MAN AND RESPIRATORY VIRUSES

BY OLADEINDE OGUNBI

LAGOS UNIVERSITY PRESS . 1981
INAUGURAL LECTURE SERIES

MAN AND RESPIRATORY VIRUSES

An Inaugural Lecture delivered at the University of Lagos
on Friday, 10th May, 1974

By

OLADEINDE OGUNBI
Professor of Microbiology and Parasitology
University of Lagos

University of Lagos Press
1981

ISBN 978-22-64-11-3

Summary

Man was able to overcome most bacterial infections with antibiotics. With the exit of bacteria came the viruses; the smallest pathogens of man, which characteristically thrive within the living cell and take over the cells' metabolism after infection, replicating and eventually destroy the host – the cell.

Owing to this intimate relationship between the virus and the cell, up to date, we have no specific agent that will selectively destory or inhibit growth, without, at the same time injuring the host – the cell. A number of prospective agents are under investigation currently.

This lecture is concerned with the activities of those viruses that infect primarily the respiratory tract of man which include Influenza, Para-Influenza, Respiratory Syncytial virus, Adeno, Rhino, Coxsackie, Echo, Corona and other viruses.

The concept of virus infection existed long before the agent itself was discovered in 1933 by a process of bacterial elimination. That viruses are the major causes of respiratory infections is proved by statistics. A break-down of different viruses with percentage of infections of this symptom complex is also available in literature, including the range of adult and infant infectivity.

There is difficulty in establishing a clinical diagnosis, as a great variety of agents provoke the same symptom complex. They range from flu, and febrile respiratory infection to sore throat, common cold, croup, acute bronchitis and bronchiolitis besides atypical and viral pneumonias.

Influenza

It is a droplet infection transmitted from man to man, in epidemics and sometimes in pandemics, with rapid spread and high fatality. The onset is abrupt, with short incubation period of 24 hours to 3 days. The symptoms are malaise, nausea, headache, chills and high temperature with pain in limbs. The virus persists in man.

The disease has been rife in the world from at least fifth century B.C. There was a period ignorance until the first epidemic was casually reported in 1557, followed by one in 1530 and others in 1697 and 1732. We have two pandemics in the 19th century, followed by two in 1918 and 1957. The last two originated in China. First virus isolation was made in ferret in 1933 followed by 53 new strains using emryonated egg technique. The most important aspect of influenza epidemiology is its antigenic change ranging from A to B and C and also from A_0 to A_4. Several explanations are offered for this antigenic change in the virus.

The Influenza Virus belongs to an RNA group of Viruses and is sensitive to either. It has a helical ribonucleoprotein core with a loose protein envelope with cylindrial projections. The diameter of the virus particle is 80 to 110 nanometres. It can be identified rapidly by Immuno-fluorescene and serologically by specific anti-bodies. It can be cultured not only in embryonated egg but in tissue culture.

The only effective method of prevention of infection is by Vaccination. The inactivated Vaccine in use to date is prepared from virus cultured in the allantoic cavity of embryonated eggs combined with an adjuvant. Interferon, a protein synthesised by cell exposed to the action of foreign nucleic acid is a natural antiviral substance on which great hope was placed. Because of antigenic variations, a quadri-valent

vaccine with feasibility of combining antigens was prepared and used in France. Usual standardization procedure and purification were followed before use. Except during pandemics, the best period for Vaccination is Autumn with a booster injection every year to yield satisfactory immunity. For primary inoculation, the vaccine is given in two doses. Not only the dosage and schedule of vaccination are discussed but also the persons who should be vaccinated. While the value of the inactivated vaccine has been proved, the attenuated vaccine given intranasally still remains unproved in long term protective value.

Febrile Sore Throat

Next in importance to Influenza and Febrile Acute-Respiratory infection is Sore Throat. One third of cases is usually caused by streptococci. The second-third is caused largely by by Adeno and the remaining third is caused by Influenza A & B, Coxackie, Echo & Rhino-viruses.

The Common Cold

Rhinoviruses are the major agents. Adeno and RSV viruses play a minor role in this symptom complex. The Rhinoviruses belong to the picorna group of viruses and can be differentiated from enteroviruses by their instability to acid pH. There are over 80 serotypes. The prevalence of different serotypes makes its epidemiology a changing mosaic and thus, the problem of multiple colds, resulting from multiple infections with no cross protection by one antibody against a different serotype. This has hindered the development of an effective vaccine.

R S V

R S V is the most important viral respiratory pathogen of infancy, affecting mainly the lower tract with an infective rate ranging up to about 30% in ones study with symptom of

bronchiolits and pneumonia. The epidemics are sharply circumscribed and last three to five months mostly during autumn in temperate countries and in cooler months in sub-tropical regions.

The virus is a medium sized RNA virus with serotypes. Inactivated vaccine is not suitable as its use led to complications and had to be abandoned. Attenuated vaccine is undergoing trials.

