Current Surveys

TYPHOID FEVER

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Relapses and the Carrier State

Chloramphenicol has solved most of the therapeutic problems of typhoid fever; but two remain—relapse and the carrier state. Chloramphenicol has made very little, if any, change in the incidence of either: and it is quite useless in the treatment of the carrier state.

Some experimental tissue culture work seems to be relevant. When tissue cultures are infected with *Salmonella typhi*, and then treated with an antibiotic, the organisms continue to divide for up to one hour, after which multiplication ceases, in organisms both inside and outside tissue culture cells. With penicillin or synnematin, but not with chloramphenicol, another phenomenon is noted. The extracellular organisms adopt a spherical shape, the spheroplast, and within an hour or two the cytoplasm of the spheroplast is extruded, and the spheroplast becomes a ghost cell. Spheroplast formation does not take place in the intracellular organisms, so long as the tissue cell is alive, but, if the cell is killed, the organisms inside the dead cell begin to form spheroplasts after one hour. These findings seem to indicate that the antibiotic does penetrate the cell, but that, so long as the tissue cell remains alive, *Salmonellae typhi* inside it are in some way protected against the full effect of the antibiotic.

If infected tissue cultures are treated with antibiotics, it is possible to "cure" them, but it takes time, and the cultures must be "followed up". Some were rendered free of *Salmonella typhi* and remained free: but, in others, the "cure" was not permanent, and *Salmonella typhi* reappeared as long as a month after treatment commenced, and nine days after it was stopped. All these experimental findings seem to have very striking relevance to the problem of relapse and the carrier state in the human. The original articles should be consulted. (Showacre, Hopps and Smadel, 1961; Hopps, Smadel, Bernheim, Danauskas, and Jackson, 1961; Watson, 1955.)

Intensity of Excretion

The intensity of excretion by a carrier may vary widely: even in the same patient, it may range from 45 million organisms to less than 500 per gram of faeces (Archer, Goffe and Ritchie, 1952); figures as high as 10,000 million per gram of faeces have been quoted (Merselis, Kaye, Conolly, and Hook, 1964). Duodenal contents may

produce very high counts especially after the intravenous injection of pancreozymin which stimulates the gall-bladder to contract: 1 ml. of duodenal juice may then contain up to 100 million organisms. A carrier may excrete intermittently, but probably less often than is thought. A good deal may depend on the thoroughness of the search: it is obviously more difficult to isolate the organism in culture when there are only 500 per gram of faeces than when there are 45 million. Epidemiological factors, other than intermittency, may be responsible for the varying infectivity of carriers. A very full account of the carrier problem is given in Ledingham and Arkwright's monograph, (Ledingham and Arkwright, 1912) written in 1912, but still highly relevant and with many important experimental data.

Agglutination Tests

When H and O antibodies are produced in a patient's serum, whether by a natural infection or by inoculation of T.A.B., they remain at a high level for about six months, after which the O antibodies fall rapidly, but the H may remain at a high level for years. Clearly, then, in interpreting a Widal test, a high H titre is of much less significance than a high O. There is some sharing of the O antigen between *Salmonella typhi* and the paratyphoid organisms, but there is no sharing of the H antigen. If, then, O antibody is present to both typhoid and paratyphoid A and B organisms, the cause may be active infection: but if H antibody is present to all three, the cause can only be previous inoculation. In an uninoculated patient, in an area of low typhoid incidence, a titre of 1/40 for O or H, or both, should suggest active infection. If an inoculation response is present, a repeat test in a few days time may help, but, if the initial titres are high, there is often no rise in the second test, even in the presence of active infection (Mol, 1948). The H antibody is said to rise in response to non-specific stimuli, the anamnestic reaction. This may be so, but a rise in H titre during afebrile illness is much more likely to be due to typhoid fever (Weil and Saphra, 1953).

The Vi agglutination test is of some help in detecting carriers. A titre of 1/5 is said to indicate the presence of *Salmonella typhi* in the body. But at least 25% of carriers have negative Vi tests, and

a large number of normal people have positive Vi titres. In an unselected population, the number of Vi reactors who are non-carriers is much higher than the number who are carriers. In an area where typhoid is common, the Vi test is likely to be of little use in detecting carriers. In Britain, provided one is working in a narrow field of suspects, the test is more useful, though even then, it will detect only three out of every four carriers. The question is fully discussed in several surveys (Bokkenheuser, 1964; Bokkenheuser, Smith and Richardson, 1964; Report, 1961).

