THE BRITISH ENCYCLOPAEDIA OF MEDICAL PRACTICE

INCLUDING

MEDICINE SURGERY
OBSTETRICS GYNAECOLOGY
AND OTHER SPECIAL SUBJECTS

MEDICAL PROGRESS 1962

EDITOR IN CHIEF
THE LORD COHEN OF BIRKENHEAD,
P.R.S.H., M.D., D.Sc., LL.D., F.R.C.P., F.R.C.P.I., F.A.C.P., F.D.S.R.C.S.,
F.F.R., F.R.I.C., F.B.Ps.S., F.P.S., F.S.A.
PROFESSOR OF MEDICINE, UNIVERSITY OF LIVERPOOL; PRESIDENT,
GENERAL MEDICAL COUNCIL

LONDON
BUTTERWORTHS
1962

FOREWORD

The outstanding event of public interest and of medical import during the past 12 months is probably the recognition that the drug thalidomide, which is sold under many trade names, if administered during pregnancy, may interfere with limb growth and produce other foetal malformations. Dr. Francis, in his contribution to this volume, gives a factual summary of the events of this tragic episode, which has raised many questions relating to drug testing, clinical trials and the early recognition of long-term adverse effects of drugs, which will need to be fully investigated. Already there is experimental evidence that a large variety of drugs, including chlorpromazine, reserpine and the antihistamines, may produce foetal damage.

Many contributors draw attention to the toxic effects of other drugs, *e.g.* the liver damage from chlorpromazine, and the amine oxidase inhibitors, such as pheniprazine, nialamide, phenelzine, and iproniazid, which might carry a 15 per cent mortality. There is now recorded, also, jaundice following the use of isoniazid and zoxazolamine. The ocular complications—corneal deposits and retinopathy—of chloroquine and its derivatives have limited its use in the treatment of rheumatoid arthritis in which it was being more widely exhibited. The adverse effects of drugs are indeed becoming much more widely recognized and appreciated. Even the chronic purgative addict faces the hazard of excessive loss of potassium with resulting renal damage and pareses.

The corticosteroids are being used with greater discretion in the rheumatic and 'collagen' diseases; the immense benefit which results from their careful use in properly selected patients with chronic asthma and other allergies, and in heart block, is fully discussed in the ensuing pages.

As was foreseen last year, new penicillins derived from 6-amino-penicillanic acid have in the past year been marketed which give higher blood levels when administered orally, and have a wider bactericidal and bacteriostatic spectrum, but resistant strains appear with varying rapidity, and this has often limited the usefulness of the newer penicillins.

Hypotensive drugs come and go, though used with proper care they make an important contribution to the management of the hypertensive patient. But the discovery of a remediable cause and its removal has always been the ultimate therapeutic aim in hypertension, and in the past this has often been achieved when a phaeochromocytoma, coarctation of the aorta, chronic pyelonephritis and other unilateral renal lesions have been found. More recently the discovery that renal artery stenosis is a not uncommon cause of hypertension which is amenable to surgical repair, has led to the development of methods for its detection which are fully discussed by Professor Donald and his colleagues.

In the diagnostic field many useful advances are recorded. Amongst these may be mentioned the use of isoenzymes in diagnosis, the newer techniques in diagnostic radiology, the fiberscope in direct visualization of the gastric mucosa, the radiotelemetering capsule in gastro-intestinal disease, and the community application of exfoliative cytology in the prophylaxis of cancer of the cervix.

Immunization against measles and German measles has been extensively studied, though not widely applied; the routine use of Sabin's vaccine against poliomyelitis is now practically universally accepted, though the recent development of quadrivalent vaccines against diphtheria, whooping-cough, tetanus and poliomyelitis might well modify the schedules of immunization hitherto suggested.

In surgery the fascinating immunological problems of tissue grafting continue to stimulate research; and in anaesthesia, the clearer definition of the uses of hypothermia and of dehydration in cerebral oedema are topics of current interest.

The total involvement of the body in disease is shown in many contributions, notably in the comprehensive review of auto-immune reactions in thyroid and other diseases, and the 'carcinoid' and Cushing's syndromes in lung disease.

In the field of human genetics the main spearheads of advance are the study of human chromosomes and the variations in their number, size and appearance in disease, which are now being studied in many centres in this country; the inheritance of enzymatic defects associated with metabolic diseases, mental subnormality, and the haemoglobinopathies; the mechanism of Rh haemolytic disease; and the predisposition of genotypes to various diseases.

I referred last year to the fascinating and rapidly developing field of pharmacogenetics in which interesting advances continue to be made.

The report of the Royal College of Physicians on *Smoking and Health*, the social problems of illegitimacy, the disquieting increase in the incidence of venereal disease, the need for developing methods of health education, recent medical legislation and many other topics in the field of social and preventive medicine are given due prominence in this year's *Medical Progress* volume.

We are grateful this year, as ever, to our contributors for making available to our readers all the major advances in medicine and its allied disciplines during the past year, and for the critical assessments of their significance.