Para-Influenza

These are also the pathogens of early life like RSV, affecting the children and infants to the extent of 50% causing croup. Usually it is endemic in communities but occasionally it assumes epidemic proportion.

The viruses are pleomorphic with a size ranging from 120 to 200 nanometres with known types 1 to 4. The first three have a world wide distribution and the type 4 is found only in U.S.A. Primary infection confers resistance to subsequent severe illness, but reinfections have been reported.

It is diagnosed in the laboratory by syncitial changes in Tissue Cultures with strain 2, and with haemadsorption of Tissue Culture cells in the others as they do not produce cytopathogenic changes. No vaccines are available.

The remaining viruses belonging to Adeno, Entero and Reo-viruses do occasionally cause respiratory infections but they are not important.

Viral Respiratory Infection in Lagos

A serological study of the incidence of C. F. antibodies to different serotypes and strains of Influenza, Para-influenza, Adeno, RSV and Psittacosis viruses in 309 samples of sera from Nigerians was carried out in 1965. The incidence values of 54, 54, 53, and 35% were obtained respectively for the above infections. In a second survey of acute respiratory tract infections by both virus and bacteria in Nigerian children it was found that RSV, Para-influenza, Herpes simplex and Adenoviruses were responsible for 24, 24, 18 and 4% respecitvely of acute bronchiolitis. In the above group 35.5% were of viral origin.

Atypical pneumonia now largely reserved for pneumonia due to Mycoplasma pneumoniae (about 55%) and Adenoviruses, Psittacosis and Q fever accounted for about 45%.

Pneumonia following viral infection was largely due to secondary bacterial invasion in about 60% of cases. PPLO, Influenza A and B, Adenoviruses and Para-influenza viruses were reponsible for for the remaining 40% (17).

Introduction:

With the Antibiotic era following the discovery of penicillin some three decades ago, man soon overcame, practically all the bacterial infections. With the exit of the bacteria came the viruses. These are the smallest micro-organisms that are pathogenic to man. Characteristically, they thrive only within living tissue. On infecting the cell the virus takes over the control of the cell's metabolism, replicating itself and eventually destroying the cell. Owing to this intimate relationship between the virus and the cell, up to date we have no specific agent that will selectively destroy or inhibit the growth of the viruses without at the same time injuring the host cell. A number of likely agents are currently under investigation. This lecture is concerned with the activities of those viruses that infect primarily the respiratory tract of man. The concept of virus infection existed long

before the actual agents were known. Cases of viral pneumopathy were originally diagnosed by excluding bacterial infections not by isolating pneumotropic viruses. This led to the diagnosis of primary atypical pneumonia, a term reserved for pneumonia of virus aetiology. The discovery in 1933 by Smith, Andrew and Laidlaw of the influenza virus and its culture marked the beginning of the new era in the understanding of viral respiratory infections.

Viruses are the major cause of respiratory infections. Dingle and Feller (8) estimate that they are the causal agents in 66 per cent of cases. In 1960 Evans (10) indicated that bacteria were responsible for only 10 per cent of respiratory infections. Chanock and Parrot (6) in the U.S.A. after seven years of investigations involving seven thousand, nine hundred and thirty-eight (7,938) children with respiratory disease reported that the virus was isolated in 44 per cent of the patients but only 8.2 per cent of the control subjects. According to a survey, (Wilder, C. S. 946) carried out in United States between 1957 and 1962 an estimated two hundred and twenty-seven million (227,000,000) respiratory infections per year occurred in the general population. It was estimated that over 90 per cent of the infections were due to non-bacterial agents. In 80 per cent of the cases the patients' activity was decreased and in 52 per cent of the cases the patients had to remain in bed for at least one day. Investigations among Urban and Rural populations have shown that acute respiratory infections are the main cause of morbidity. They represent the motive for 35 per cent of all visits to or by physicians.

The viruses associated with respiratory tract infections:

Influenza viruses are said to be responsible for less than 0.5% of viral respiratory infections (6) but may hold the foremost place during epidemics with 28.7% (2).

of the respiratory infection, particularly in children. Respiratory syncytial virus is now recognised as a deadly pathogen in children, being responsible for 29.6% of the respiratory infections. Adenoviruses are less important being responsible for a small percentage of relatively mild respiratory infections. The Rhinoviruses account for most of the common cold in the population. Some Coxsackie, Echo, and Corona Viruses have been associated with respiratory tract infection.

The difficulty of establishing clinical diagnosis is emphasised by the great variety of agents that may provoke the same clinical picture particularly in the absence of epidemic. However, precise diagnosis must not be seen as a hopeless task to the clinician. Two physicians established diagnosis that proved to be exact in 89% of cases of influenza and 70% of cases of primary atypical pneumonia in a study of two general practices (2) in Britian.

