did not prevent infection because the new strain is antigenically distinct. Dr Wilson also found that a prior attack of whooping cough afforded little protection.

Since November 1963 Glaxo pertussis vaccine has contained 1, 3 strains. It is clear from the M.R.C. trials that it is the mouse protection test, not the ability to produce agglutinins in children, that is decisive for a clinically effective vaccine. It is also clear from these trials that vaccine made by the methods employed at Glaxo was effective. It is known from the work of Professor Lacey, that different methods of culture profoundly affects the agglutinability of pertussis organisms. It would seem therefore that the preparation of pertussis vaccine from these new strains by established methods will protect against the disease despite inability to detect agglutinogen in them.]

DISCUSSION

Dr Kathleen Pearson (*Westmorland*): Why does the Ministry of Health policy still defy the consensus of expert opinion; i.e., vaccination forms are sent at three months old and the B.C.G. is given to 12–13 year olds?

Professor Cruickshank: If Dr Pearson refers to the policy of vaccinating children against smallpox over the age of one and not under the age of one, then that can be answered fairly satisfactorily by saying that really modern statistics make it quite clear that the group under one year of age are at particular risk. We should not be surprised at this change, because in fact we have been steadily reducing infant mortality in the last 40 years, and therefore smallpox as a cause of killing children is being highlighted. I would myself disagree perhaps with Dr Beale in vaccinating babies at one month old with B.C.G. in view of the value of the Mantoux test as a diagnostic agent in the young child, but 12–13 years is a very good age for vaccinating negative reactors in order to ensure them freedom at industry.

Dr A. Wilson (*Innerleithen*): Can Dr Beale please confirm that adenovirus can produce the full clinical picture of the whooping cough syndrome? Is it indistinguishable clinically from that produced by pertussis?

Dr Beale: All I can say is that in outbreaks studied by Joan Davies in L.C.C. schools where a clinical diagnosis of whooping cough had been made, no pertussis organisms were isolated but only adenoviruses, particularly adenoviruses of types 1, 2 and 5. Whether the criteria by which these cases were diagnosed as whooping cough would satisfy every clinician I am not willing to state.

Dr Watson: I am quite certain that the syndrome of the adenovirus

3 infection would not be mistaken for whooping cough. It is a characteristic illness. The child gets an obstructive rhinitis with a rising temperature with a peak on the third day, but even though its temperature is 104°F it is never ill; convalescence is immediate and the condition is certainly not likely to be confused with whooping cough. For the last 18 months, however, an epidemic has been going round Britain of something which is being called whooping cough and this is worrying the doctor making the diagnosis because many of the children have been adequately immunized against whooping cough. A small proportion of those have undoutedly been Eaton agent infections and in the big epidemic which I saw last year a high proportion of cases could have been called whooping cough. Those are two alternative solutions to this problem of whooping cough in the well-immunized child, which is one of the puzzles that we in general practice have to solve.

Professor Cruickshank: I am a great protagonist, of course, of pertussis being considered a *Bordetella pertussis* infection. I know there is a lot of criticism of this attitude among some of my clinical colleagues. We have been looking at this very carefully among all the young children admitted to the City Hospital in Edinburgh, and it is perfectly true that among the cases diagnosed as whooping cough the highest incidence of isolations is of the adenoviruses, but if you look at the overall picture, 95 per cent of these labelled whooping cough show either a significant titre against Bordetella or a rise in titre. I would ask you not to be too ready to look for a virus aetiology for a condition that seems to be like pertussis until you have made sure that in fact it is not pertussis. Do not necessarily assume, because you have given the child two or three doses of pertussis vaccine, that therefore it must be protected against pertussis. This is something we must ask the family doctor to look at very carefully, to see whether in fact our pertussis vaccines are maintaining a high level of resistance. We are in your hands.

Dr Mitchison (*Town*): I would like to support what Professor Cruickshank has just said. I think we are making the bacteriological diagnosis difficult because we treat our patients so quickly with an antibiotic that rapidly gets rid of the organism.

Dr Beale: I agree with that for the most part. Most clinical pertussis syndromes are probably due to pertussis organisms, though some of the cases may be due to other agents. It is important to have this proved by aetiological studies.

Dr G. Walker (*Glasgow*): Is polio immunization with Sabin vaccine safe in pregnancy?

Dr Beale: The evidence is clear that Sabin vaccine is safe at any stage of pregnancy. Quite a lot of studies of the use of Sabin vaccine

in pregnant women, particularly in the early stage of pregnancy, have revealed no effect on the foetus.

