Current Practice

Prevention and Treatment of Influenza

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Eleven years after the first appearance of the Asian (A2) family of human influenza A viruses, a new virus offspring differing antigenically from all previously known A2 relatives has appeared. The A2/Hong Kong/68 virus, which caused a large outbreak of influenza in Hong Kong in July, has since been found in sporadic cases or outbreaks in many areas, including Malaysia, the Philippines, India, the U.S.A., Britain, and the Netherlands. Some outbreaks appear to have been extensive, others local happenings, and though the first isolation of the new strain was made in England in August there were remarkably few cases or outbreaks for the next four months. Many have remarked on the similarity in behaviour between the A2 virus of 1957 and its remote relative of 1968, but there have in fact been many epidemiological differences. Probably these relate to the circulation during 1967 and early 1968 of strains of A2 viruses with a minor cross-relationship with the A2/HK antigen, so that the latter virus has met many obstacles in the course of its spread. Again, no antibodies were detected in 1957 against the first A2 virus excepting those in persons over 65, whereas low titres of antibodies are detectable in many children and adults against the A2/HK virus at the present time. Experience in the U.S.A. suggests that these antibodies are inadequate to prevent epidemicity of the A2/HK virus once the requisite setting has been achieved. It is timely therefore to review briefly the prevention and treatment of influenza.

Features of Epidemic

Before detailing available prophylactic measures, the probable effects of an A2/HK epidemic in Britain may be forecast. With any antigenically "new" influenza virus the most susceptible elements of the population are likely to be children and young adults. This was certainly so in the autumn of 1957, when the age group 5 to 15 suffered the highest attack-rate. There have been remarkably few explosive outbreaks in residential schools since that date, nor have day-school children been affected in epidemic proportions. In children influenza is usually briskly pyrexial with sudden onset and rapid recovery after three to five days of fever. Sore throat is more prominent than in adults, epistaxis and mild conjunctivitis may be troublesome, and control of coughing is usually necessary. Headache and muscle pains are not prominent compared with the same symptoms in adults. The need to examine the chest in order to detect signs of bronchitis or incipient pneumonia arises from the desirability of restricting chemotherapy to those who really require it. A severe case of influenzal pneumonia is only likely in very young or physically handicapped children.

Among adults the hazard of influenza is its troublesome tendency to attack many people simultaneously. The clinical severity of A2/HK influenza is reported to be average, which in the age-group 20 to 40 means a one, two-, or three-day fever with prominent headache and cough but relatively rapid

recovery. The attack-rate in this age-group is likely to be lower than in children, except among residential communities, including nurses, students, and Servicemen. Complications affecting the chest, apart from a simple tracheitis, occur chiefly in those with pre-existing disease such as asthma, chronic bronchitis, bronchiectasis, valvular heart disease, diabetes, and chronic renal disease. Bronchitis, bronchiolitis, or pneumonia may ensue during the attack or in the week after it. Such complications are likely to be bacterial as well as viral in nature and the pneumococcus, *Haemophilus influenzae*, and *Staphylococcus pyogenes* the chief pathogens. The relatively uncommon case of fulminant staphylococcal pneumonia occurs in both young and middle-aged adults and may affect previously well persons without warning.

It is in those over 50 that the risk of a serious illness is greatest. The actual attack-rate of influenza will probably be lower in this sector of the population, at least during the first wave of A2/HK attack, than in younger persons. Indeed, the sera from persons over 65 contain reasonably good antibodies to A2/HK influenza, perhaps because of an antigenic cross-relationship with the viruses of former epidemics. But the mortality of an epidemic is likely to be largely confined to persons over the age of 60 in whom chest complications or heart failure may supervene. Bacteria are again likely to be the chief cause of mortality, with the pneumococcus and *Staph. pyogenes* occurring alone or together. Chemotherapy appears to be indicated in this sector of the population even before complications are detected, except in previously hale and hearty persons. Those persons with pre-existing chest and heart disease have long been selected as a priority group for immunization against influenza, but so far there is no positive evidence that mortality is lowered by immunizing persons over the age of 65.