Respiratory syndromes and the respiratory viruses

Influenza and febrile actute respiratory illness resembling influenza. About 50% of this clinical manifestation are due to the influenza viruses particularly influenza A virus, followed by B and with some contribution from C influenza viruses. Adenoviruses 3, 4, 7, 14 and 21 will account for some 25% of this syndrome, while Coxsackie A & B and Echo 11 and 30 will account for some 20% of this group of illness in man.

Febrile sore throat (Pharyngitis and tonsillitis) with haemolytic streptococci accounting for about a third of the illness, is largely a viral infection with Adenoviruses 3, 4, 7, 14 and 21 responsible for about a third, and influenza A & B, Coxsackie, Echo and Rhinoviruses accounting for the remaining third.

Common cold:

Fifty per cent of this is accounted for by the Rhinoviruses, with Para-influenza virus accounting for some 10%. Respiratory syncytial virus, Coxsackie, Echo, Influenza and Adenoviruses account for another 10% leaving some 15% with currently unknown aetiological agents.

Croups in infants

These are obstructive tracheo-laryngo bronchitis, about 80% of which are due to the para-influenza viruses, 1, 2, 3 and 4. Echo and Influenza A accounting for the remaining 20%.

Acute bronchitis in children is largely due to rhinoviruses (50%), RSV 10%, Para-influenza viruses 10% and PPLO, Eaton agent and influenza viruses responsible for the rest.

Acute bronchiolitis in infants is largely due to Respiratory Syncytial virus, being responsible for about 65%, with Para-influenza accounting for 15%, Influenza A and B 15% and PPLO and Eaton agent 5%. This is a rapidly fatal disease in infants.

The Problems of Future Research

In the past two decades many new viruses have been isolated and associated with respiratory illnesses. Their taxonomy and virology is under investigation.

The Western, Chinese and Russian Literature confirm that RSV is the major pathogen with some serotypes of Adeno and Para-Influenza causing severe illness in childhood. The para-Influenza viruses are more sporadic and are associated with croup and mild to severe upper respiratory tract infection. Available records in Lagos showed that 20.9% of

all admission and 19.3% of all deaths in children were due to respiratory tract diseases excluding T.B. and measles.

In Lagos, Influenza with its characteristic antigenic shift has been and continues to be a problem as it is evident from the recent epidemic during the last harmatan, which continued during the early part of the year. These facts not only substantiate the importance of these infectious agents but the need for further systematic study of this problem.

Influenza

This is a contagious disease, transmitted from man to man by droplets from the respiratory tract. It is characterized by dreadful pandemics with very rapid spread, resulting in high fatality involving all mankind and wreaking more havoc than the bloodiest wars. It is chiefly a disease of the respiratory tract. The incubation period is very short usually 24 hours to three days and even shorter. A previously healthy subject, abruptly feels acutely ill. He has severe malaise, nausea, head-ache and diffuse pains in the limbs, he often has chills and his temperature quickly increases within a few hours to 38.5^{o}, 39^{o}, 40^{o} or more. The subject suddenly feels as if he were "seized in the claws" of the disease.

This disease has been rife in the world for many centuries. In the 5th century B.C. Hippocrates (32) in the sixth book of "Epidemics" wrote, "a contagious disease raged at Perinthos in Trace. It began towards the winter solstice. Some cases were of short duration, the others lengthy, there were numerous pneumonia... the throat became inflamed, there was lassitude and were pains in the thighs and in the legs, there was a frequent cough with expectoration; in those whose respiration rate became accelerated, it was very severe, for in this case there was febrile heat..."

Up to the sixteenth century, one finds almost no description of epidemic disease. The first epidemic studied casually was that of 1557-1558. In 1580 a respiratory infection of pandemic character spread over all Europe. Other epidemics of the same type but with abrupt onset were described in 1658; 1697; 1732-1733.

In a number of these epidemics, epizootic infections in certain domestic animals were recorded preceding the human epidemic.

The nineteen century witnessed two important epidemics of pandemic proportions, one in 1837 and the other 1889-1890. We have had two pandemics in this century, 1918-1919 and 1957. Both epidemics of this century originated from China.

Influenza pandemics are characterized by speed and intensity of spread and evolution in successive waves giving rise, during the interpandemic periods, to seasonal epidemics with some minor antigenic modifications.

The first strain of influenza viruses was isolated in 1933, employing first ferret and by 1935, some 53 new strains were isolated. This was soon followed by the culture of the virus in embryonated egg, a technique perfected by Burnet in 1935.

Epidemiology

With the culture of the influenza virus in the embryonated egg, strains of the virus with antigenic difference were noted. In 1940, Francis (12) isolated à strain which proved to be clearly different from those previously studied. It was designated B, while the former strains were designed A. In 1947, Taylor (39) isolated the type C. In 1946, a strain of type A, designated A_1 was isolated in Australia. Minor

antigenic variations in A_1 were noted betwen 1947 and 1956. A major antigenic strain of A was seen in 1957, designated A_2 and was responsible for the pandemic of that year.