Dr Watson: I would like to draw attention to Dalton's paper on premenstrual syndrome in the April 1964 *Proceedings of the Royal Society of Medicine*. One of the things which she makes a point about is that the progesterone phase lowers resistance, and she remarks on the high progesterone content in pregnancy. I have a number of trains of thought about which I am unhappy. I have a patient who has only ever caught one disease of this sort and that was rubella in pregnancy. She has survived almost every other contact but became ill with rubella in pregnancy. We know that polio is more troublesome in pregnant women. Influenza is certainly a very serious illness in pregnancy and I would ask you to look critically at pregnancy from this point of view of lowering of resistance to infection. Is resistance lowered particularly in pregnancy?

Chairman: That is a good point, Dr Watson. The other I would add is that there is a very good study coming from Madras leaving little doubt that smallpox in the Indian woman has a very much worse prognosis in pregnancy.

Dr Blackadder (*Edinburgh*): A child vaccinated at 18 months developed vaccinial encephalitis and two years later still suffers convulsions. Is this a contraindication to vaccinating his two younger siblings?

Chairman: I would say that in this country, having had a disaster in the family wth one child of this nature, one would be very hesitant at vaccinating any of the siblings in a routine fashion. I think we are reaching a stage when we will need to be constantly reviewing our immunization programmes. We cannot go on adding and adding other things to it. One of the areas in which we need to have a second think is whether in this country, with all the modern resources available for the tracing of contacts, etc., we need to have primary vaccination in infancy at all. If epidemics were better handled from the point of view of the press and wireless, with all the modern views that one might put across, this would not be much of a problem. I should just add that Dr Beale mentioned the use of Marboran as a possible prophylactic. No one seems to have paid attention to the two letters in the *Lancet* when the toxicity of Marboran and such substances is being assessed. Two reputable investigators had to stop using it on white persons because of its toxicity. I was therefore rather distressed recently to discover that this drug had been written up in the *British Medical Journal* and no comment made on the toxicity at all.

Dr Blackadder: A female child had virus encephalitis at six months and still has intermittent convulsions. Should vaccination be

avoided in her case? It is possible that her parents may have to go abroad in a few years' time.

***Chairman*:** This is the converse of the previous case. If a parent is taking his child to an area in which smallpox is endemic, then it would be quite ridiculous to consider taking the child unvaccinated. One has to be quite dogmatic about that. If the parents must go abroad to a smallpox area, then their accompanying children must be vaccinated.

***Professor Cruickshank*:** Could I add a rider about smallpox vaccination? It seems to me that we have a great deal to be ashamed of in regard to the present status of smallpox vaccination. We still use this stuff that we rub on to the belly of a calf or a sheep, then we scrape it off and treat it with glycerol and then we rub this on to the arm of a young baby. This is something that the medical profession has a great deal to answer for, and I am very glad that at last within the last few years there is a real step forward towards using better types of vaccines against smallpox. If we had given a tenth of attention to smallpox vaccine that we have given to polio vaccine, we would not have to worry about these cases of encephalitis and dirty arms and all the rest of it. This is a reflection on ourselves and the sooner we can rub out this blot the better.

***Dr Beale*:** There is an economic point that perhaps I should make as a manufacturer of vaccines. Will an improved vaccine be bought by the Ministry of Health? This is not the present position with vaccinia vaccine.

***Dr Watson*:** I can tell Professor Cruickshank that we have taken some steps forward. A patient of mine who was born in India still remembers a calf being brought up to the sixth floor. She was vaccinated direct from the blister on the calf's belly. On the more serious side, I have two patients who come into this sort of category. One is a man who had a severe encephalitis and is still lamed by it. He travels a lot and has been armed with the necessary certificate to say that under no circumstances must he be revaccinated. That has worked all right until quite recently he came through South America to North America, from an area where there was smallpox. We were all quite interested and surprised when I got a letter from the American authorities asking about his present state of health as part of the international surveillance. This raised the question of what should we do if he really did come into contact with smallpox on his travels. The answer from one consultant was: " He really ought to be revaccinated under cover of cortisone ". I did not like the answer because cortisone would upset chickenpox and I did not quite know if it was going to help him over smallpox. The answer from Professor Stuart-Harris is that he ought to be given killed vaccine if he runs into this situation. The other problem concerns

a person on continuous steroid therapy for severe rheumatoid arthritis who is going abroad. Do you vaccinate him or not? I would like to hear some panel discussion on vaccination of patients on steroids.

Dr. T. L. Henderson (*Grantown-on-Spey*): Have any fatal reactions followed the use of antigens in children?

Professor Cruickshank: This is not a type of vaccine likely to cause a fatal issue unless there is something which would already predispose to this in the child.

Dr Ashcroft (*Newcastle*): Is there any contraindications to giving oral polio vaccine on the same occasion as triple antigen?