Prophylaxis of Influenza

Inactivated Vaccine

Inability to limit the spread of influenza viruses throughout the world has focused attention on the possibility of enhancing individual resistance to infection. It is now 25 years since the first controlled trial of inactivated, formalized influenza virus vaccine showed its potential value in the prevention of the disease. Since then limitations in the application of this type of vaccine have become apparent, though repeated confirmation of its ability to protect has also been obtained. For two to three months after injection inactivated vaccine will prevent approximately two-thirds of the expected cases of influenza in a community. One year later the protection is much less, though the attack-rate may still be reduced by 20% to 30%. After two years the protection induced by saline vaccine has disappeared, and only oily vaccines in an emulsified form and containing an adjuvant have been shown still to exert a measurable effect.¹ The temporary character of the protection induced by inactivated vaccine is a major drawback and is attributed

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to the waning antibody response with time. Inactivated vaccine stimulates the formation of virus-neutralizing antibodies in the serum and has little or no effect on antibodies in nasal secretion. The serum antibody response is proportional to the quantity of virus antigen in the inoculum.

The need to match the virus composition of the vaccine with the antigens of the influenza viruses currently appearing in the community is well recognized. On those occasions when immunized persons have shown no enhanced protection at all against natural infection the virus has been antigenically distant from that composing the vaccine. Such an event occurred in 1947 when vaccines made from influenza AO virus failed against the epidemic A1 virus and similarly A1 vaccine failed against A2 virus in 1957. As the A2/Hong Kong/68 virus shares only a minor component with the antigens of the 1967 and earlier A2 viruses, it can be expected that it will be necessary to incorporate the A2/HK virus in future vaccines in order to protect against this strain. Apart, however, from years with major alterations of virus antigens, influenza vaccines can surmount the minor year-by-year antigenic changes, probably because of the breadth of the antibody response recalled by the inoculation. A single subcutaneous dose of vaccine thus promotes a rise of antibodies in an adult with demonstrable protection seven days later. Two doses possess no advantage over a single dose except when the virus antigen is so novel that even adults have been unexposed to its action in past epidemics.² Two doses of vaccine may also have to be used in children and in the exploitation of purified haemagglutinin "split" vaccines in order to obtain a maximal antibody response.

Apart from the timing of the inoculation and the dosage the third necessity in the use of inactivated influenza vaccine is the avoidance of harmful reaction. All inactivated whole influenza virus vaccines have a capacity to produce a local erythema and a sharp febrile reaction in certain persons. Different batches of vaccine vary in this property, which is partly related to the concentration of the virus antigen in the inoculum. Indeed, it is this fact which limits the quantity of antigen which can be safely incorporated in each dose, even though as much antigen as possible is desirable in order to induce the maximal antibody response. Vaccines are therefore tailored by the manufacturer so that not more than 5% to 10% of inoculated persons develop fever or more than 20% experience local reactions. Nevertheless reactions are a serious handicap and have led to a search for more innocuous materials. It appeared at first that a vaccine which was trouble-free yet powerfully antigenic could be made from a water-in-oil emulsion containing an emulsifier (Arlacel). However, a small proportion of inoculated persons developed local nodules, cysts, or abscesses two to four months after inoculation. In spite of the lack of immediate reaction and excellent antibody-stimulating properties such vaccines have ceased to be used on any scale.

Davenport and his colleagues³ introduced a process for separating the virus haemagglutinin protein from its nucleic acid using ether and found the material to be both antigenic and free from fever-producing effects. Difficulties in manufacture have limited the use of this material, though efforts continue. In Australia, Webster and Laver⁴ separated haemagglutinin from the rest of the virus particle by using deoxycholate. A vaccine prepared in this way is now being marketed. It is understood that a two-dose schedule is recommended. The vaccine is said not to be pyrogenic though actively immunogenic. The protective power of such "split" vaccines has yet to be measured, though there is no reason to doubt that the serum antibody response will indicate the order of protection likely to be obtained.