Antigenic Variation

The internal structure of the viruses is constituted by a nucleo protèin which corresponds to the solube antigen. It determines the type to which the virus belongs; all type A viruses (Ao, A1, A2) have an idential nucleo protein, while those of types B & C are different.

The envelope of the influenza virus is lipo protein and is responsible for its surface characteristics. The associated protein is the haemagglutinin. It is this haemagglutinin that manifests the minor antigenic or mutational variations of influenza strains within a single type.

A number of hypotheses has been advanced to explain the mechanisms of antigenic variations of influenza viruses. Several authors including Salk of USA, without excluding mutation, have thought that influenza is caused by a family of viruses whose members are linked immunologically.

A certain member of the family may be predominant at a given time, then decline when the majotiry of the population have become immune. With passage of time, the immunity to this particularly virus strain diminishes and the population is no longer immune and thus becomes vulnerable.

According to this hypothesis there would be only a limited number of antigenic variations. Thus, it would be necessary to protect the population against the disease and not merely against a variant responsible for an epidemic.

Mulder and Mesurel (29) in Holland supported this hypothesis by demonstrating antibodies to strain of 1957 virus in the sera of persons over 75. In certain of these persons vaccination provoked appearances of antibodies at a much higher level, than levels obtained in younger persons.

The other theory involves antigenic modifications of the virus due to external conditions, in particular the passages through partially immunized human beings. The appearance of a new strain is not necessarily due to mutation, but might be due to the emergence of a resistant strain from a population mixed particles, following neutralization of sensitive strains by antibodies.

Inhibiting and occasionally neutralizing substances have been revealed in the normal sera of different animal species. These substances no doubt play a role in the evolution of different strains of influenza viruses.

Is there a relationship between human influenza and animal influenza? Shope and co-workers (35) over 40 years ago contributed substantial facts that permit the supposition that man can transmit the human virus to the pig. Has this animal now become a reservoir?

This has not been demonstrated with certainty. Human influenza is endemic and the virus therefore persists in man.

Virology

The influenza viruses belong to the orthomyxoviruses group. Their fundamental structure is helical; a loose envelope surrounds the hellically arranged ribonucleoprotein. The diameter of the particle varies from 80 to 110 nanometres. There are both spherical and filamentous forms in unequal proportion. The envelope is not rigid; it is composed

of a membrane from which project cylindrical protuberances 9 nanometres long and 1 to 2 nanometres in width. They are RNA viruses and sensitive to either.

Laboratory Diagnosis

The virus can be isolated employing embryonated egg or tissue culture. Serological studies will reveal specific anti-bodies in the patient's blood, while very paid diagnosis might be made by "direct" examination with the immunofluoressence technique.

Prophylaxis of Influenza

The only effective method of prevention is vaccination, the vaccine being prepared from inactivated virus. Such vaccines injected subcutanously protect much more effectively than live attenuated vaccine administered by nasal route.

All the anti-influenza vaccines in use to date are prepared from virus inoculated into the allantoic sac of the embryonated egg. The virus multiplies readily in the allantoic cells. This virulent suspension serves for vaccine preparation, in which the principal stages are, concentration and purification of the virus, titration, formaldehyde inactivation and association with an adjuvant.

The concentration of virus is controlled by quantitative haemagglutination tests. The efficacy of the vaccine is verified by measuring the antibody level in vaccinated mice.

Efforts have been made to adapt the different types of influenza virus to different types of cell-cultures, *in vitro* with the purpose of preparing a vaccine in a manner similar to that used, for example, for antipoliomylitis vaccine. To date, all these attempts have failed to give a sufficient concentration of virus.

When influenza appeared in China early in 1957, the national centres throughout the world were alerted by W.H.O., which advised them as soon as the first strain isolated in China was available. A number of countries then proceeded to prepare appropriate influenza vaccine for the pandemic.

Except during pandemics, the best period for vaccination is the autumn. A booster injection at the same period every year yields satisfactory immunity. If, as there is every reason to believe, the minor antigenic variations produced by the passage of the virus from partially immunized subjects and which are additive from year to year are, in the main, responsible for seasonal epidemics, especially of type A, a booster injection with a vaccine containing one of the last strains isolated has every chance of protecting sufficiently. The immunity acquired by an acute infection appears to be solid and durable in most individuals, but it is active only in regard to the strain responsible for this disease. Vaccination does not seem to impart as solid an immunity and this is why booster injections are called for. They have a double purpose to consolidate the plurivalent immunity acquired and to provoke specific antibodies for the strain in its current gradual antigenic evolution.

The inoculation of two doses of inactivated vaccine properly spaced (15 to 21 days) is recommended for primary vaccination — a single injection may be given when an epidemic is imminent. When vaccination is carried out at the proper time with respect to appearance of the epidemic and with a vaccine containing the strains required for the immunization, the protection can be of the order of 75 to 80 per cent. These rates were reported by almost all laboratories, that had verified the effectiveness of their vaccination within closed communities.