ENGLAND: BUTTERWORTH & Co. (PUBLISHERS) LTD.
LONDON: 88 KINGSWAY, W.C.2

AFRICA: BUTTERWORTH & Co. (AFRICA) LTD.
DURBAN: 33/35 BEACH GROVE

AUSTRALIA: BUTTERWORTH & Co. (AUSTRALIA) LTD.
SYDNEY: 6-8 O'CONNELL STREET
MELBOURNE: 473 BOURKE STREET
BRISBANE: 240 QUEEN STREET

CANADA: BUTTERWORTH & Co. (CANADA) LTD.
TORONTO: 1367 DANFORTH AVENUE, 6

NEW ZEALAND: BUTTERWORTH & Co. (NEW ZEALAND) LTD.
WELLINGTON: 49/51 BALLANCE STREET
AUCKLAND: 35 HIGH STREET

U.S.A.: BUTTERWORTH INC.
WASHINGTON, D.C.: 7235 WISCONSIN AVENUE, 14

MADE AND PRINTED IN GREAT BRITAIN
BY THE CHAPEL RIVER PRESS LTD.
ANDOVER, HANTS

CONTENTS

ACUTE INFECTIOUS DISEASES

By A. B. CHRISTIE, M.A., M.D., D.P.H., D.C.H.
Physician Superintendent, Fazakerley Hospital, Liverpool

CHEMOPROPHYLAXIS OF INFECTIONS

The widespread use of antibiotics to prevent infection has not yet led to a clear understanding of their role, and practice is sometimes based more on wishful thinking than on scientific facts. Petersdorf (1961) has calculated that three-quarters of all antibiotics are given to *prevent* rather than to *treat* infection and that not enough attention is paid to the three major disadvantages of antibiotics, namely toxic and allergic reactions, superinfection and expense. The infant is given one antibiotic to prevent ophthalmia, another to avoid infection from a breast abscess and further doses to protect it against the 'bacterial' complications of measles, chicken-pox or the common cold: at school he may be given an antibiotic to prevent streptococcal or intestinal infection and in later life to protect him against post-operative sepsis, the complications of respiratory, kidney or cardiac disease or the hazards of tracheostomy tubes, indwelling catheters or sutures. Yet the evidence for these prophylactic measures has rarely, according to Petersdorf (1961), been scrutinized. Aimed at one specific pathogen, for example streptococci in rheumatic subjects, antibiotic prophylaxis can be highly successful, but used as a widespread umbrella in patients exposed to unspecified infections it may result only in a shower of resistant organisms.

Petersdorf and Woodward (1961) in experimental work on scrub typhus, Q fever and tularaemia showed that a drug given in the incubation period might not prevent the disease, but simply prolong the incubation period, unless the drug were bactericidal. They also showed that the time interval between infection and prophylaxis or between the onset of illness and the beginning of treatment affects the development of immunity and the occurrence of overt signs or of relapse: and that the various factors operated differently in different diseases. When volunteers were inoculated with *Rickettsia orientalis* and given 1·0 g of chloramphenicol daily from the time of infection, they remained well till 5 days after the drug was stopped, when they then developed scrub typhus. If prophylaxis were withheld for 7 days and chloramphenicol then given in varying doses, the result depended on the dose: a higher dose suppressed the disease, though rickettsaemia developed, but on a lower dose the volunteers developed the disease. Treatment of the disease with chloramphenicol on the first day of illness brought about a dramatic clinical response, but relapses were frequent: if treatment were withheld till the fifth day, results were good and relapses rare. Volunteers infected with *Pasteurella tularensis* and given streptomycin within one hour remained well: those given chloramphenicol developed tularaemia when the drug was stopped. Volunteers infected with *R. burneti* and given terramycin within 24 hours developed Q fever when the drug was stopped: those given the drug late in the incubation period remained well: patients suffering from the disease and treated within 24 hours responded rapidly and there were no relapses.

Scrub typhus, Q fever and tularaemia are all caused by intracellular parasites and it does not follow that the same factors operate in infections with the more common coccal infections: indeed, antimicrobial drugs used against haemolytic streptococci, meningococci and some staphylococci usually prevent clinical disease, and it may be that in these infections the immune mechanism is less important. Yet Petersdorf, Browder and Feinstein (1961) referred to various controlled experiments not all of which showed that routine prophylaxis was of value. The widespread use of antibiotics in maternity wards and nurseries had not led to a clear understanding of infection in the neonatal period, and the almost universal use of antibiotic cover for surgical operations was frequently not justified and often unsupported by scientific facts. The use of antibiotics in non-bacterial upper respiratory disease, in whooping cough or in measles rested on an insecure base, and in severe poliomyelitis was of

no value at all. The College of General Practitioners (1956) had already shown that the routine use of sulphonamide prophylaxis in measles increased rather than decreased the total complications, and the routine use of antibiotics in measles was considered expensive and largely unnecessary. The prophylaxis of infection is not a simple matter.

POLIOMYELITIS

Vaccination

By the end of 1960, 77,479,000 people in the U.S.S.R. had received by mouth all 3 types of live poliovirus vaccine: throughout 1961, the use of oral vaccine has been continued on a very wide scale in the U.S.S.R. and neighbouring states. In western European countries and in America, killed vaccine has been mainly used over the same period and it might be thought that there is now sufficient evidence to assess the relative value of the two vaccines. That this is only partly true is due largely to the variability of the epidemic behaviour of poliomyelitis which makes it impossible to forecast what is likely to occur in any place at any given time. Nevertheless it is possible to make fairly confident statements about the two most important factors regarding the vaccines, namely their efficiency and their safety.

Efficiency of vaccines

Both live and killed vaccines lead to the production in the human body of antibodies against poliomyelitis virus. The Public Health Laboratory Service's report (1961) claimed that oral Sabin vaccine stimulated the production of antibodies equally as well as killed Salk vaccine, but Dick and Dane (1961a), in criticizing the report, pointed out that any comparison of antibody level should be related to the potency of the vaccine used, and that in the trial ten times as much virus had been fed as in most other trials. Elsewhere, Dick and Dane (1961b) referred to the very high potency of Purivax killed vaccine, a single 0·5 ml dose of which can apparently produce antibody at a protective level within four days. It is of course only fair that best should be compared with best, and the Public Health Laboratory Service workers were as entitled to use high dosage of live vaccine as Dick and Dane to use Purivax. Chumakov and colleagues (1961) in reporting very large scale use of live vaccine stated that the immunological activity of Sabin strains compared quite favourably with the *best* standards of killed Salk vaccine and was even superior to them with regard to the time of seroconversion and its duration.