The scope of immunization at the time of writing this article is hard to define. It is clear that supplies of inactivated A2/HK virus vaccine are limited, and under these circumstances one has to urge their use in the best possible way from the community standpoint. An epidemic once under way cannot be

controlled by inactivated vaccine, but its effect on the community will be lessened by keeping fit those whose task it is to tend the sick. Residential communities suffer a higher attack-rate than persons living at home. Therefore nurses in hospital are most at risk, then the younger members of the hospital staff, orderlies, porters, ambulance drivers, and technicians. A single dose of vaccine is probably sufficient. The next priority should be those groups of chronically sick persons with chest, heart, and kidney disease who have been recommended for influenza vaccine by W.H.O. and by the Ministry of Health.

Logically it is only after these groups have been immunized that vaccination in industrial undertakings should take place. Beyond the immediate outlook for this present winter immunization will doubtless return to the pre-1968 practice of protection of special groups and of those in residential communities subject to exceptional attack-rates. As Turtle⁵ has shown, the regular annual use of vaccine containing both A2 and B viruses in residential schools has provided a considerable advantage over the years compared with the experience in other schools not using influenza vaccine. It is only by revaccination at one, two, or more yearly intervals of time that such a benefit can be conferred. Where this is done in adults, as in the U.S.A. Armed Forces,⁶ that portion of acute respiratory disease due to influenza viruses can undoubtedly be controlled.

Other Measures

Live Attenuated Virus Vaccine.—Live influenza virus vaccines prepared from attenuated strains of virus have now been used for several years in the U.S.S.R.⁷ Their protective effect arises both from the local stimulation of antibodies in the nasal secretion and in the blood during the symptomless infection. Unfortunately the degree of attenuation of the virus cannot readily be predicted, and failure to infect with absence of antibody response has occurred unexpectedly in small-scale British trials.⁸ When the attenuated virus is capable of inducing infection it appears to be more actively protective against homologous challenge than an inactivated vaccine made from the same strain and given subcutaneously.⁹ Experiments designed to discover laboratory markers which may be related to human virulence of laboratory-cultivated viruses promise ultimate success¹⁰ but have not yet advanced to the stage when prior test in man is unnecessary.

Large-scale field trials in the U.S.S.R. suggest that live attenuated vaccine reduces the incidence of influenza in vaccinated persons to between one-half and one-third that in unimmunized persons. A similar experience has been recorded in Japan.¹¹ The use of live vaccine in the U.S.S.R. appears to have been more encouraging¹² in the early fifties than in the period 1964–66. It has proved necessary to change the virus strain used for immunization as frequently as in the case of inactivated vaccine, and a large proportion of the population at risk must receive vaccine in order to produce a significant effect. Thus neither with inactivated vaccine nor with live attenuated vaccine has it proved possible to achieve control of community epidemics.

Antiviral Chemoprophylaxis.—Two recently introduced groups of compounds exert a significant prophylactic action on influenza in man. 1-Adamantanamine hydrochloride (amantadine) is active against A2 influenza viruses in tissue cultures and in mice. Field tests indicate that it is active in man^{13 14} but its low therapeutic/toxic ratio suggests that its use will be limited.¹⁵ The isoquinolines evolved at Pfizer Laboratories at Sandwich exert a different action from amantadine in that they are actively virucidal. Though laboratory activity is only moderate, they have been shown to be capable of a prophylactic action against attenuated influenza viruses in man.¹⁶ It is clear, however, that there is no likelihood of a wide-scale application of either of the compounds at the present time.

Simple Hygienic Measures.—The source of influenza virus during an outbreak is the infected human. Segregation of patients from their families by confinement to bed is therefore sensible. So also is the use of paper handkerchiefs to wipe away nasal and oral secretion and sputum. These should later be burnt. Gauze masks may help to render a patient less infective to his environment, but they will not protect healthy persons going about their normal occupations. The avoidance of overcrowding and the use of free ventilation in crowded public rooms are sensible measures not well tolerated by the community.