Dr Beale: No. The Ministry of Health has not been in favour of this, because there were some fears about the general safety of attenuated polio vaccines and the risk of inducing paralysis, but as confidence in the safety of attenuated polio vaccine has increased, so this problem has become less. It has also been established that the two vaccines can be given together without affecting the immune response.

Dr E. V. Kuenssberg (*Edinburgh*): How can maternally transferred immunity hinder the development of immunity from inoculation, as in diphtheria immunity in a very young baby?

Dr Mitchison: I can only answer that question in very general terms. There is evidence from a variety of experimental studies that antigen injected in the presence of an antibody immunizes relatively poorly. There is also good evidence now that mixing antigen and antibody before inoculation tends to induce allergy rather than normal circulating antibody, at least when very small amounts are given. I can think off-hand of one irrelevant instance where the presence of antibody helps immunization, and that is in some types of immunization against erythrocytes, red cell antigens and other types, removal of red cells by antibody prevents immunization. That has come out very clearly in ABO incompatibility reducing the incidence of rhesus immunization.

Dr Stewart (*Peebles*): Would the panel please give details of tetanus prophylaxis?

Dr Longmore (*Lochmaben*): After primary vaccination with tetanus toxoid, how many booster doses at five-year intervals, are required before lifelong immunity to tetanus is acquired?

Professor Cruickshank: The procedure recommended now following Army experience, is that there should be two doses of toxoid with a six week interval followed by a third dose six months later. This is the routine procedure for the primary course of tetanus immunization. Tetanus toxoid happens to be a very powerful

antigen. Small doses are very effective and I believe that this primary course of immunization will give protection for periods of up to ten years, although people play safe and say: " Give another booster at five years ". Immunization at infancy as part of the triple vaccination and a booster dose of tetanus and diphtheria toxoids at school entry takes care of the child throughout his school years. You would only give a dose of tetanus toxoid if he had an accident and knew he had been actively immunized. This is very difficult to find out. If you are sure he has been immunized give a further dose of tetanus toxoid. In fact late booster doses against tetanus are unnecessary; there is a good deal of American evidence that this is so.

***Dr Watson*:** It is my own practice, whenever a patient comes up to have an injection like penicillin with which tetanus toxoid would easily mix, to make up his penicillin in toxoid rather than in water.

***Chairman*:** The practice in recent years of using triple vaccine would mean that any child under the age of five years may now be regarded as having had tetanus toxoid and therefore on injury could be treated with toxoid. In addition, when you see a person in the early stages of his injury, there is a good deal nowadays to be said for prophylaxis with tetracycline, in that the tetanus organism at this stage is very susceptible. One hundred per cent of organisms tested have been shown to be susceptible to tetracycline.

Dr Knox (*Edinburgh*): Could Dr Mitchison give some explanation of the failure in tolerance demonstrated by Dr Watson's case of the child already marked by rubella *in utero* and later developing the disease?

***Dr Watson*:** I can comment on that. It is now fairly well established that for tolerance to endure it is necessary for antigen to be readministered at intervals or to remain present in the body. I did not go into that in discussing the mice, but it is interesting and in fact highly significant in mice. These mice were not only tolerant of donor skin given them in foetal life but they were also chimeras. They still had cells from the original graft given *in utero* present in their lymphoid tissue and bone marrow. There is no doubt at all that without this chimerism, without this continuance of the original antigenic stimulus their state of tolerance would have been lost.

Dr Johnson (*Alumick*): I have noted an increase in febrile reaction following triple injections. When a mother reports this I usually give the diphtheria-tetanus toxoid mixture and leave out the whooping cough vaccine for the second and third injections. Is this a wise thing to do or is it necessary?

***Professor Cruickshank*:** I am very interested that this has been brought up because undoubtedly this has been happening. Perhaps Dr Beale may want to come in on this, but it would seem to be a

great pity to give up the pertussis fraction because this is probably the most important thing of the three. Manufacturers must see that they give us pertussis vaccine relatively free from risk of producing these febrile reactions.

***Chairman*:** Testing of some of the vaccines produced by different manufacturers has revealed great variation in the number of organisms present and indeed great variation in the count as carried out in a research laboratory and the number of organisms alleged to be there.

***Dr Watson*:** I usually give half quantity for the first dose, which is another way round the same problem.

***Dr Beale*:** This is a problem that manufacturers know about and all manufacturers are very active in investigating and trying to improve.

Dr W. G. Mathews (*Westmorland*): Is there any evidence that the use of antibiotics early in mild bacterial illness reduces the immunity response—for example, in acute otitis media?