While it is probably fair to say that both vaccines properly prepared will produce satisfactory antibody levels and therefore presumably protection against paralytic illness, there is claimed to be a marked difference in the effect of the two vaccines with regard to protection against subsequent infection, as distinct from illness. Successful vaccination with live vaccine produces in the intestinal tract resistance to colonization with poliovirus: vaccination with killed vaccine has no such effect. The person vaccinated with killed vaccine may therefore later become infected with wild virulent poliovirus and may pass this on to others by faecal spread, and it would therefore seem that such a person can be a danger to the community in a way that a Sabin-vaccinated person cannot. Against this view, however, Dick and Dane (1961b and 1961c) point out that vaccination with killed vaccine does prevent multiplication of virus in the pharynx. They admit that poliomyelitis can spread even in the absence of poliovirus in the pharynx of patients, but suggest that pharyngeal secretions are more important sources of infection than faeces and that if pharyngeal colonization can be prevented, this may be enough to prevent spread in the community.

Dick and Dane (1961c) did not in fact accept completely the concept that local intestinal immunity develops only in response to intestinal infection. They fed live vaccine to children previously vaccinated with killed vaccine. In one group, with a mean type II antibody titre of 1 in 525, the children after being fed live type II vaccine excreted virus in their faeces in the same fashion as another group of children fed type II vaccine but not previously immunized with killed vaccine. In a second group of children, in whom a type I antibody titre of 1 in 2,230 was obtained by previous immunization with killed vaccine, virus was excreted in the faeces in smaller

amounts and for a shorter period than from a control group of children fed live vaccine but not previously immunized. They suggested therefore that some intestinal resistance may be induced by the antigenic stimulus of a killed vaccine injected into a site remote from the intestinal tract.

A factor which affects the efficiency of live but not killed virus vaccine is the possibility of 'interference' with colonization of the gut by other enteroviruses. In the Public Health Laboratory trial (1961) most of the infants given oral vaccine were infants without siblings, and Dick and Dane (1961a) objected that this produced an environment in which the danger of infection by other enteroviruses was reduced below the level occurring in more normal communities. Chumakov and colleagues (1961) stated that most failures with live polio vaccine were due to the influence of interference in the vaccination process: they suggested that vaccination should be carried out in winter months when natural infection with enteroviruses was at its lowest and that interference could be overcome by particularly massive vaccinations, with involvement of no less than 50 per cent of the susceptible population, and by repeated vaccinations during at least three years. They felt that more complete study of the factors governing interference was an urgent matter.

Safety of the vaccines

Killed vaccine, properly prepared and thoroughly tested, is a safe vaccine. With live vaccine, the possibility of increased neurovirulence following human passage has to be considered and it is now accepted that such increased neurovirulence, by intrathalamic or intraspinal inoculation of the monkey, does occur (Verlinde and Wilterdink, 1961; Hoskins and Udall, 1961; Dick and Dane, 1961c): the neurovirulence is always much less marked than with a virus strain isolated from a paralysed patient, increased neurovirulence for human nervous tissue has never been demonstrated and no case of poliomyelitis has ever been traced to the use of live vaccine. In any case, increase in neurovirulence takes time to develop and, in a mass immunization scheme, the population would be protected by the live vaccine before increased neurovirulence could take place. Chumakov and colleagues (1961) found that the problem was practically non-existent under conditions of mass simultaneous immunization of a population and the Public Health Laboratory Service report (1961) included the comment that in comparing the values of Salk and Sabin vaccines the factor of safety could be neglected.

Contamination of live vaccine with other viruses is another danger, especially with virus SV40: it is doubtful if this virus is pathogenic for humans though Sven Gard claimed at the VIIth European Conference Against Poliomyelitis (Unpublished, 1961) that he had successfully infected 8 human volunteers all of whom excreted SV40 and developed antibodies to it. This particular danger is not altogether absent from killed vaccine as SV40 is less readily inactivated than polio virus. With both vaccines, extreme care in production is essential.

Practical application

Three or four doses of killed vaccine produces a high degree of protection against poliomyelitis; with more potent vaccines, such as Purivax (Dick and Dane, 1961b), fewer doses may be required. Live vaccine given as 3 doses of trivalent vaccine or 3 doses of monovalent vaccine produces equally good antibody protection (Public Health Laboratory Service Report, 1961). In addition, the individuals vaccinated develop an intestinal immunity against subsequent infection. Vaccinees in the infectious stage pass attenuated virus in the faeces, and contacts, especially young children, readily become infected, and develop immunity. Live vaccine has therefore a direct effect on the immunity of the population at large. Killed vaccine has no such effect on contacts though, as already stated, Dick and Dane (1961c) claimed that, by the prevention of excretion of virus in the pharynx, community protection is provided by killed vaccine, albeit in a somewhat negative manner.

The ease with which live vaccine can be administered—the Russians give it in candy—makes easily possible the vaccination and revaccination of whole populations: it is hard to believe that the vaccination of more than 77,000,000 Russians would

have been achieved so rapidly, if at all, had 3 or 4 injections been involved. Dick and Dane (1961a), however, pointed out that the addition of killed polio vaccine to diphtheria-tetanus-pertussis triple vaccine is a simple matter and claimed that this is the easiest method of adding poliomyelitis vaccine to our present immunization programme for children; but it takes no account of the difficulty of persuading adults to have injections, and our knowledge of the antigenicity of quadruple vaccines is still incomplete.

The Ministry of Health is offering an oral vaccine, prepared in Great Britain from the Sabin strains, as an alternative to the 'Salk' vaccine and makes the following suggestions on its use.

