Experiments have shown that flies may spread the virus by faecal contamination of food, and food ought of course to be protected from flies; but there is as yet no epidemiological evidence to justify an anti-fly campaign as a major item in a programme for the control of poliomyelitis. No vaccine is available, and there is no convincing evidence of the value of immune serum in prophylaxis; there is in fact some evidence[7] that serum antibodies do *not* confer immunity to paralysis.

A state of panic is rather easily produced by Press publicity, and it is to be hoped that the daily papers in this country will not draw undue attention to the present outbreak. In any year the cases and deaths due to poliomyelitis will be far fewer than the injuries and deaths caused by road accidents. The natural anxiety of parents might be allayed to some extent if it were more generally known that attack rates in large populations during the most severe epidemics have been only 2 or 3 per 1,000 and that second cases in families are uncommon. It should also be emphasized that the ultimate prognosis is not so bad as is popularly imagined. In a series of 296 cases in Baltimore[8] 50% recovered completely and 29% regained practically normal movement. There was marked paralysis in 18%, and 3% died. Similar results were recorded[1] in the Mauritius epidemic.

STREPTOMYCIN IN TUBERCULOSIS

A number of speakers at the recent Commonwealth and Empire Health and Tuberculosis Conference in London gave the medical world at large some idea of what at this stage may be expected from streptomycin in the treatment of tuberculosis. Dr. H. S. Willis, Superintendent of the W. H. Maybury Sanatorium, Michigan, said that six or more laboratories were now concentrating on research into streptomycin, and that in the U.S.A. they already had records of 1,000 patients who had completed a course of streptomycin—the average course lasting from 90–120 days. According to Dr. H. C. Hinshaw, of the Mayo Clinic, something like 500 kg. of streptomycin are being produced commercially each month. The American workers stressed the fact that in such a serious disease as tuberculosis a co-ordinated study was essential. While they had enough evidence to show that the use of streptomycin was a real advance in the treatment of tuberculosis, it was emphasized that only a small proportion of tuberculous cases were at present amenable to this treatment, and that the drug by no means replaced other current methods of caring for the tuberculous.

Streptomycin is looked upon as being an essential in the treatment of miliary tuberculosis, tuberculous meningitis, acute pulmonary tuberculosis, and certain other pulmonary lesions. Dr. P. M. D'Arcy Hart, a member of the Scientific Staff of the Medical Research Council, said that at the end of 1946 the M.R.C. had received from the U.S.A. about 50 kg. of streptomycin, sufficient to treat between 150 and 200 cases. The Report of the M.R.C. on streptomycin is awaited, but its main conclusion may be anticipated from Dr. Hart's statement that streptomycin benefits at least a small proportion of cases of miliary tuberculosis and tuberculous meningitis, and that the results were sufficiently promising to justify considering a wider use of the drug in these two conditions. He added, however, that the long-term results of treatment were still in doubt.

These observations are similar to those summarized in a report of the Committee of the American Trudeau Society which has just come to hand. This Committee and its Subcommittee on Streptomycin Therapy, under the chairmanship of Dr. H. C. Hinshaw, have carried out a series of trials with streptomycin during the past year and have also had the opportunity of reviewing results of trials conducted by the U.S. Veterans' Administration, the U.S. Army, and the U.S. Navy. They have also reviewed results of work previously undertaken at Cornell University, Mineral Springs Sanatorium, and the Mayo Clinic. The Committee considers that cases of tuberculous meningitis should receive intensive parenteral and intrathecal streptomycin therapy. It is pointed out that, though clinical remissions are frequently brought about by such treatment, subsequent relapse is likely to occur—this underlines Dr. D'Arcy Hart's cautious observation. The Committee also observes that "residual neurologic disorders are frequently noted." In view of the importance of prompt treatment the Committee states that this must often be instituted before bacteriological diagnosis is made. The Committee also recommends streptomycin for acute haematogenous miliary tuberculosis, tuberculous laryngitis, ulcerating tuberculous lesions of the oropharynx, and for progressive tracheobronchial tuberculous ulcers. It is not clear yet whether in this last condition results are superior when aerosol is combined with parenteral administration.