Selective and intensive vaccination of large semi-closed boarding schools, army camps, or factories may be worthwhile to prevent social dislocation, but it is more important to protect those known to be at special risk during influenza epidemics; that is, pregnant women, chronic brochitics, patients with rheumatic heart disease and the elderly infirm. The latter categories should be revaccinated regularly, especially when new strains emerge. Inactivated vaccine will protect over 70% of patients for 9-12 months. These vaccines tend to induce more antibody in the blood stream than in the respiratory mucosa, where it may be more useful, but intranasal spray vaccines of attenuated or killed virus remain unproved in long term protective value in major epidemics. As a result of E.D. Kilbourne's work in the USA, it is now possible to produce in the laboratory genetic recombinants between the new variant influenza A virus and a well-established and rapidly growing laboratory strain. In the case of the A/England/42/72 strain high-yielding recombinants identical to the new variant were made in at least two laboratories within a few days of recognizing the epidemiological significance of the new variant. Such recombinants are now in use in the production of vaccine and should reduce by several months the time taken to produce the first 250,000 doses.

Vaccination against influenza, is justified because we have no effective specific therapy against the disease.

Epidemics of pandemic proportions are seen only every 30 or 40 years, but the seasonal epidemics, on a lesser scale also take a heavy toll of human lives. Influenza is also an economic scourge, it can paralyze the life of a country, and even when it does not attain catastrophic proportions it drains considerable sums from the national economy every year.

Thus effective prophylaxis of influenza remains one of the major goals of the specialists in this field. Substantial improvements will probably be made soon.

Chemotherapy

It is possible, under certain experimental conditions, to block the synthesis of the virus at one or several states of the intra-cellular process, but the substances that interfere with the synthesis of the viral nucleic acid are often also harmful to the cell that harbours the virus so that they have no therapeutic value. A great number of substances have been studied, certain of which have shown an antiviral activity *in vitro*, but in man the results proved to be entirely different. The biguanide derivatives, for example, appeared highly promising but their promise was not fulfilled.

Interferon a protein synthesized by cells exposed to the action of a foreign nucleic acid, is a natural substance on which great hope was placed. Extensive investigations have been made. The potency of interferon is weak; it must be administered very early in the infection, or even before; it is difficult to prepare. The search for a specific antiviral therapy continues.

The Common Cold

The major aetiological agents of the common cold are the Rhinoviruses (1, 16, 18, 20, 25, 39, 40, 42, 44, 45). Other viruses which may be responsible for the common cold are Adenoviruses, Respiratory syncytial virus, Para-influenze viruses, and Enteroviruses.

The viruses of the common cold are spread by person to person contacts. The Rhinoviruses belong to the picornavirus group and are differentiated from the enteroviruses by their instability in acid pH. There are well over 80 serotypes of rhinoviruses. The prevalence of different rhinovirus strains

and serotypes at different times in the year have been recorded by Bloom and colleagues. It has been shown that colds occurred most frequently in the winter months in temperate zones and in the cooler months of the year in tropical and subtropical regions of the world.

Characteristically, the epidemiology of rhinovirus infection is a constant changing mosaic involving different serotypes. These viruses are major cause of upper respiratory tract infections.

Problems of Prophylaxis

High Antibody response follows infections by M strains of rhinoviruses while infection by H strains evokes antibody response less frequently and with lower levels. Antibody does not appear to persist as long as in M strain infections.

Antibody to one rhinovirus does not afford protection against infection produced by another; hence the problem of multiple colds as a result of multiple infections by viruses of different serotypes.

A useful vaccine would need to contain multiple serotypes and be given parentally owing to the large number of serotypes involved; the outlook for an effective vaccine is not encouraging.

Specific Antiviral and Non-Special drugs

Resistance to heterotypic strains following infection have been demonstrated. This is probably due to interferon. It has not been possible to use interferon in protecting against rhinovirus or other viruses causing common colds. This is probably due to the inability to maintain a sufficient concentration of interferon within the nose to protect a significant number of cells, since it is washed away by the mucociliary blanket.

The Respiratory Syncytial Virus (RSV)

In a study of nearly 8,000 children, Chanock *et. al.* isolated R. S. virus in 29.6% of cases of bronchiolitis and 9.5% of those of pneumopathy. It is the most important viral respiration pathogen of infancy, affecting mainly the lower respiratory tract.

R. S. virus is a medium size (90–130) nanometres), rather sensitive virus with helical symmetry and containing RNA. S. R. virus has been associated with 32 to 75% of bronchoiolitis and 9 to 39% of preumonia in infancy and childhood. These types of illnesses are often life threatening. RS virus epidemics are sharply circumscribed, generally lasting three to five months. In temperate countries, it occurs in autumn, winter and spring while in tropical and sub-tropical countries, it occurs during the cooler months of the year.