(a) A full course of 3 doses of 3 drops each at intervals of 4 to 8 weeks may be given to persons in the priority group who have not received any injections of 'Salk' vaccine.

(b) If 1 dose of 'Salk' vaccine has been given, the course may be completed with 2 further doses of 'Salk' vaccine if the first of these can be given within 8 weeks of the primary injection; otherwise a course of 3 oral doses should be given.

(c) If 2 doses of 'Salk' vaccine have been given the course may be completed with a third dose of either 'Salk' or oral vaccine if within 2 to 12 months of the previous 2 doses; otherwise a new course of 3 doses of either 'Salk' or oral vaccine should be given.

(d) To children aged 5–12 years, who have had 3 injections of 'Salk' vaccine, a fourth booster dose of vaccine, either 'Salk' or oral, should be given.

The Ministry suggests that oral vaccine should not be given to anyone already acutely ill, especially with any intestinal complaint: nor, without previous consideration, to anyone in indifferent health or on corticosteroid therapy. Pregnancy is not a contra-indication and the oral vaccine may be given at any season and during epidemics of poliomyelitis. Any other immunizing procedure or surgical operations should be postponed, if possible, till 3 weeks after any dose of oral vaccine: tonsillectomy should not be done till the course has been completed. Any disease of the central nervous system occurring within 21 days of any dose of oral vaccine should be thoroughly investigated.

Use of epidemics

Hale and colleagues (1959) described an outbreak of type I poliomyelitis in Singapore and the feeding of live type II polio vaccine in an attempt to stop, by interference, the spread of the virulent type I virus. Knowelden, Hale and Gardiner (1961) analysed the findings and concluded that a substantial reduction in the risk of paralytic disease occurred as a result of vaccination. Triple live vaccine has been used in a similar manner in Florida, West Berlin and Tashkent (Stuart-Harris and Knowelden, 1961; Dick and Dane, 1961a) but without conclusive results; but the use of trivalent, instead of monovalent, vaccine made it difficult to diagnose in West Berlin and Florida the cause of some neurological illnesses which followed the vaccinations, it being impossible to distinguish the vaccine virus from the wild virulent virus. Polio type II virus establishes itself more easily in the gut than the other two types and there is therefore a theoretical basis for preferring it to triple vaccine when the interference mechanism is on trial against a type I or type III epidemic. Whether this preference will continue to be held and what types of attenuated virus should be used against a type II epidemic are matters which only wider experience can settle. There seems reason to hope that, by one vaccine or another, the end of poliomyelitis as an epidemic disease may now be in sight.

Hypothermia in acute poliomyelitis

Hyperpyrexia is of grave prognosis in the acute stage of poliomyelitis and may be taken as an index of virus involvement of vital brain centres. Anything which can lower the temperature may also slow down metabolism in these centres and give brain nuclei a chance of surviving the virus attack, just as nerve cells serving skeletal muscles often recover rapidly after the acute stage of the illness. Harries and Lawes (1961) described the use of hypothermia in 9 patients, cooling being effected by a

water bed and shivering prevented by intravenous injections of promethazine, chlorpromazine and pethidine. The temperature need not go below 90°F (32·2°C) nor be prolonged for more than 5 to 6 days. Six of the patients survived, including 3 who had temperatures of over 104°F (40°C) for 3 to 10 days after the onset of paralysis: all the patients were critically ill and to save 6 of 9 such patients is an encouraging achievement.

MEASLES

Vaccine prophylaxis

Live measles vaccine can now be prepared with relative ease and is an effective immunizing agent against measles. What remains in doubt is whether sufficient attenuation of the virus has yet been achieved and whether the clinical reactions to vaccination justify its use on a wide scale. In a trial of measles vaccines in Nigerian children by Collard and colleagues (1961), 35 of 38 children developed rashes, mainly less severe than in unmodified measles, but one child had a haemorrhagic rash. Aldous and colleages (1961) gave the vaccine to British children: 82 per cent developed fever and 86 per cent a rash: more than half of the children were 'distinctly ill'. The antibody response and protective effect were satisfactory but the authors felt that further attenuation of the measles vaccine was desirable.

An attempt to modify the reactions to measles vaccine by the simultaneous use of gamma globulin was described at the International Conference on Immunization against Measles in Washington (*Brit. med. J.*, 1961). When the Edmonton B attenuated virus was given without gamma globulin, 30 per cent of the children developed pyrexia of 103°F (39·4°C) or over and 60 per cent had rashes: when given with gamma globulin, only 14 per cent of the children had pyrexia over 103°F (39·4°C) and rashes and other symptoms were uncommon. Other attenuated strains of virus and a killed virus vaccine were under trial.

SMALLPOX

Interpretation of reactions to vaccination

Cross (1961) investigated the significance of reactions to vaccination and the relationship of technique to vaccination failures. He distinguished between the pearly appearance of the lesion of primary vaccinia (PV) and the haemorrhagic necrotic appearance of a revaccination vaccinia (RVN): a rare type of revaccination vaccinia (RVP) was indistinguishable from primary vaccinia. An accelerated reaction (AR) gave no difficulty in diagnosis or interpretation but the immediate reaction (IR) caused great difficulty in interpretation. This is an indurated papule occurring on the second day after vaccination accompanied by itching: induration and slight erythema are still present on the seventh day. This reaction can be produced by inactivated vaccine and therefore is probably a sensitivity and not an immunity reaction: yet, when produced by active vaccine, rises in pock-inhibition titres do occur in the serum of some subjects so that these reactions may be accompanied by an immunological response. The author suggests that if an immediate reaction to vaccination occurs more than 2 years after a previous vaccination the vaccination should be repeated in order to exclude technical failure.