Treatment

Uncomplicated Cases

Symptomatic treatment is usually required, and this is best achieved by bed rest, which also assists the segregation of the patient from his or her relatives. Of the three symptoms of headache, cough, and restless sleep, it is the headache and discomfort which are the chief complaints on the first day of illness. Self-medication with aspirin is to be deprecated, yet it is undoubtedly practised widely. Paracetamol is better and 0.5 g. should be given as often as required. Cough originates in the pharynx and upper part of the trachea. It may be distressing and at night interrupts sleep. If the chest is free from physical signs cough should be suppressed with a linctus containing codeine or pholcodine. Hypnotics are not likely to be required if pain and cough are relieved. Dichloralphenazone (650 mg.) or glutethimide (250 mg.) will probably prove adequate if necessary. Confinement to bed should be continued until the temperature is normal, but subsequent convalescence may be delayed either by depression in those past middle-age or a troublesome cough when tracheitis has been severe. The average patient with a three-day fever usually needs seven days in all away from work.

Chemotherapy should be avoided in simple influenza unless the patient is known to suffer from chronic bronchitis or if there is sputum in the absence of chest signs. In such cases oral treatment with tetracycline 0.5 g. eight-hourly or ampicillin 250 mg. eight-hourly will reduce the risk of secondary bacterial infection with pneumococci or *H. influenzae*.

Complicated Influenza

Severe laryngo-tracheitis, bronchitis, bronchiolitis, and pneumonia are the chief complications of influenza which call for treatment. I described these in the *B.M.J.* in January 1966.¹⁷ Laryngotracheitis with hoarse voice and substernal soreness on coughing requires treatment with humidified air (steam-kettle with friar's balsam). If sputum is being raised oral chemotherapy with tetracycline or ampicillin should be given. Sometimes an obstructive laryngotracheitis develops in children, causing distress and cyanosis. This requires careful observation and even perhaps laryngeal intubation or tracheostomy. Aspiration of thick tenacious secretions will relieve the obstruction.

The lower respiratory tract including the bronchi and bronchioli may be the main target of attack by the virus, and bacteria may or may not be concerned as well. Nevertheless, the existence of a raised respiration rate, a productive cough, and signs such as wheezing or râles in the chest are an indication for chemotherapy. The absence of pain in the chest renders pneumonia less likely, but if the respiration rate is over 30 there is a strong likelihood of at least patches of consolidation. Cyanosis is hard to evaluate in patients with pre-existing chronic bronchitis, but in patients with previously good health cyanosis should be assumed to be an indication of pneumonia and also of the need for therapy with oxygen.

Chemotherapy must often be given without waiting for a laboratory report on the sputum. But in all patients who become rapidly and severely ill with dyspnoea and cyanosis a stained film of sputum or of nasopharyngeal mucus should be examined for staphylococci. This is important, because adequate therapy for influenzal-staphylococcal pneumonia is always urgent. In hospital culture of the sputum and tests of the antibiotic sensitivities of pathogenic organisms should always be done.

Assuming that the diagnosis is one of acute bronchitis, bronchiolitis, or pneumonia the choice of treatment lies between penicillin (benzyl-penicillin, 0.5 mega units) combined with streptomycin (0.5 g.) intramuscularly six-hourly and oral treatment with tetracycline or ampicillin in the dose of 0.5 g. six-hourly. At home oral treatment will probably be preferred, but in hospital parenteral therapy is often wise. The latter is particularly desirable if the patient is severely ill or dehydrated, chiefly because absorption from the alimentary tract is often delayed under these conditions.

When influenzal-staphylococcal pneumonia is suspected because of severe dyspnoea, cyanosis, and tachycardia, and when staphylococci are present in quantity in the sputum, treatment should be based on the assumption that the staphylococci are equally likely to be sensitive or resistant to penicillin. Therefore penicillin (benzyl-penicillin 1 mega unit) and either methicillin (1 g.) or cloxacillin (0.5 g.) should be given intramuscularly until the results of antibiotic sensitivity are available. Therapy can then be continued either with penicillin or with methicillin or cloxacillin as indicated. Oral treatment with cloxacillin should not be given until clinical recovery has commenced. Fucidin may be added to the oral therapy (0.5 g. six-hourly) if progress is unsatisfactory. It must always be remembered that a mixed bacterial infection with both pneumococci and staphylococci or with *H. influenzae* is far from rare. However, the therapy outlined above will suffice for all except Gram-negative organisms, which may require alternative therapy such as ampicillin or other drugs appropriate to the sensitivities of the organisms.