There are at least four RS virus serotypes. Diagnosis of RSV infection can be made by virus isolation and/or demonstration of a rise in antibody during convalescence. Human heteroploid cell cultures (HeLa, Hep 2) are the most sensitive host system for there recovery of natural virus.

Problem of Prophylaxis

Inactivated vaccine has been evaluated. The trial of this vaccine brought to light the possible role of serum antibody (IgG) in the pathogenesis of RS virus bronchiolitis in early infancy and the live vaccine which stimulates development of neutralizing secretory antibodies in the respiratory tract secretions (IgA), is being evaluated. This vaccine given intranasally might lead to the control of the RS virus infections.

Para-influenza Viruses

The para-influenza viruses (types 1,2,3 and 4) are pleomorphic and vary in size from 100 to 200 nanometres. Type 1,2, and 3 para-influenza viruses have wide geographical distribution. Thus far type A viruses have been discovered only in the United Sates and Great Britain.

The para-influenza viruses are most important as respiratory tract pathogens during infancy and childhood. Types 1, 2, and 3 are largely responsible for cases of croup or acute laryngo-tracheo-bronchiolitis. They are usually endemic in the community, occasionally giving rise to epidemics. Severe respiratory tract disease caused by type 1, 2, or 3 para-influenza virus generally occurs in the first three to five years of life.

Primary infection confers upon the host a relative resistance to subsequent severe para-influenza virus illness. Reinfection has been recognized on a number of occasions, particularly with type 3 virus.

Laboratory Diagnosis

Type 2 virus usually produces focal syncytial changes in tissue cultures, whereas strains of type 1,3 or 4 usually do not produce a cytopathic effect. Strains of the latter are recognised when infected cultures are tested for haemadsorption. The clinical features of para-influenza illness are not sufficiently distinctive to permit differentiation from disease caused by other respiratory tract pathogens. Diagnosis can therefore only be established by appropriate laboratory tests.

Problems of Prophylaxis

No vaccines for the parainfluenza viruses are available. Immunization is most urgently needed for the young infant.

Adenoviruses, Respiratory Enteroviruses and Reoviruses

These groups of viruses are associated with mild acute upper respiratory infections. Inactivated vaccines against the adenoviruses have been prepared and evaluated by American workers, and the vaccines have been found useful with the armed force' personnel.

Viral Respiratory Infections in Lagos

A serological study of the incidence of complement fixing antibodies to Influenza A, B, C and Para-influenza 1, Adenoviruses, Respiratory syncytial virus and Psittacosis virus in 309 samples of sera of Nigerians was carried out at a 1:10 serum dilution in 1965. An overall incidence of 54 per cent, 54 per cent, 53 per cent and 35 per cent for Influenza and Para-influenza viruses. Adenoviruses, Respiratory syncytial virus and psittacosis virus respectively were obtained (30, 31).

This was followed by "A study of bacterial and viral aetiology of acute respiratory tract infections in Nigeria children", which showed that the viruses associated with acute respiratory tract infections in temperate zones were also to be found in tropical Nigeria. Respiratory syncytial virus, Para-influenza viruses, Herpes simplex virus and Adenoviruses were responsible for 24%, 18% and 4% respectively of acute bronchiolits in Nigerian children under 5 years. An epidemic of Respiratory Syncytial virus infection was noted in the relatively cooler month of August in Lagos. These four virus groups mentioned above occurred more frequently in Nigerian children with acute lower respiratory tract infections than in those suffering from the milder acute upper respiratory tract infections. In the study group 35.5% were of viral origin compared with 14.3% of bacterial origin (33).

The Problem and Future Research

Within the past two decades, many new viruses have been isolated and associated with respiratory illness in humans and their taxonomic positions determined. It is useful to assemble the known characteristics of each of these and related isolates into a uniform format. In this attempt, G. G. Jackson & R. L. Muldoon (1973) have published two out of their proposed series of five articles up to end of 1973, which are very comprehensive.

The literature in the Western World (7,4,5,14,11,21, 28) and others from China (43,23) and Russia (9) confirmed R. S. virus as the major pathogen, with some serotypes of Adenoviruses and para-influenza viruses, as killers in the child population. An international workshop on Influenza covering the biochemistry of the virus particle, and its antibodies, the immunological methodology in Influenza diagnosis, current research, specific immunity in Influenza including the natural history and pathogenesis and the surveillance and vaccination in relation to epidemiology was held at the N.I.H., at Bethesda (USA) during December, 1971.

Para-influenza virus infections tend to be more sporadic and are associated with such illnesses as croup, pneumonia and mild or moderately severe upper respiratory tract infections in young children (19,6,2,18). The majority of these studies have been in industrialised countries in temperate zones, with very few exceptions, for example, a recent study in the West Indies by Grant and Jennings (15). There is still a number of acute respiratory illnesses from which no infective agents have been isolated. The extent and significance of bacterial infection of respiratory tract also require assessment.