Completely negative vaccination reactions are rare but do occur in some highly immune vaccinated subjects. The essential factor in vaccination technique is to get sufficient vaccine into the deeper layers of the epidermis. The single scratch and multiple puncture techniques can both achieve this if the vaccinator is aware of the importance of depth of insertion: Cross (1961) considers the single scratch method is simpler and quicker though not everyone will agree with him on this point. He regards the drawing of blood in vaccination as desirable as it shows that a sufficient depth has been reached.

Freeze-dried or liquid vaccine

It is essential of course that the vaccine used should be sufficiently potent for its purpose. Hobday and colleagues (1961) compared the efficacy of fresh Indian buffalo-calf lymph with that of English freeze-dried vaccine. It was known that the former

gave nearly 100 per cent positive results in primary vaccination but, in revaccination, positive takes were under 10 per cent. The authors revaccinated over 100 non-smallpox patients with one or both vaccines: the successful take rate with the English freeze-dried vaccine was 66 per cent compared with 27 per cent with the Indian liquid vaccine. This latter rate was higher than that obtained by public vaccinators in India (less than 10 per cent) and the difference was probably due to the better storage conditions during the investigation. It is obvious, however, that even with good refrigeration the buffalo-calf lymph was not good enough for revaccination purposes. The authors consider that a freeze-dried vaccine would be both more effective and more economical. An alternative would be a vaccine produced on embryonated eggs: a potent vaccine can be produced relatively cheaply in this way and production is not held up periodically, as it is in India, by outbreaks of disease in cattle.

Antibody levels after vaccination

More than half of the patients admitted with smallpox to the Madras Infectious Diseases Hospital in 1960 showed good scars from primary vaccination in earlier life, and Downie and colleagues (1961b) therefore investigated the smallpox antibody levels in the sera of vaccinated adults in the city. Samples of sera were obtained from blood donors, from patients in hospital with chicken-pox and from patients in the Tuberculosis Chemotherapy centre—most were young adults. The results showed that 10 per cent of the subjects had little or no neutralizing antibody in their sera. There was no apparent relationship between the number of scars or the age of the patient and the antibody levels in the serum. Haemagglutination-inhibiting antibody did not persist as long as neutralizing antibody. The titre of antibody in patients convalescent from smallpox was very much higher than that following vaccination. The 10 per cent of the population of Madras who appeared to have lost their immunity, along with 10 per cent or 20 per cent who escape vaccination, might provide a nucleus of non-immune inhabitants sufficient to maintain smallpox as an endemic disease, a situation which could be altered by universal vaccination and revaccination with potent lymph.

Gamma globulin in prophylaxis

Neutralizing antibodies do not appear in the blood till 11–13 days after primary vaccination, or show a definite increase till 7 days after revaccination (*W. H. O. Chronicle*, 1961). This may explain why vaccination or revaccination of family contacts of smallpox is not always successful.

Kempe and colleagues (1961) studied the efficacy of immune gamma globulin, derived from recently vaccinated adults, in the prophylaxis of smallpox in close contacts of smallpox patients. Among 326 contacts, vaccinated and given gamma globulin, there occurred 5 cases of smallpox: among 379 contacts, vaccinated but not given gamma globulin, there were 21 cases. Children under 5 years old were given 5 ml of a 12 per cent solution of gamma globulin, adults received 10 ml. Nine neonates infected *in utero*, at birth, or shortly after were each given 5 ml of immune gamma globulin and only 3 developed smallpox. There was approximately a 70 per cent reduction in the incidence of smallpox in close contacts and the authors felt that if gamma globulin derived from patients convalescent from smallpox were used the reduction would be even greater. They suggested that the method of prophylaxis should be very valuable in India for contacts at special risk of contracting severe disease, for example pregnant women and unvaccinated infants. In Indian villages where the disease is not endemic, and where outbreaks are therefore likely to be severe, it might be used for unvaccinated contacts of early cases and might then limit the spread and lessen the mortality. In countries where the disease is not endemic, but where it is occasionally imported, as in Great Britain, outbreaks are usually rapidly controlled by public health measures, but not before one or two fatal cases have occurred: immune gamma globulin might prevent these deaths.

Smallpox virus in mouth washings

Downie and colleagues (1961a) attempted in Madras to grow variola virus from mouth washings of patients suffering from smallpox and from contacts suffering

from a febrile illness, possibly variola *sine eruptione*. In none of five specimens taken on the first two days of illness was virus recovered and this was regarded as confirming the opinion of epidemiologists that smallpox is not infectious before the rash appears. Virus was most frequently obtained from mouth washings between the sixth and the ninth day of illness when lesions in the mouth were ulcerating. After the twelfth day virus was not recovered probably because at this stage patients suffering from mild or moderate smallpox probably have little or no virus in the mouth. The patient appears to be most infective in the first few days of the eruptive stage of the illness.

Air sampling in smallpox hospital

Meiklejohn and colleagues (1961) attempted to recover variola virus by sampling air in the wards of a smallpox hospital in Madras. Vacuum pumps with appropriate sampling devices were used: samples were taken from areas presumably highly infected, full of the dust from blankets or from droplets from patient's breath: runs lasted from 2 to 60 minutes and volumes from 20 to 18,000 litres were collected. Yet, of 38 samples only 1 yielded positive results. With experimental smallpox virus aerosols the same procedures were shown to be capable of detecting 200 pock-forming units of virus in 5 minute runs, and theoretically should have been capable of detecting 1 pock-forming unit per titre in 30 minute runs. Failure to isolate virus under normal ward conditions was therefore disappointing. The authors considered it probable that the air movement in the wards led to considerable dilution of the virus and that the virus excreted in saliva or swabs was not efficiently detected by the methods used. More sensitive methods might lead to more accurate answers and elucidate the means of transmission of smallpox virus.