When airway obstruction is suspected, as in the case of patients with previous bronchitis, when the sputum is viscid and difficult to raise, or the lung slow to show signs of resolution, humidification of the inspired air should always be attempted. This applies also to patients receiving oxygen in whom the temptation to use oxygen directly from a piped supply should be resisted unless water vapour is also given. Oxygen should, of course, invariably be given in patients who are cyanosed, but care is required in patients with respiratory failure from chronic bronchitis. Inspired oxygen should then be limited in concentration (28%) in order to avoid CO₂ narcosis.

Supportive therapy for patients with severe pneumonia and accompanying hypotension should not be forgotten. An intravenous drip of saline containing hydrocortisone (100 mg. to the bottle) is to be preferred to injections of vasoconstrictor drugs such as metaraminol tartrate. The latter in a 10 mg. dose is useful as an intramuscular supplement when intravenous therapy has already raised the blood pressure. Ancillary treatment for cardiac arrhythmia, myocarditis, or congestive heart failure is beyond the scope of this article. Delayed complications such as lung abscess or empyema are fortunately far less common than in preantibiotic days, but must always be considered when fever continues in spite of signs of resolution of pneumonia.

Conclusion

It is as easy to overtreat as to fail to give adequate therapy. Influenza is a treacherous disease at any age, and this is one of the reasons for the heavy burden of an outbreak in general practice. The remedies now available, when used correctly, are unquestionably responsible for many recoveries of patients who

would formerly have died from secondary bacterial infection. This is some consolation for the lack of any major breakthrough in the prevention of the uncomplicated disease.

REFERENCES

- ¹ Report to the M.R.C. by its Committee on Influenza and other Respiratory Virus Vaccines. *Brit. med. J.*, 1964, 2, 267.
- ² Holland, W. W., Isaacs, A., Clarke, S. K. R., and Heath, R. B., *Lancet*, 1958, 1, 820.
- ³ Davenport, F. M., Hennessy, A. V., Brandon, F. M., Webster, R. G., Barrett, C. D., jun., and Lease, G. O., *J. Lab. clin. Med.*, 1961, 63, 5.
- ⁴ Webster, R. G., and Laver, W. G., *J. Immunol.*, 1966, 96, 596.
- ⁵ Turtle, P. de B., *Practitioner*, 1968, 200, 254.
- ⁶ Davenport, F. M., *Pan Amer. Hlth Org., Sci. Publ.*, 1967, 147, 3.
- ⁷ Zhdanov, V. M., and Soloviev, V. D., *Amer. Rev. resp. Dis.*, 1961, 83, 178.
- ⁸ Beare, A. S., Tyrrell, D. A. J., McDonald, J. C., Pollock, T. M., Taylor, C. E. D., Howells, C. H. L., and Tyler, L. E., *J. Hyg. (Camb.)*, 1967, 65, 245.
- ⁹ Beare, A. S., Hobson, D., Reed, S. E., and Tyrrell, D. A. J., *Lancet*, 1968, 2, 418.
- ¹⁰ Hobson, D., Gould, E. A. and Flockton, H. I., *J. Hyg. (Camb.)*, 1967, 65, 255.
- ¹¹ Okuno, Y., and Nakamura, K., *Biken's J.*, 1966, 9, 89.
- ¹² Zhdanov, V. M., *Pan Amer. Hlth Org., Sci. Publ.*, 1967, 147, 9.

- ¹³ Wendel, H. A., Snyder, M. T., and Pell, S., *Clin. Pharm. and Therap.*, 1966, 7, 38.
- ¹⁴ Finklea, J. F., Hennessy, A. V., and Davenport, F. M., *Amer. J. Epidem.*, 1967, 85, 403.
- ¹⁵ Sabin, A. B., *J. Amer. med. Ass.*, 1967, 200, 943.
- ¹⁶ Beare, A. S., Bynoe, M. L., and Tyrrell, D. A. J., *Lancet*, 1968, 1, 843.
- ¹⁷ Stuart-Harris, C. H., *Brit. med. J.*, 1966, 1, 149, 217.