Gans (13) commenting on paediatric problems of Lagos recorded that 20.9% of all admissions and 19.3% of all deaths in children were due to respiratory tract diseases

excluding tuberculosis and measles and broncho-pneumoniae. Ogbeide (34) emphasized the dimension of the problem when he gave respiratory infections as the commonest killing diseases in children with a case fatality of 30.5%.

Influenza virus with its characteristic shift and the rhinoviruses are major world-wide causes of morbidity in all ages killing the very young and the old.

The periodicity of epidemics caused by influenza A is varied. Occasionally there is a pandemic which spreads over the world rapidly, some of which have been serious. At least two such great pandemics are known in the recent years, one in 1918 and the other in 1957.

Between great pandemics, epidemics occur in a number of countries during the cold seasons of the year. The appearance of an epidemic of influenza is associated with the emergence of a new antigenic conformation on the surface of virus particle.

The last harmattan season in Nigeria, December 1973/ January, 1974 was associated with an epidemic of febrile catarrh, which both public health doctors and clinicians have put down to the influenza virus. These facts substantiated not only the importance of these infectious agents but the need for further work in a systematic way.

REFERENCES

1. Andrewes, C. H., Burnet, F. M., Enders, J. F., Gard, S., Hirst, C.K Kaplan, M. M., & Zlidanoc, V. M.: Taxonomy of viruses infecting vertebrates: present knowledge and ignorance. *Virology,* 15 52, 1961.

2. Banatvala, J. E., Anderson, T. B., & Reiss, B. B.: Viruses in acute respiratory infection in a general community. *J. Hyg. (Camb),* 63: 155, 1965.

3. Bloom, H. H., Forsyth, R. R., Johnson, K.M., & Chanock, R. M.: Relationship of rhinovirus infection to mild upper respiratory disease. Result of a survey in young adults. *J.A.M.A.,* 186: 38, 1963.

4. Chanock, R. M., Kin, H. W., Vargoake, J., Daleve A., Johnson, K. M., Cumming, C., & Parrott, R. M., *J. Amer. Med. Ass.* 176, 647, 1961.

5. Chanock, R. M., Johnson, K. M., Kapikian, A. Z., & Bell, J. A., Amer. Rev. Resp. Dis. 88 (suppl.), 152, (1963).

6. Chanock, R. M. & Parrott, R. H. Acute Respiratory disease in infancy and childhood: present understanding and prospects for prevention. *Pediatrics,* 36: 21, 1965.

7. Chanock, R.M., Parrott, R.H. Cook, K., Andrews, B.E., Bell, J. A., Reichelderfer, T., Kapikian, A. E., Mastrote, F. M. & Huebner, R. J., *New Engl. J. Med.,* 288, 207, 1958.

8. Dingle, J. H. & Feller, A. E.,: Non-influenza viral infections of the respiratory tract. *New Engl. J. Med.,* 254: 465 (1956).

9. Doeizen, R. S. Zhukova, E. K., & Kniazova, L. D. *Vop. Okrany Materin. Dets* 5, 19 (Russian). (1960).

10. Evans, A. S. Infections with hemadsorption virus in University of Wisconsin students. *New Engl. J. Med.* 263: 233, (1960).

11. Elderkin, F. M., Gardner, P. S., Turk, D. C. and White, *A.C., Brit. Med. J.* 2, 722, (1965).

12. Francis T. Jr. New type of virus epidemic influenza. Science, 92, 405-408, 1940.

13. Gans, B., Menamava, F. N., Morley, D., Thompson, S.W., & Watt, A. *W. African Med. J.*, 10 253, (1961).

14. Gardner, P.S., Stanfield, J. P., Wright, A.E., Court S. D. M. and Green, C. A., *Brit. Med. J.* 1 1077, (1960).

15. Grant, L. S. & Jennings, R., Respiratory viruses in Jamaica: A virologic and serologic study. 1. Virus isolations and serologic studies on clinical specimens. *Amer. J. Epid.* Vol. 86, No. 3, (1967).

16. Gwaltney, J. M., and Jordan W. S. Rhinoviruses and respiratory disease. Bact. Rev. 28: 409, (1964).

17. Hamre, D., Connelly, A. P., and Procknow, J. J. Virologic studies of acute respiratory disease in young adults. Some biologic and serologic characteristics of seventeen rhinovirus serotypes isolated, October 1960 to June, 1961, *J. Lab. Clin. Med.*, 64: 450, (1964).

18. Hamparian, V. V., *et al.:* Epidemiologic investigation of rhinovirus infections. *Proc. Soc. Exp. Biol. Med.*, 117: 469, (1964).

19. Hilleman, M. R. Reilly, C. M., Stokes, J. Jr. & Hamparian, V. V., *Amer, Rev. Resp Dis.* 88 (Sppt.), 274. (1963).

20. Hobson, D., and Schild, G. C.: Virological studies on natural common colds in Sheffield in 1960, *Brit, Med. J.* 2: 1414, (1960).

