By the time our safari ended the first of the inoculated mice were showing signs of encephalitis after being inoculated intracerebrally with the reconstituted vaccine at the end of our inoculation sessions—a good test of potency. Later a few mouse protection tests carried out by Smith at Yaba on the sera of inoculated soldiers showed that the vaccine was effective even under the unfavourable conditions in which it had to be used. So it became possible to issue the new Rockefeller vaccine for widespread use by medical officers in the field, who were duly instructed in its use either by Murgatroyd or by Smith.

Incalculable threat

Yellow fever did not appear in Egypt or India. Whether our efforts with the vaccine determined this good result we shall never know. Murgatroyd was doubtful to the end. The risk was theoretically there, he agreed. In Egypt and India the transmitting mosquito was present and the population had never experienced yellow fever. The case mortality rate in susceptible populations could be any-

thing from 20% to 50%—and the Egyptians and Indians must be rated as susceptible, unlike the Africans, who might have yellow fever as a serious illness that could be fatal or one so mild that it might be only a passing fever of short duration. Perhaps, Murgatroyd argued, there were in Egypt and India viruses that could interfere naturally with the establishment of yellow fever virus even if it got there by an infected mosquito or passenger.

At any rate, we had done what we could against a threat which we could not measure but which could have been disastrous. Unfortunately there was an unwelcome price that had to be paid in the hepatitis that followed inoculation with some batches of Rockefeller yellow fever vaccine incorporating human serum. This was later replaced by harmless alternatives but until these hepatogenic batches had been identified and called in we continued to have to check whether outbreaks of jaundice with fever were due to yellow fever virus or not. Yellow fever vaccine is now rated as safe and effective for at least 10 years. Its successful use in the field in west Africa was a reassurance to the military authorities for whom the west African air route was essential until the enemy was cleared out of Africa in May 1943.

Lesson of the Week

Three cases of illness during a drug trial in healthy volunteers

E J FAZACKERLEY, N P C RANDALL, B J PLEUVRY

At the invitation of a drug company we undertook a trial to investigate the effect of an orally administered respiratory stimulant on respiratory depression caused by parenteral morphine in healthy volunteers. The drug has long been used safely intravenously, and tablets are already marketed in France.

The ethical committee approved the trial, with the drug company accepting full liability. Twelve paid volunteers consented to enter the trial. Satisfactory health was determined by history, examination, and blood profiles. Each volunteer attended four times to receive the trial drug or placebo, and morphine 0.12 mg/kg or placebo, in double blind and fully randomised fashion. Sedation, ventilation, pain threshold, and plasma drug concentrations were then assessed for eight hours. The trial proceeded uneventfully for five weeks, and seven volunteers began treatment.

Case reports

Case 1—A doctor received three treatments and then reported a maculopapular rash on her forearms followed by pain and swelling in the hand,

Healthy volunteers who become ill during a drug trial should be investigated by an informed physician not participating in the trial

elbow, and knee joints. She consulted a rheumatologist, who found that the full blood count, erythrocyte sedimentation rate, antinuclear factor titre, and results of sheep cell agglutination tests were normal. A viral aetiology was suspected and serum samples taken during the acute and convalescent phases of her illness. A drug reaction could not be completely discounted so she was excluded from the trial. Her symptoms resolved spontaneously over three days.

Case 2—A doctor received three treatments and then reported that he had rubella (self diagnosis). Symptoms began with a rash on the arms followed by slight malaise and arthralgia lasting for five days. He recovered and completed the trial.

Case 3—Two weeks after completing the trial a dentist noticed a rash on her arms followed by severe pain, stiffness, and paraesthesia in the hands, elbows, and knees. Her general practitioner prescribed aspirin and hydrocortisone and notified the trial investigators. Recovery was slow, with symptoms persisting for several weeks.

The trial sponsors were notified and the double blind code broken; this showed that the trial drug had been given once to one volunteer (case 1) and twice to the two others (once before and once after the illness in case 2, and twice before the illness in case 3). Inquiries in other centres investigating the trial drug showed that no other reactions had occurred, even to multiple and larger doses. The three volunteers affected had had contact with each other both at the trial and at work, but no similar cases had been reported locally. The trial was suspended pending further investigation.

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Four weeks later a colleague of two of the volunteers (cases 1 and 3), unconnected with the trial, suffered a similar illness. The viral studies in case 1 showed that IgM specific for parvovirus was present in both serum samples, indicating recent infection with parvovirus. The trial then continued, all 12 volunteers completing it without ill effect.