Streptomycin appears to be highly effective in the treatment of tuberculous sinuses of the skin. Although it is recommended that tuberculous pneumonia should be treated with streptomycin, it is not recommended for all types of pulmonary tuberculosis. Streptomycin is not indicated for chronic fibroid or fibrocaseous pulmonary tuberculosis, for acute destructive and apparently terminal types, or for early cases with a favourable prognosis; but encouraging results have been reported in the treatment of recent but extensive and progressing lesions. Streptomycin, it should be added, is apparently ineffective in the treatment of chronic tuberculous empyema. It is stressed that tuberculosis with a favourable prognosis should not be treated with streptomycin until more is known about toxicity and the appearance of drug-resistant strains; the latter seems to be one of the gravest drawbacks to streptomycin therapy. Drug resistant strains of *Mycobacterium tuberculosis* undoubtedly appear. This may be either because a normal bacterial population contains certain bacteria which are naturally resistant to streptomycin and flourish because the more sensitive organisms are killed off, or because a specific resistance to the drug is acquired, selection then coming into play. If the latter suggestion were proved it would seem, incidentally, to offer support to the Lamarckian theory of evolution. In a paper read at the

[7] Burnet, F. M., and Jackson, A. V., *Austral. J. exp. Biol. med. Sci.*, 1939, 17, 261.
[8] *Facts and Figures about Infantile Paralysis*, National Foundation Infantile Paralysis, New York, 1946.

Atlantic City Centenary Meeting of the American Medical Association, Drs. H. J. Corper and Maurice Cohn said that in experimental work on tuberculosis in guinea-pigs they found that prolonged treatment with streptomycin, while it retarded the disease, did not prevent the death of animals from tuberculosis, and that positive cultures could be obtained from the organs of animals treated for as long as 181 days. "In no treatment test in animals," they observed, "have we definitely been able to prevent a lethal outcome from tuberculosis by the use of streptomycin, although we have been able to delay such issue." This observation shows how necessary it is to be extremely careful in assessing the results of treatment. But Baggenstoss, Feldman, and Hinshaw,[1] describing five fatal cases of miliary tuberculosis treated with streptomycin, provide post-mortem evidence "of an inhibitory action exerted by streptomycin on human miliary tuberculosis and tuberculous meningitis." They demonstrated regression and healing in the miliary tubercles of the lungs, liver, and spleen—and by healing they meant the occurrence of fibrosis, hyalinization, and the absence of caseation: tubercle bacilli could, however, be demonstrated in the lesions. They stressed two important factors—namely, the size or mass of the lesion at the time of treatment, and the concentration of streptomycin in fluids and tissues. One striking fact was the presence of a significant concentration of streptomycin in the cerebrospinal fluid in contrast to its complete absence from the brain. The drug was given in these cases at 3-hourly intervals with a daily dosage ranging in the five cases between 1 and 10 g. Some workers in the U.S.A. at the moment seem to be obtaining satisfactory results with a daily dose of 1 g.

Much has been written about the toxic effects of streptomycin, but U.S.A. workers believe the greatest drawback to the use of the drug is the appearance of drug-resistant strains of the tubercle bacillus. Four types of toxic reaction have been observed: (1) the so-called histamine reaction characterized by flushing, headache, and an abrupt fall in blood pressure; (2) anaphylactic reactions; (3) disturbances of vestibular function and occasional deafness; (4) irritation of the kidney. This question of toxicity is the subject of a recent article by Farrington, Hull-Smith, Bunn, and McDermott[2] in an investigation conducted under the direction of the National Research Council Committee on Chemotherapeutics and Other Agents, under the chairmanship of Dr. Chester S. Keefer. It is not certain whether the toxic effects are due to streptomycin itself or to other substances present in the impure product. These observers believe that the so-called histamine reaction is the effect of the latter. In experiments with "chemically pure" streptomycin Molitor and his colleagues[3] found that daily doses of 25 mg. per kg. of body weight produced a fatty change in the liver and occasionally also in the kidney—changes which apparently were reversible. Evidence of labyrinthine or cerebellar disturbance was also noted. Farrington and his colleagues[2] have investigated the toxic effects in a group of human subjects given a four-month course of treatment with highly purified streptomycin sulphate, a product "at least 95% pure." Sixteen patients received 3 g. of the drug daily for about 120 days, given at 3-hourly intervals in doses of 0.375 g. Three hours after injection the average concentration of streptomycin in the blood was between 10 and 20 micrograms per ml. of serum. In only two of the sixteen patients was it necessary to interrupt treatment because of toxic effects, in both cases anaphylactic—maculopapular rash, rise of temperature, nausea and vomiting, hypotension, and eosinophilia, and in one case an acute synovitis of the interphalangeal joints of the extremities. Apart from these obvious manifestations of anaphylaxis, Farrington and his colleagues observed eosinophilia in 14 of their 16 cases at one time or another during the 120 days of treatment. They regard this as a disquieting phenomenon "in view of the work of Rich and others[4] on the possible association of sensitivity to the drug with the development of diffuse vascular disease." Casts appeared in the urine of 14 of the patients and were related to the acidity of the urine. If the urine was kept neutral or slightly alkaline casts could be demonstrated in only one of these patients. In 14 of the 16 patients tests showed that renal function remained within normal limits throughout the period of treatment. Post-mortem observations on three patients who had received streptomycin up to 154 days and who had had numerous casts in the urine showed no renal abnormality. Deafness as a complication is a matter of excessive dosage and can be avoided.

