B, and the proportion of cases among children has remained small. If it is assumed that other causes of hepatitis do not play a large part in the aetiology of infectious jaundice these figures imply that there has been a very substantial fall in the number of cases of

Table 1.4 Notifications of infectious jaundice (OPCS) and of HBsAg positive cases of acute hepatitis B (PHLS) for 1969, 1974, 1978

	1969	1974	1978
Notifications of infectious jaundice	23 572	7609	4663
% of total notifications that are cases < 15 years	59.8%	41.5%	24.5%
HBsAg positive cases of hepatitis reported to the Public Health Laboratory Service	—	779	979*
% of total HBsAg positive cases < 15 years	—	2.5%	1.9%

* provisional figure

Data provided by Dr Sheila Polakoff

hepatitis A over the last decade, and that this is mainly due to a much lower incidence of hepatitis A in childhood. The incidence of hepatitis A in adults has not changed to the same extent, perhaps because, while exposure is less common, fewer adults are now immune. Another factor in sustaining the incidence of hepatitis A in adults is that a relatively large proportion of infections are now contracted abroad.

The extent to which recent changes have modified the epidemiology of hepatitis A

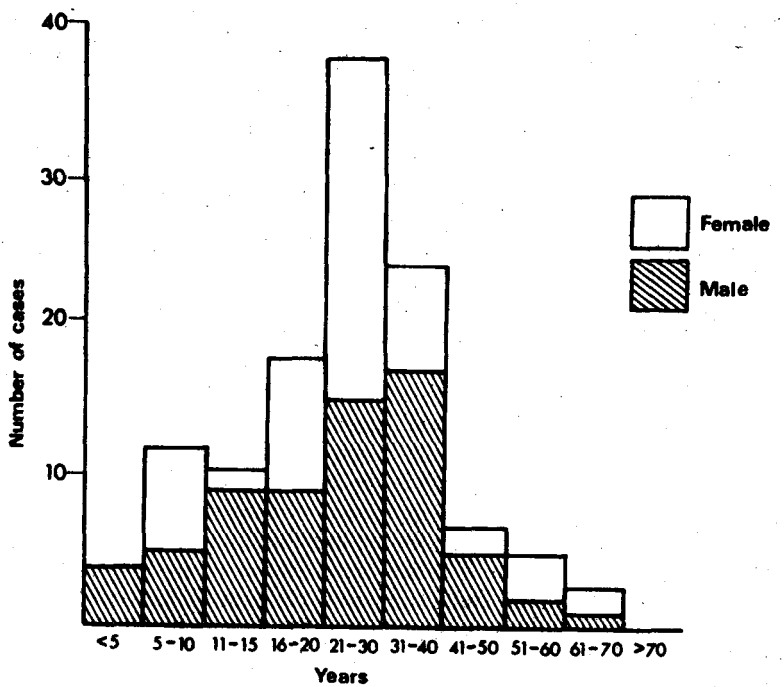


Fig. 1.2 Age/sex distribution of 122 laboratory-confirmed sporadic cases of hepatitis A, England 1978–1979.