21. Holzel, A., Parker, L., Patterson, W. H., White, L. L. R., Thompson, K. M. & Tobin, J. O. H. *Lancet,* 1. 295, (1968).

22. Holzel, A., Parker, L., Patterson, W. H., Cartmel, D., White, L. L. R. Purdy, R., Thompson, K. M. & Tobin, J. O. H., *Brit. Med. J.* 1, 614 (1965).

23. Hsing, G. A. *Clin. Med. J.*, 82, 390. (1963).

24. Jackson, G. G. & Muldoon, R. L. Viruses causing common Respiratory infection in man. *(i)* Rhinoviruses J. Inf. Dis. 127, 328 *(ii)* Enteroviruses and Paramyxoviruses. *J. Inf. Dis.* 128, (1973).

25. Johnson, K. M., and Rosen, L. Characteristics of five newly recognized enteroviruses recovered from human oropharynx. Amer. *J. Hyg.*, 15, (1963).

26. Killeman, M. R. Hamparian, V. V., Ketler, A., Reilly, C. M., Clelland, L., Cornifield, D., & Stokes, J., Acute respiratory illness among children and adults. Child study of contemporary incidence of several viruses and appraisal of the literature. *J. A. M. A.* 180: 445, (1962).

27. Macleland, L., Hillman, M. M., Hamparian, V. V., Ketler, A., Reilly, G. M., Cornifield, D. and Stokes, *J. Jr. New Engl. J. Med.* 264, 1169, (1961).

28. Medical Research Council Working Party on Acute Respiratory virus infections a report *Brit. Med. J.* 2, 319 (1965).

29. Mulder, J. & Masurel, N. Pre-epidemic antibody against 1957 strains of Asiatic influenza in serum of older people living in the Netherlands. *Lancet,* 1, 810-814. (1958).

30. Njoku-Obi, A. N. & Ogunbi, W. Viral Respiratory Diseases in Nigeria, 1. *J. Trop. Med. & Hyg.* Vol. 69, pp. 81-84 (1966).

31. Njoku-Obi, A. N. & Ogunbi, O. Viral Respiratory Diseases in Nigeria, 11. *J. Trop. Med. & Hyg.* Vol. 69, pp. 147-149, (1968).

32. Oeuvres, D'Hippocrate Epidemies livre Vi Javal et Bourdeaux, Vol. 2 pp. 81-83, (1933).

33. Ogunbi, O. Bacteriological and viral Aetiology of Bronchiolitis and Broncho-pneumonia in Lagos children, *W. Afr. Med. J.* Vol. 13, No. 6, 11, 58 (1970).

34. Ogbeide, M. I. Paper read at the Institute of child health, Surulere Seminar, 23rd-25th July, (1965).

35. Shope, R. E., Swine influenza 1. Experimental transmission and pathology. *J. Exp. Med.,* 54: 349, (1931).

36. Smith, R. H., & Kaye, H. S.: A survey of respiratory illnesses in a population. 1. Viral studies. *Amer. J. Hyg.* 75: 18, (1962).

37. Stuart-Harris, C. H., Respiratory viruses, ciliated epithelium, and bronchilis, *Amer. Rev. Resp. Dis.* 23, 150, (1966).

38. Taylor, R. M.: Studies on survival of influenza virus between epidemics and antigenic variants of the virus. *Amer. J. Publ. Health,* 39: 171-178, (1949).

39. Taylor-Robinson, D., & Bynoe, M. L. Inoculation of volunteers with H. rhinoviruses, *Brit. Med. J.* 1, 540, (1964).

40. Taylor-Robinson, D.: Laboratory and volunteer studies on some viruses isolated from common cold (rhinoviruses), *Amer. Rev. Resp. Dis.,* 88, 262 (1963).

41. Taylor-Robinson, D., Johnson, K. M., Bloom, H. H., parrott, R. H. Mufson, M. A. and Chanock , R. M., Rhinovirus neutralizing antibody responses and their measurement. *Amer. J. Hyg.* 78, 286, 286, (1963).

42. Taylor-Robinson, D., & Tyrrell, D. A. J.: Serotypes of viruses (rhinoviruses) isolated from common colds. *Lancet,* 1: 452, (1962).

43. Teng, C. H. *Clin. Med. J.* 80, 331, (1960).

44. Tyrrell, D. A. J., and Bynoe, M. L. Some further virus isolations from common colds. *Brit. Med. J.* 1-393, (1961).

45. Tyrrell, D. A. J., Bynoe, M. L. Hitchcock, G., Pereira, H. G. and Andrewes, C. H. Some virus isolations from common colds, I. Experiments employing human volunteers, *Lancet,* 1: 235, (1960).

46. Wilder, C. S.: Acute respiratory illnesses reported to the U.S. National Health Survey during 1957 to 1962. *Amer. Rev. Resp. Dis.* 88: 14, (1963).