Disturbed vestibular function is the commonest and most marked toxic effect and appeared in all 16 patients, usually between the 17th and 25th day of treatment. In 4 fatal cases of meningitis treated with streptomycin, Stevenson and his colleagues[5] found liquefactive necrosis in the ventral cochlear nuclei, and in two of them similar changes in the inferior vestibular nucleus; during treatment these patients had become deaf. In 14 of the 16 patients described by Farrington and his colleagues no tinnitus or impairment of hearing was observed, nor any other form of neurological abnormality. As to other toxic effects, leucopenia without granulocytopenia was observed in 2 of Farrington's cases. Repeated tests for liver function showed no evidence of damage. Although Farrington and his colleagues still consider that some of the toxic effects may be caused by residual impurities in the streptomycin preparation, they consider it is the streptomycin itself which irritates the kidney and causes the disturbance of vestibular function, brought about, in their opinion, by central action. Their general conclusion is as follows: "It is evident that highly purified streptomycin is a chemotherapeutic agent of low toxicity, since it was possible to administer moderately large doses of the drug for such a long period to persons who were seriously ill." The grave disabilities suffered by many patients temporarily recovering from tuberculous meningitis are, it would seem, the after effects of the meningitis rather than the after effects of the drug. Patients with disturbed vestibular function seem to be able to compensate for the disability when streptomycin therapy is discontinued, and in the view of U.S.A. observers the disability is slight compared with

[1] *Amer. Rev. Tuberc.*, 1947, **55**, 54.
[2] *J. Amer. med. Ass.*, 1947, **134**, 679.
[3] *J. Pharmacol.*, 1946, **88**, 151.
[4] *Johns Hopk. Hosp. Bull.*, 1942, **71**, 123.
[5] Observations which will be recorded in *Proc. Soc. exp. Biol.*, N.Y.

the disability of a severe illness. It should be added that repeated intrathecal administration of 0.1 g. of streptomycin is well tolerated.

Apart from the toxic effects of streptomycin there is another peculiar complication that has worried many thoughtful people in this country during the past few months, and that is the intermittent appeals sent out over the air from the B.B.C. for supplies to individual patients. This disquieting innovation in conducting medical treatment is, we believe, partly the result of the secrecy that has prevailed—a secrecy that was lifted when we were able to publish in the *Journal* of June 7 the names of those centres where treatment is being conducted on a very small national allocation of the drug. It seemed pertinent to inquire what were the results of the B.B.C. broadcasts, and this was done by the Public Relations Department of the British Medical Association. These are the results: Between Nov. 19, 1946, and April 17, 1947, the B.B.C. broadcast 21 appeals at the instance of hospital authorities. Twenty-one hospitals were asked for results of the appeal. Of the 18 who replied 15 stated that no streptomycin had been received as a result of the appeals. One hospital received 150,000 units, one received 3 g., and one received 5 g. When it is recalled that each of the patients studied by Farrington and his colleagues received 3-g. doses of streptomycin daily for approximately 120 days—a total dosage of 360 g. each—further comment hardly seems necessary. The response to the appeal produced totally inadequate supplies of the drug and can have done little but harm in that the appeal must have raised false hopes in the minds of the sufferers or their relatives. Streptomycin is still in very short supply. There is still need for prolonged investigations before the position of this drug in the treatment of tuberculosis can be accurately assessed, and there is still need for a far greater allocation of the drug from America until our own manufacturers are able to produce it in adequate quantities. Great Britain still seems to be getting less streptomycin than, for example, France. While we may sympathize with the B.B.C.'s desire to aid those who ask for an appeal to be made, we cannot but believe that the use of the radio for this purpose is improper.