MUMPS

Arthritis

Lass and Shephard (1961) describe 3 cases of arthritis presumably due to mumps. A boy of 5 years developed arthritis of the left ankle 12 days after the onset of parotitis: another boy aged 5 years had arthritis of the left hip 2 weeks after parotitis and suffered at the same time from symptoms suggesting pancreatitis: a man of 43 years developed arthritis of the left ankle 2 weeks after the onset of parotitis. In all 3 cases the diagnosis of mumps seemed definite, clinically or serologically, or both. The authors suggest that arthritis as a complication of mumps may be commoner than is supposed and may occur, as do other complications, without preceding parotitis.

Skin test

Mumps skin test antigen injected intradermally produces a local area of erythema in patients resistant to mumps infection. Angle (1961) investigating an outbreak of mumps used the test in 170 adults without history of mumps and found that 153 were in fact resistant: only 2 of the 153 developed mumps and in both the skin test was considered questionable. Of the 17 presumably susceptible subjects, 15 were given 2 doses of mumps vaccine and 10 of them had in addition 5·0 ml of gamma globulin. None of the 10 developed mumps, but 3 of those given only vaccine did, as well as the 2 given neither. It would appear that the skin test is of considerable value in separating out non-susceptibles in adult populations exposed to mumps: that vaccine gives little or no protection after exposure but that gamma globulin probably does and might be used in special cases. Dermal sensitivity to mumps antigen probably has not developed at the stage of parotitis, so that the skin test may have some value in the diagnosis of parotid swellings.

HERPES SIMPLEX

Illness due to herpes simplex infection is not always mild. Severe ulceration of the lips, tongue and mouth in infants and young children is not infrequently due to herpes simplex virus. Antonova (1960) isolated the virus from 14 out of 16 children by inoculating mice intracerebrally with scrapings from the lesions. Sheward (1961)

described herpes simplex on the perianal region of twins aged 2 years: the father of the children had suffered from a 'cold sore' about the same time and had used an ointment which was also used to treat the twins' napkin rash. Ross and Stevenson (1961) gave clinical and virological details of 8 cases of meningoencephalitis due to herpes simplex infection: a fourfold or greater rise in complement fixing antibody was demonstrated in each case. Three of the patients were over 25 years old, the other 5 were under 3 years: only one, the youngest, aged 6 months, died.

PSEUDOMONAS PYOCYANEA MENINGITIS

Clifford and Stewart (1961) described the use of a new preparation of polymixin B—the sodium salt of polymixin B methane sulphonic acid—in the treatment of 5 infants suffering from meningitis due to *Pseudomonas pyocyanea*: all the infants recovered, the treatment lasting between 11 and 35 days. The preparation seems to be free of tissue-damaging effects and the authors found no evidence of toxicity. Intramuscular injections did not produce satisfactory levels in the cerebrospinal fluid and the drug was therefore given intrathecally as well, in doses of 5,000 to 10,000 units every 2 or 3 days.

LEPTOSPIROSIS

Serological diagnosis

Ross and Ives (1960) examined sera, in Glasgow, from 250 patients with abacterial meningitis and found evidence of *Leptospira canicola* infection in 12 and of *L. icterohaemorrhagiae* in 1, a total of 5·2 per cent. Both complement fixation and agglutination-lysis tests were positive, the former becoming type-specific earlier in the illness than the latter. The authors considered the tests of considerable importance in abacterial meningitis. Pike and Schulze (1961) carried out agglutination tests, in the U.S.A., on the sera of 521 patients, some suspected of leptospiral infection, others because of jaundice: 31 specimens (6 per cent) were positive: the types were *L. canicola* 13, *L. pomona* 12, and *L. grippotyphosa* 6. The incidence was higher (11·8 per cent) in one area where most of the patients came from rural areas and lower (3·8 per cent) where they came from urban areas. At the end of a period of dry years the overall incidence was 2 per cent, compared with an incidence of 14 per cent in a very wet year. An excellent account of the laboratory diagnosis of leptospirosis is given by Babudieri (1961).

Infection from pigs

Coghlan and Norval (1960) mentioned 16 cases of canicola fever in patients in Edinburgh, 11 of whom worked on pig-farms. Serological investigation of pigs at 5 farms concerned revealed infection in from 33 to 100 per cent of animals tested. Examination of pigs at 2 farms implicated in an outbreak 5 years earlier showed that the herd was still heavily infected. These findings indicate that the pig may be as effective a carrier of *L. canicola* as the dog and that there is a danger especially to newly employed young workers on pig farms.

LIVER-FLUKE INFECTION

Facey and Marsden (1960) reported the occurrence of 6 cases of liver fluke infection in England, and Taylor (1961) described another 2 cases. The symptoms were pyrexia, upper abdominal pain and enlargement of the liver along with marked eosinophilia—in Facey and Marsden's cases the average initial level of eosinophils was 34 per cent. All the patients had eaten watercress and lived in areas where *Fasciola hepatica* infection in animals was very common—in the Ringwood area of Hampshire infection of cattle was almost 100 per cent (Facey and Marsden, 1960). The cercariae of the liver fluke emerging from the water snail, *Limnaea trunculata*, soon encyst on the watercress as barely visible white cysts. After ingestion, the parasite loses its cyst form, penetrates the bowel wall and passes through the peritoneal cavity to the liver: it burrows its way through the liver to the bile-ducts where it matures and lays eggs. In the human, ova may not be found in the faeces until 3 months after infection and

diagnosis must be based on the clinical manifestations and the eosinophilia: the fasciola complement fixation test was positive in all Facey and Marsden's patients. The condition responds to treatment with chloroquine and emetine.