***Chairman*:** There is a little evidence that the antibody titre rises satisfactorily when typhoid is treated with chloramphenicol, but I am not a great believer in the quotation of titres, because titres can vary so considerably from one laboratory to another. One is rather inclined to think that there is a kind of canonical significance because somebody says the titre of this person's antibody is one in 32. If you went to three different laboratories you might find it was one in 16 in one, and one in 256 in another. It depends how the laboratory carried out the test. This is the difficulty in comparing the results of one laboratory with another.

***Professor Cruickshank*:** I do not believe that giving antibiotics to a child with acute otitis media makes it more susceptible to re-infection or re-attack. Because we know that among these pyogenic infections there is an almost infinite variety of serological types. Whether the antibody is damped down by antibiotics does not matter a hoot. If the child is to get another attack of otitis media it will get it with some other type, and what you have done before does not really affect the issue.

***Dr Watson*:** The only example I have from my own knowledge is that of a child who had three attacks of streptococcal otitis media. One might have thought that they were relapses, but they were in fact all due to three different strains.

Dr J. D. Cruickshank (*Edinburgh*): Are not the complications in primarily vaccinating the 15–plus age child accentuated by the severe local reactions which occur in this age group? Would it be preferable perhaps to immunize these people against smallpox by giving a single prick with the needle?

***Chairman*:** I would be inclined to think that there is something in this, but what happens when you reduce the number of multiple pressures is something about which there is not a great deal of evidence.

***Dr Beale*:** Primary vaccination over the age of one year and re-vaccination at 15 will reduce the amount of reaction.

***Professor Cruickshank*:** I must say that we in the medical school are very cowardly. We have to see that all medical students have been primarily vaccinated when they come to us and we still find that about a quarter of these students have never had primary vaccinations, so we tell them: " We are not going to do anything to you; you go and see your family doctor."

***Chairman*:** We in Glasgow vaccinate everybody when they start to take the infectious diseases course. There is something to be said for doing this to doctors because it seems to me an appalling situation that a student could qualify and still be unvaccinated. One of the deaths in the Glasgow 1950 outbreak was in fact in a person taking a D.P.H. class, sadly enough not known to me to be quite unvaccinated. Since then I have made up my mind that, primary vaccination or no, nobody will be shown cases in my unit who has not been vaccinated against smallpox.

***Dr J. D. Cruickshank*:** Why should children be advised after B.C.G. vaccination to stop swimming?

***Dr Beale*:** Occasionally (in 0.1 per cent) after B.C.G. vaccination a little ulcer appears. When this occurs it is much better to allow it to dry out and for this reason swimming is not recommended. Reverting to smallpox vaccination, I might add the comment that Professor Dick's view is that in this country general infant vaccination is not justified but he does vaccinate all medical students who come to his class, rather as Professor Anderson does, because he believes that for medical men who may be exposed to smallpox at any time it is much more important that they should be vaccinated.

Dr H. F. Martin (*Bunessan*): Why should triple vaccination be postponed to six months when whooping cough is so deadly to any child under six months and whooping cough in older children who have been immunized is never serious?

***Professor Cruickshank*:** I take issue with Dr Beale and with Professor Dick about the period at which triple vaccine should be given. I think there is a cleavage of viewpoint between the immunologists and the family doctors. I think the time to give a child three jabs of this triple vaccine at monthly intervals is between three and six months of age when the child will not become allergic to a doctor with a syringe in his hand; if you do this you get the immunity that is necessary to establish the basic resistance. I am dead against the

proposal to defer these triple vaccines till after six months of age.

Dr Wier (*Durham*): What does the panel think of some form of compulsory National Health Card on which all vaccinations and immunizations could be entered?

Professor Cruickshank: By all means let us have some method of finding out what vaccinations a child has had, but how can you ensure that these cards are going to be available when you want them? This is the problem. There have been all kinds of answers to this—discs on a bracelet, or tattoo marks or what you will. I do not know what the answer is. The Midlothian health authority looked at this fairly carefully and found that less than half of the parents could produce the cards issued to vaccinated children, so that one does not know the answer to this, until parents take this thing a bit more seriously.

Chairman: There is one last question from our president, and it is an interesting comment on the fact that in 1914–18 the Highland Division in Bedford suffered one of the most severe and widespread measles epidemics with a very heavy death rate. He thought that Professor Picken wrote this up at the time, suggesting that the epidemic illustrated the lack of acquired immunity in young adults coming from remote highland villages not visited by measles for many generations.

Professor Cruickshank: If an individual gets an attack of measles in adult life he gets a much more severe attack, and if by living in a Highland village he has not been exposed to the hazard of measles then, of course, this certainly happens. There have been instances where measles has invaded some of the islands and decimated whole populations. In the study I mentioned of the incidence of complications, as late as 1963 it was the infants under a year and the adults who suffered most from these.