CONFIDENTIALITY AND ANNOUNCEMENTS

The Chairman reminded members that the proceedings and information before them was confidential and should not be disclosed. He welcomed Dr Frank Sheffield who was attending particularly for item 9.

2. APOLOGIES FOR ABSENCE

Apologies for absence had been received from Professor A Dudgeon.

Apologies were also received from the following DHSS Officials,

Dr Alderslade, Dr Barnes, Dr Holgate, Miss Horridge and Miss Purvis.

3. MINUTES OF THE MEETING HELD ON 29 OCTOBER 1982

These were agreed and signed by the Chairman as a correct record of the meeting.
4. Matters arising from the minutes

4.1 Hepatic Function and Influenza Vaccine

Further references to this matter were considered:-

(i) Stockley I H, Pharmaceutical Journal, ARVI/83/1A
    229, 703-4 (Dec. 1982).

    16, 670-672 (Sept. 1982).

Dr Smith said that the observed effect of influenza vaccine causing
depression of hepatic drug metabolising enzyme systems might extend
over the whole range of vaccines since it could be a response to
antigenic stimulation. However he noted that the patients most
likely to be at risk would be those receiving influenza vaccine by
reason of age or chronic disease. Professor Hull remarked that
influenza itself could evoke a similar response as shown by its
effect on the clearance of theophylline.

4.2 Whooping Cough and Whooping Cough Vaccine: The Risks ARVI/83/2
    and Benefits Debate, Miller D L, et al, Epidemiological

The Chairman thanked Professor Miller for drawing attention to this
paper which had most helpful data. Members were pleased to receive
this paper for information.

4.3 Murine Model for pertussis vaccine encephalopathy: ARVI/83/3
    linkage to H-2, Steinman L. et al, Nature 229,
    738-740 (1982).

The Chairman said that the members had seen a preliminary report of
this study at their June 1982 ARVI meeting and had expressed a wish
to see it in full. This paper described a possible animal model
for pertussis immunisation encephalopathy. Mice possessing a
susceptible H-2 genotype following immunisation with killed pertussis vaccine and sensitization to bovine serum albumen (BSA) developed an encephalopathy. Dr Smith stated that the Sub-Committee had heard at an earlier meeting that there was no agreed characteristic histological change in the post vaccination encephalopathy which occurred in humans. Dr Sheffield observed that a very large dose of pertussis vaccine had been given. The dose for a 15 gm mouse was 1½ times the dose given to a 10 kg. child. The 1 mg. dose of BSA was also very large and Dr Sheffield found it very difficult to assess the relevance of the experiment to the human subject. Members agreed that the link between this study and human encephalopathy was tenuous.

4.4 Sudden Infant Death Syndrome:


The Chairman said that members had seen the preliminary report of this NICHD Co-operative study on Sudden Infant Death Syndrome (SIDS) at its June 1982 meeting.

This paper described the design of this multi-centre population based case-controlled study and presented the preliminary findings of the analysis of the first 400 of 844 SIDS cases, 400 age matched controls (Control Group A) and a further 400 controls matched for age, birthweight and race (Control Group B). The SIDS cases were found to have received substantially fewer DTP immunisations compared with control groups A and B (39 per cent versus 56 per cent and
57 per cent). When vaccinated children were considered a similar proportion of SIDS and control group 3 cases had received DTP inoculations less than 24 hours, 1-14 days, or over two weeks before death or interview respectively as one per cent, 23 per cent and 76 per cent (SIDS) and two per cent, 23 per cent and 75 per cent (Control Group 3 cases) respectively.

Members noted that it was reassuring that only 36% of SIDS cases were immunised compared with 56% of control cases but were concerned there might have been a bias in the selection of the control groups. It was hoped that when the full study was published further demographic data and information about the risk factors in the control groups would be provided which would strengthen the preliminary conclusions of this study.


This paper was also received for information.

5. "What is wrong with vaccination" - A report from APVDC

5.1 The Chairman introduced this paper which the Association of Parents of Damaged Children had distributed to DHSS, Health Authorities and Community Health Councils and made two general points:

5.1.1 It was a basic misconception to assume that any vaccine could be completely safe.
5.1.2 The likelihood of time coincidence apparently relating vaccine and encephalopathy had been ignored in the APVDC paper.

5.2 In discussion the following points were made:

5.2.1 Members of the Sub-Committee noted that the purpose of the paper was to promote the Association's campaign to improve compensation for vaccine damaged children rather than to reopen the controversy concerning pertussis vaccination. The first section dealing with the questions of adverse reactions, promotion of vaccination and advising parents of risks was a preamble to the main issue of compensation.

5.2.2 If individual members in an unofficial capacity were to meet Mrs. Fox, they could try informally to alleviate her apparent concern. However, going over the past events with Mrs. Fox would only lead to renewed controversy.

5.2.3 The Sub-Committee agreed that a small drafting Committee should prepare notes in response to the APVDC report for internal departmental use.

5.2.4 Members observed that it was a very difficult matter to assess a remote risk. The public did not realise that the Yellow Card system could not provide rates of incidence of
adverse reactions but that its purpose was to signal rare events. The problem was that with the occurrence of a serious adverse reaction it was difficult to convey to the public the fact that the incidence was very small. The Sub-Committee considered that it was important to promote the positive benefits of vaccination.