REFERENCES

Aldous, I. R., Kirman, B. H., Butler, N., Goffe, A. P., Lawrence, G. D. and Pollock, T.M. (1961). 'Clinical Trial in British Children.' *Brit. med. J.* **2**, 1246

Angle, R. M. (1961). 'The Use of Mumps Skin Test in Adults.' *J. Amer. med. Ass.* **177**, 9, 650

Annotation (1961). 'Immunization Against Measles.' International Conference in Washington. *Brit. med. J.* **2**, 1489

Antonova, N. I. (1960). 'Virological and Serological Investigation of Acute Aphthous Stomatitis in Children.' *Acta Virologica* **4**, 6, 383

Babudieri, B. (1961). 'Laboratory Diagnosis of Leptospirosis.' *Bull. World Hlth. Org.* **24**, 45

Chumakov, M. P., Voroshilova, M. K., Drozdov, S. G., Dzagurov, S. G., Lashkevih, V. A., Mironova, L. L., Ralph, N. M., Gagarina, A. V., Dobrova, I. N., Ahmarina, E. E., Shirman, G. A., Fleer, G. P., Tolskaya, E. A., Sokolova, I. S., Elbert, L. B. and Sinyak, K. M. (1961). 'Some Results on the Work of Mass Immunization of the Population in the Soviet Union with Live Poliovirus Vaccine from Albert B. Sabin's Strains.' *VIIth Symposium, European Association Against Poliomyelitis, Oxford*

Clifford, H. E. and Stewart, G. T. (1961). 'Intraventricular Administration of a New Derivative of Polymixin B in Meningitis due to *Pseudomonas pyocyanea*.' *Lancet* **2**, 177

Coghlan, J. D. and Norval, J. (1960). 'Canicola Fever in Man from Contact with Infected Pigs.' *Brit. med. J.* **2**, 1611

Collard, P., Hendrickse, R. G., Montefiore, D., Sherman, P., Van der Wal, H. M., Morley, D., Goffe, A. P., Lawrence, D. G. and Pollock, T. M. (1961). 'Vaccination Against Measles, Clinical Trial in Nigerian Children.' *Brit. med. J.* **2**, 1244

College of General Practitioners Research News Letter. *The Complications of Measles.* A Report by a Study Group of the College of General Practitioners, Parts I and II. (1956) No. XI, 3, 2, Suppl and (1957) No. XIV, 4, 1, 51

Cross, R. M. (1961). 'Observations on the Classification and Interpretation of Reactions to Smallpox Vaccination.' *Bull. World Hlth. Org.* **25**, 1, 7

Dick, G. W. and Dane, D. S. (1961a). 'Oral Poliomyelitis Vaccine.' *Brit. med. J.* **2**, 1146

— — (1961b). 'The Control and Prevention of Outbreaks of Poliomyelitis.' *Med. Offr.* **105**, 25, 369

— — (1961c). 'Vaccination Against Poliomyelitis with Live Virus Vaccines. Effect of Previous Salk Vaccination on Virus Excretion.' *Brit. med. J.* **2**, 266

Downie, A. W., St. Vincent, L., Meiklejohn, G., Ratnakannan, N. R., Rae, A. R., Krishnan, G. N. V. and Kempe, C. H. (1961a). 'Studies on the Virus Content of Mouth Washings in the Acute Phase of Smallpox.' *Bull. World Hlth. Org.* **25**, 1, 49

— Hobday, T. L., St. Vincent, L. and Kempe, C. H. (1961b). 'Studies of Smallpox Antibody Levels of Sera from Samples of the Vaccinated Adult Population of Madras.' *Bull. World Hlth. Org.* **25**, 1, 55

Editorial. 'Oral Poliomyelitis Vaccine.' (1961). *Brit. med. J.* **2**, 293

Facey, R. V. and Marsden, P. D. (1960). 'Fascioliasis in Man: An Outbreak in Hampshire.' *Brit. med. J.* **2**, 619

Hale, J H., Doraisingham, M., Kanagaratnan, K., Leong, K. W. and Monteiro, E. S. (1959). 'Large Scale Use of Sabin Type II Attenuated Poliovirus Vaccine in Singapore During a Type I Poliomyelitis Epidemic.' *Brit. med. J.* **1**, 1541

Harries, J. R. and Lawes, W. E. (1961). 'The Use of Light Hypothermia in Acute Life-Threatening Poliomyelitis.' *S. Afr. med. J.* **35**, 28, 573

Hobday, T. L., Rao, A. R., Kempe, C. H. and Downie, A. W. (1961). 'Comparison of Dried Vaccine with Fresh Indian Buffalo-Calf Lymph in Revaccination against Smallpox.' *Bull. World Hlth. Org.* **25**, 1, 69

Hoskins, J. M. and Udall, V. (1961). 'Variation of Sabin Attenuated Type I Polio Virus during Growth in the Human Alimentary Tract.' *VIIth Symposium, European Association Against Poliomyelitis, Oxford*, p. 175

Kempe, C. H., Bowles, C., Meiklejohn, G., Berge, T. O., St. Vincent, L., Sundra Babu, B. V., Govindarajan, S., Ratnakannan, N. R., Downie, A. W. and Murthy, V. R. (1961). 'The Use of Vaccine Hyperimmune Gamma-Globulin in the Prophylaxis of Smallpox.' *Bull. World. Hlth. Org.* **25**, 1, 41

Knowelden, J., Hale, J. H. and Gardiner, P. S. (1961). 'Measurement of the Protective Effect of Attenuated Poliovirus Vaccine.' *Brit. med. J.* **1**, 1418