Discussion

Serum sickness is caused by a foreign serum or drug. Drugs are often modified and combined with body protein to form an antigen, and the body makes complement fixing antibody to the antigenic protein.¹ Testing for drug reactions is unrewarding because the exact antigenic determinant is unknown. Symptoms develop eight to 10 days after inoculation and consist of fever, itching, urticarial rash, lymphadenopathy, muscle pain, swollen painful joints, abdominal pain with vomiting, and neurological problems, which last for four to five days.²

Information on infection with parvovirus has accumulated since 1981.^{3,4} Antibody is usually acquired in childhood after an episode of erythema infectiosum (a mild fever and maculopapular rash spread by nasal droplet). In adult volunteer studies inoculation is followed by viraemia at six days, rash from day 17 to day 22, and joint disease from day 22 to day 24.⁵ Diagnosis is by a rise in IgM specific for parvovirus. In 1983-4 Anderson *et al* took serum from 164 patients with a rash: 8% had parvovirus, and arthralgia was common.⁶ White *et al* found 19 patients with infection with parvovirus, all women, among 153 patients at a synovitis clinic.⁷ They had symmetrical arthritis of the hands, knees, ankles, and shoulders, sometimes accompanied by an illness similar to influenza or a rash similar to rubella. Most cases resolved within two weeks, but in some symptoms were still present at two months. Reid *et al* reported on 42 patients, mostly young women,⁸ with similar symptoms to those reported by White *et al*.

Serum sickness and infection with parvovirus have similar symptoms and are distinguished by serological examination. In case 1 the symptoms would have fitted either disorder. Factors against serum sickness were the lack of systemic upset and the short interval (five days) between the administration of the trial drug and the onset of symptoms. The patient's management by a consultant rheumatologist, who was aware of her participation in the trial, was undoubtedly the most satisfactory, and her investigation provided the only proof of parvovirus infection.

In case 2 the volunteer had milder symptoms and made his own diagnosis of rubella. He had used the same trial room and water filled spirometer as the volunteer in case 1. A chance to prove a viral

aetiology was missed because of our acceptance of his diagnosis and assumption of cross infection. After recovery he received his last treatment (morphine, glucose, and the trial drug), which by chance contained all possible triggers of a reaction; he did not suffer any further problems.

The volunteer in case 3 was the most ill and serum sickness was more likely. Symptoms started after she had received the trial drug twice, the last exposure having been two weeks before; this latent period is slightly long for a drug reaction. She used the same trial room and spirometer as the two other volunteers who were ill, and she worked with one of them (case 1). We did not have access to her during her illness, and it was her general practitioner's concern that led to suspension of the trial. We did not have any proof of a viral aetiology, but because of her symptoms and history of contact parvovirus infection was possible.

Research on healthy volunteers poses ethical problems of informed consent, inducement, and balancing risks against objectives. To maintain the reputation of such trials we used highly qualified volunteers with jobs, who were screened for fitness. They were paid for expenses, time off work, and discomfort and fully appreciated the implications of their participation.

These cases indicate the problems posed by illness in healthy volunteers. A high index of suspicion for untoward effects must be maintained. Healthy volunteers who become sick during a drug trial should be investigated by an informed physician not participating in the trial.

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Is there any need to estimate hepatitis antibody titres after giving hepatitis B vaccine?

It is important that not only anti-HBs positivity but also antibody titres be measured shortly after (usually one to three months after) the recommended course of vaccination to define the level ("test level") of response and to predict when an additional booster might become necessary since levels fall exponentially thereafter.^{1,2} At least 5-10% of young, healthy vaccinees, and up to 40% of older (>40 years) and immunosuppressed, will be poor (anti-HBs titre <10-50 IU/l) or non-responders.³ These must be informed that they are not necessarily protected from future hepatitis B infection.³ Although the actual minimum level of anti-HBs antibody that guarantees protection is unknown, most authorities would agree that titres above 10 or 50 IU/l probably indicate protection.^{1,2} Serial antibody estimations are necessary after additional, spaced booster doses in the poor and non-responder groups because it is impossible to predict the level that is achieved.^{1,2} The rise is never as high as that achieved with one additional booster in the initial responder group.^{1,2}

Whether those initial "responders" with high test levels—that is, above 1000 IU/l at seven to nine months after the conventional 0, one, and six month course—require additional booster doses once levels fall is undecided.¹ Preliminary evidence would suggest that they should be protected since antibodies rise exponentially—that is, above 10 000 IU/l—on challenge, albeit with vaccine rather than virus,^{1,2} indicating that immune memory is intact. Current policy, however, is to "play safe" and recommend

an additional booster dose if antibody levels have been predicted to be below 10-50 IU/l at follow up or after an exposure, particularly if the vaccinee belonged initially to the poor or non-responder group, or if the post-vaccination "test level" is unknown.—ELIZABETH FAGAN, lecturer, liver unit, London.

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What is the best management of a 65 year old woman with a stroke who within two weeks developed a massive deep venous thrombosis in the paralysed leg?

The best management of this patient is to give her anticoagulation treatment for three months. Anticoagulation is best avoided in the first week after a stroke as there is the potential risk of haemorrhage into the area of ischaemic necrosis in the brain. The deep venous thrombosis, however, is unlikely to develop at this early stage and after a week anticoagulation will be safe. If there has been no recovery in the paresis after three months more prolonged anticoagulation may be considered.—C W HAVARD, consultant physician and endocrinologist, London.