BOTULISM

The report of a recent inquest has again drawn attention to the rare form of food poisoning caused by the exotoxin of *Clostridium botulinum*. The best-known outbreak of this disease in Great Britain is that at Loch Maree in 1922, due to contamination of wild duck paste, but since then less dramatic episodes have occurred from time to time. An outbreak in Hampstead in 1935 due to infected "nut meat brawn" was commented on in a leading article in this *Journal*.[1] The usual sequence of events is that some article of food contaminated with *Cl. botulinum* is preserved in either tin or bottle without being adequately heated. The spores are highly resistant to heat, being able to survive for some three hours at 212° F. (100° C.) and 36 minutes at 230° F. (110° C.). The anaerobic conditions in the tin or bottle enable the organism to proliferate and produce toxin. If the contents are then eaten either uncooked or inadequately cooked the toxin causes botulism. The toxin, unlike the spores of the organism, is relatively easily destroyed by heat—for example, usually by boiling for five minutes. When the victims have taken a large dose of toxin, as at Loch Maree, symptoms will begin to appear in some in about fifteen hours.

The symptoms are vomiting, obstinate constipation, and cranial nerve palsies. Diplopia, ptosis, and difficulty in speech, swallowing, and breathing are particularly prominent. There is no loss of consciousness. In fatal cases these symptoms become worse, but consciousness generally remains to the end. Even at Loch Maree, where all eight patients died within a week, there was great variability in the rapidity of onset of symptoms; in some the onset was insidious. In cases in which the dose of toxin has presumably been small the clinical picture may be very puzzling, and the relationship of the symptoms to food poisoning may be obscured. There is usually a history of vomiting associated with constipation. The characteristic cranial nerve palsies may come on very gradually—in days rather than hours—but when they do appear they are apt to persist. Disturbances of vision and diplopia are common symptoms. Fixed dilated pupils are a common physical sign.

The mild case is probably less common than the severe because the concentration of toxin in the food is generally considerable, but it is probable that under conditions relatively unfavourable to the organism small amounts of toxin may be produced and mild cases may result. It is likely, for example, that in a large mass of foodstuff which contains spores toxin may be produced in the centre even when the surface of the foodstuff is exposed to the air. The long list of foodstuffs given by Meyer[2] as having caused botulism in the U.S.A. shows that strictly anaerobic conditions in tin or bottle are not essential. As the natural habitat of the organism is the soil, the vehicle has commonly been inadequately heated home-canned vegetables, but unsealed foods may exceptionally be to blame. Quite moderate cooking of the foodstuff before eating is sufficient to destroy the toxin.

FOOD POISONING

Food poisoning may be defined as any illness that results from the ingestion of food. This includes a wide variety of different substances, such as poisonous plants, fungi, metals, organic and inorganic chemicals, and bacteria and their products which have become incorporated in the food. In addition it may be correct to include the individual idiosyncrasies of certain persons in their reaction to, for example, shell-fish or strawberries, the eating of which may be followed by an attack of urticaria. There is a widespread tendency for the public to blame the quality of the food as being the cause of illness, instead of realizing that the food is in most cases contaminated by those who handle it and by flies and vermin that are allowed to gain access to it. There is no question that the number of outbreaks appears to be increasing, but it is difficult to say how much this is due to an actual increase and how much to the greater interest taken in food at the present time and to the fact that food poisoning is now notifiable. Communal feeding cuts both ways; thus, if an outbreak occurs in a large canteen attention is drawn to the numbers affected, whereas if the same number fed at home it would be impossible to assess how many would have been affected by a gastro-enteritis that passed off rapidly and was never reported.

[1] *British Medical Journal*, 1936, **1**, 64.

[2] Meyer, K. F., *Amer. J. publ. Hlth.*, 1931, **21**, 762.