Lass, R. and Shephard, E. (1961). 'Mumps Arthritis.' *Brit. med. J.* **2**, 1613

Meiklejohn, G., Kempe, C. H., Downie, A. W., Berge, T. O., St. Vincent, L. and Rao, A. R. (1961). 'Air Sampling to Recover Variola Virus in the Environment of a Smallpox Hospital.' *Bull. World Hlth. Org.* **25**, 1, 63

Petersdorf, R. G. (1961). 'Symposium on the Chemoprophylaxis of Infection. Introduction and General Principles.' *J. Pediat.* **58**, 2, 149

— and Woodward, T. E. (1961). 'Symposium on Chemoprophylaxis of Infection. The Use of Antibiotics to Prevent Infection by Specific Pathogens.' *J. Pediat.* **58**, 2, 153

— Browder, A. A. and Feinstein, A. R. (1961). 'Symposium on Chemoprophylaxis of Infection. Protection Against Infection in Susceptible Individuals.' *J. Pediat.* **58**, 2, 174

Pike, R. M. and Schulze, M. L. (1961). 'Incidence of Leptospiral Agglutinins in Patients. A Ten Year Experience.' *J. Lab. clin. Med.* **57**, 2, 223

'Problems in the Eradication of Smallpox.' (1961). *W.H.O. Chronicle* **15**, No. 11, 413

Ross, C. A. C. and Ives, J. C. J. (1960). 'Serological Diagnosis in Leptospiral Aseptic Meningitis.' *Lancet* **2**, 1278

— and Stevenson, J. (1961). 'Herpes Simplex Meningoencephalitis.' *Lancet* **2**, 682

Sheward, J. D. (1961). 'Perianal Herpes Simplex.' *Lancet* **1**, 315

Stuart-Harris, C. H. and Knowelden, J. (1961). 'Oral Poliomyelitis Vaccine.' *Brit. med. J.* **2**, 1146

'Symposium on the Chemoprophylaxis of Infection' (1961). *J. Pediat.* **58**, 2, 149

Taylor, A. W. (1961). 'Liver Fluke Infection in Man.' *Lancet* **2**, 1334

'Trial of Living Attenuated Poliovirus Vaccine.' Report of the Public Health Laboratory Service to the Poliomyelitis Vaccines Committee of the Medical Research Council. (1961). *Brit. med. J.* **2**, 1037

Verlinde, J. D. and Wilterdink, J. B. (1961). 'Relative Stability of Attenuated Poliovirus (Sabin Vaccine) after Human Passage as Examined by rct/40 Character and Intracerebral Monkey Neurovirulence.' *VIIth Symposium, European Association Against Poliomyelitis, Oxford*, pp. 175–184

ALLERGIC DISEASES

By D. BLAIR MACAULAY, M.B., Ch.B., M.R.C.P.
Consultant Allergist, Royal Liverpool United Hospitals and Liverpool Chest Hospital; Consultant Physician, Bootle Hospital, Liverpool

Much of the recent work in the field of allergy is concerned with the study of the metabolism of corticosteroids and attempts to elucidate their mode of action on such a widespread and varying group of diseases. At the same time new variants of the corticosteroids are being produced in an endeavour to find those with maximal anti-allergic properties and minimal side-effects.

MECHANISM OF CORTICOSTEROID ACTION

The method by which corticosteroids rapidly affect allergic reactions has not yet been explained. Antibody production is considerably diminished during administration but this response is comparatively slow. Hughes and McDowell (1958) have shown that even slight variations in the electrolyte balance of plasma can markedly affect bronchial contractility in response to histamine stimulation but this cannot be operative in the case of modern corticosteroids which produce little or no electrolyte disturbance. Diminution of capillary permeability has been thought to play some part but if this be the case it is anomalous that increased capillary fragility, giving rise to echymoses, can sometimes be a troublesome side-effect of treatment (West, 1961). It must be admitted that the mechanism of the effective and frequently dramatically rapid results of corticosteroid therapy in allergic disease still eludes us.

METABOLISM OF CORTICOSTEROIDS

Booth and his colleagues (1961) have found that cortisol occurs in human plasma in three states: (*a*) freely diffusible, (*b*) bound to a specific globulin fraction (which has been termed Transcortin), and (*c*) bound to albumin. The amount of free cortisol is always a small fraction (less than 10 per cent) of the total content. The binding to albumin probably occurs only in the high concentrations used experimentally *in vitro*. Transcortin has a high affinity for cortisol and the resulting complex is fairly stable and not metabolized readily by the liver. It would, therefore, appear to act as a reserve supply for emergency. This complex is present in higher concentration in the serum of females than males, and is still higher in pregnancy. Preliminary studies (Dixon, 1961) indicate that there is an increase in cortisol, both bound and free, during an attack of asthma with a rebound decrease following the episode. These studies still lack the confirmation of more extensive and detailed investigation.

MILK ALLERGY IN INFANTS

Allergic hazards associated with apparently normal diet can be seen in three important findings referring to cow's milk.

Cow's milk has long been recognized clinically as a dietetic factor sometimes responsible for serious illness in children, producing gastro-intestinal disturbances or atopic manifestations of the eczema–asthma type. Schloss (1924) demonstrated precipitating antibodies to milk in the serum of such children and Clein (1958) stated that 10 per cent of apparently normal infants could be shown to have such antibodies. Gunther and colleagues (1960) using more delicate techniques have found these antibodies present in almost all infants but the titre is high in certain cases—mainly bottle-fed children.

Banks (1958) drew attention to the fact that 20 per cent of all deaths between the ages of two weeks and two years were sufficiently sudden and unexpected to be notified to the Coroner. In these so-called 'cot deaths' healthy infants who had been left peacefully asleep were found dead a few hours later, without any signs of a struggle. The post-mortem findings usually showed pathological changes in the bronchioles only, which were filled with an exudate of cellular material and desquamated mucosal