Some Epidemiological Facts

Salmonella typhi does not produce gas, and therefore, if it grows inside a can of meat, it will not reveal its presence by blowing the can. But, in nearly every case, if *Salmonella typhi* is inside a can, other gas-producing organisms will also be present, and they will blow the can. This is the theory on which is based the trade practice of holding cans of meat at a temperature of 92°F for 15 days after sterilization, to allow any live organisms inside to blow the cans. Unfortunately what happens in the laboratory does not always happen elsewhere, and organisms which regularly produce acid and gas on laboratory media sometimes fail to do so inside a can of meat (Christie, 1964a; Howie, 1965). This obviously has relevance to the Aberdeen typhoid outbreak (Report, 1964b) and to post-process leakage of cans (Bashford and Herbert, 1965).

Salmonella typhi and, more commonly, *Salmonella paratyphi B* have often been isolated from sea water at bathing beaches, but the evidence suggests that people are rarely infected in this way. There is a very full and interesting report on this problem (Report, 1959) by the Public Health Laboratory Service. In another report, (Thomson, 1954) there was evidence that people got typhoid from eating shellfish from polluted water, but not from bathing in it.

Secondary Cases

Direct infection from one patient to another is uncommon, and infection, once introduced into a community, does not usually spread in a series of waves. In the Croydon water-borne outbreak (Report on Public Enquiry, 1938), there were only 16 secondary cases in a total of 299, and in the Bournemouth milk-borne outbreak (Shaw, 1937), only 4 in a total of 718.

T.A.B. Prophylaxis

Inoculated people may still get typhoid fever, and in a severe form: the course of the illness does not appear to be affected by previous inoculation (Rowland, 1961; Jordan and Everley, 1945; Syverson, 1946). But there is considerable evidence that T.A.B. inoculation does give protection, though it is far from absolute. In the Yugoslavia trials, phenol-treated vaccine seemed much superior to alcohol vaccine. Yet an alcohol

vaccine appears to stimulate a greater production of Vi antibody than a phenol vaccine. Mouse protection tests give complicating results, the active tests favouring the phenol and the passive the alcohol vaccine (Yugoslav Typhoid Commission, 1962). More recent studies (Cvjetanovic and Uemura, 1965) show that the position is still not clear, and acetone-inactivated vaccine appears to be better than phenol or alcohol vaccines. T.A.B. vaccines can play only a subsidiary role in the prevention of typhoid fever.

Treatment of the Case

The main difficulty with chloramphenicol treatment of the acute case is that relapses still tend to occur. A large number of different systems has been tried: four representative articles are quoted in the list of references (Rowland, 1961; Marmion, 1952; Watson, 1957; Woodward and Smadel, 1964). The two factors which seem to lower the relapse rate are that the course must be long enough and the dose high enough. The drug has been given in two courses, separated by an interval of several days, in the hope that, in the second course, the drug would catch the organisms that had escaped the first course: but results have not come up to expectations. For an adult, 0.5 g. chloramphenicol every four hours (3 g. daily) till the temperature has settled, usually 3 to 5 days, and thereafter 0.5 g. every six hours (2 g. daily) to a total of 14 days can be recommended as a satisfactory course of treatment.

Corticosteroids will bring the temperature down more quickly than chloramphenicol alone, but I do not think they should be given, except in extremely toxic cases where life is in danger. There is some evidence that chloramphenicol interferes with the immune response (Watson, 1957) and so predisposes to relapse: corticosteroids can only increase such a tendency. It may well be to the patient's immunological advantage that his temperature should be allowed to settle without the interference of corticosteroids.

Treatment of Carriers

Ampicillin is much more successful than chloramphenicol in the treatment of carriers. It must be given in a dose of at least 3 g. daily, possibly along with probenecid, for at least one month, possibly for as long as two or three months (Christie, 1964) and the carriers should be followed up, preferably for at least two years. If gallstones are present, or gall-bladder function deficient, cholecystectomy may still be required, but the carrier should first be given the benefit of a thorough treatment with ampicillin. The same applies to urinary carriers, but it must be remembered that, in chronic urinary carriers, there is usually some abnormality of the urinary tract. Full urinary investigation must be carried out and operation should not be too long delayed, for there is a considerable risk that typhoid infection may spread from one side of the urinary tract to the other (El-Sadr, 1953).

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