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Axis Deviation and Respiration

Q.—Should the effect of respiration be taken into account in calculating axis deviation in an electrocardiograph? How may the effect of respiration be eliminated or reduced?

A.—The effect of respiration on the anatomical axis of the heart is slight, and there is therefore little resulting change in the electrical axis. This was elegantly shown by Thomas Lewis¹ in a patient with a bullet-wound of the heart. Radiographs of the chest were taken, in systole and diastole, in full inspiration and full expiration. In expiration the bullet moved only 8° in an anticlockwise direction.

This order of change is of no significance in interpreting the electrocardiogram, and there is therefore no need to eliminate the effect of respiration.

REFERENCE

- ¹ Lewis, T., *Clinical Science Illustrated by Personal Experiences*, 1934. London.

Inheritance of Diabetes

Q.—What chance of developing diabetes has a man aged 27 whose mother and maternal uncle are diabetics and whose maternal grandfather and grandmother were diabetics?

A.—No information is given in the query on the age of onset of the diabetes, but presumably it was of early onset. To consider first only the mother's diabetes, if the age of onset here was under the age of 30 years the chance of similar diabetes in the son would be of the order of 4%—that is, about 20 times the population incidence. This risk would have to be increased because of the presence of the other affected relatives, perhaps to about 10%.

The general prevalence of late onset diabetes is appreciably higher than that for

early onset, and the heritability is appreciably lower. If the mother's diabetes was of late-onset type the risk of similar diabetes in the son would be only about 5 times the population incidence, say about 5% for diabetes by the age of 60 years.¹

REFERENCE

- ¹ Falconer, D. S., *Ann. hum. Genet.*, 1967, 31, 1.

Management of Infertility

Q.—What can be done to help an infertile couple in whom repeated postcoital tests show apparently normal, non-motile sperm, and the cervix is healthy and its secretions appear normal?

A.—The information supplied is insufficient to permit an adequate assessment of this couple's problem. Nothing is mentioned about the activity of the spermatozoa in seminal analysis; if this reveals asthenospermia then the defect may be presumed to lie with the husband, but if sperm activity is satisfactory in the seminal fluid the postcoital findings represent either genuine incompatibility between cervical mucus and spermatozoa (possibly immunological) or point to defective coitus, the deposition of semen not being in sufficiently close proximity to the cervical mucus.

The treatment of asthenospermia is notoriously unsatisfactory. A procedure which sometimes is helpful consists in giving the husband a small dose of androgen—for example, fluoxymesterone, 5 mg. every other day—intermittently so as to avoid depression of spermatogenesis. A convenient time is during the first fortnight of the wife's menstrual cycle. True mucus-sperm incompatibility, whether immunological or otherwise, does not appear to respond to therapy. Artificial insemination with the husband's semen (provided the latter is of good quality) —a small quantity of semen being placed

within the uterine cavity—may overcome the cervical hostility; it carries with it a small but definite risk of introducing pelvic infection.

Prophylaxis of Haemorrhagic Disease of Newborn

Q.—Is there any particular prophylactic measure that would prevent haemorrhagic disease of the newborn?

A.—This condition usually occurs in the first five days after birth, and is due to temporary deficiency of the vitamin-K dependent clotting factors—namely, prothrombin, factors VII and X, and probably IX (Christmas factor) as well. It can be prevented by administering vitamin K to the newborn infant; administration to the mother before labour has been tried but has not proved satisfactory. In many clinics it is the practice to give a regular prophylactic dose of vitamin K to all premature and full-term infants. The preparation at present favoured is phytonadione ("Koniakon"), which is a watery suspension of vitamin K₁; the dose is 1 mg. intramuscularly.

Intragastric Photography in Stomach Cancer

Q.—Is intragastric colour photography a valuable diagnostic aid in carcinoma of the stomach, and does it show anything which cannot be equally well seen through a gastro-scope?

A.—Intragastric colour photography is indeed a valuable aid in the diagnosis of carcinoma of the stomach, but it is less valuable than gastroscopy in expert hands, particularly if the new Olympus gastroscope incorporating a channel for biopsy forceps is used. Colour photographs may also be taken with this instrument.