5.2.5 The available information relating to the balance of the risk and the advantages of vaccination must be available to doctors who take the decision, whether or not to immunise an individual patient.

5.2.6 The Sub-Committee noted that this document had been discussed in a House of Lords debate on the Vaccine Damaged Patients Act 1979 on 1 December 1982.

6. Adverse reactions to Poliomyelitis Vaccines

The Sub-Committee discussed the revised draft of this report. Certain alterations were suggested and it was agreed that the amended report should be submitted to the CSM and the JCVI.


7.1 This item was taken immediately after item 4.4.2 on the agenda.

7.2 It was noted that this study had found that 39 (1.4 per cent), of 2,776 American children, who had one or more seizures during the first seven years of life, had been immunised during the previous 14 days of the occurrence of the convulsion. Ten of these children had received DTP and the remainder other vaccines. All except one of
these 39 children were febrile at the time of the convulsions. Thirty seven of the forty seizures recorded lasted less than 30 minutes and had the characteristics of febrile convulsions. One child had a right focal seizure lasting six hours after DTP immunisation and had a significant speech defect at the age of seven. No neurological handicap was found on follow-up of the other children at the age of seven and it was reported that none were mentally retarded.

7.3 Dr Smith observed that the method of recording the temperature was not stated. Dr Wilson said that a relationship between fever and convulsions was sometimes tenuous as it was rare to have the temperature recorded before the fit occurred. The fit itself could cause a rise in temperature. Dr Pollock emphasised that in acute infections, fever could cause convulsions. His own study and that of Cody et al had shown a slight rise in temperature occurred in some children following vaccination and that this occurred more frequently following DTP than DT immunisation.

8. **Adverse reactions to Diphtheria and Tetanus Vaccines:**


8.1.1 Dr Zutshi in introducing this paper said that there were two points of particular interest in this study. Firstly, protective levels of diphtheria antitoxin were found in 45 per cent of the subjects studied. This was in agreement with recent serological surveys which have shown that approximately half of the working population in the United Kingdom do not have protective levels of diphtheria antitoxin
in their sera. Secondly, an adult-type tetanus diphtheria vaccine containing reduced levels of diphtheria toxoid (2Lf) produced a rate and level of tetanus antitoxin response similar to that achieved with adsorbed tetanus vaccine without causing a statistically significant increase in clinical reactivity. However, the combined vaccine caused a slightly higher incidence of local reactions (pain, redness and swelling) while recipients of adsorbed tetanus vaccine more frequently experienced pain.

8.1.2 Dr Smith drew the Sub-Committee's attention to Balfour's recent paper in the British Medical Journal (1983, i: 624-626). Balfour had found similar good boosting of immunity with a low dose (1Lf) diphtheria/tetanus vaccine. However, he recommended adults should not be vaccinated against diphtheria without previous screening for antibodies because of the relatively high incidence of local reactions. In response to the question as to whether amyloid disease had been associated with repeated tetanus vaccine, Dr Smith said that studies carried out at the American Bacteriological Unit, Fort Dietrich had not revealed any evidence of this complication.

8.2 Initial draft report on Adverse Reactions to Diphtheria and Tetanus Vaccines - ARVI/82/3rd Meeting (Attached as Appendix to 8.1). Dr Zutshi said this paper had previously been seen by ARVI at its October meeting. He was exploring the possibility that computer programmes could be written to refine the CSM data further. He hoped this would clarify whether the diphtheria or tetanus vaccines had been administered separately, together or with pertussis as a triple
vaccine so that the suspected antigen associated with a particular adverse report could be more closely identified.

8.3 Data from the National Childhood Encephalopathy Study and the Public Health Laboratory Service North West Thames and Hertfordshire Studies

8.3.1 Dr Zutshi introduced this paper which presented the adverse reactions associated with tetanus and diphtheria immunisation that had been reported in these studies.

8.3.2 Professor Miller observed that in the NCES study the relative risk of convulsions and encephalitis together was 1.74 in the first week following DT vaccination compared with controls. However there was a deficit in the ensuing two weeks and the rates were identical in the fourth week. The increased incidence in the first week might be due to immunisation acting as a non specific priming factor in children prone to convulsions.

8.3.3 Dr Zutshi noted that the PHS North West Thames Study had not produced any evidence to support an association between suspected neurological adverse reactions and DT immunisation. The Hertfordshire Study showed the incidence of local reactions increased with each subsequent dose but the incidence of crying and fever did not vary with a particular dose. Further there was very little tendency for infants who had suffered a particular symptom to experience it again after a subsequent dose of DT vaccine.
8.3.4 The figures in Table X relating to the Hertfordshire study were queried in the context of Table IX. Dr Zutshi undertook to check these with Dr Pollock. Dr Badenoch observed that Table X would be clearer if the following headings 'after one dose' and 'after two doses' were changed to 'after a single dose' and 'after each of two doses' respectively.

8.4 Armed Forces Experience (Tabled Paper) ARI/83/12

8.4.1 Dr Zutshi introduced this tabled paper in which

Brigadier England had reviewed adverse reactions associated with tetanus vaccination reported during the last three years in the Army. The schedule of vaccination differed from that recommended for civilians. Furthermore, up to the age of 35 Armed Forces adults received tetanus vaccine in the form of intradermal TATB and thereafter tetanus toxoid BP subcutaneously. Between September 1979 and November 1982, 107 adverse reactions associated with TATB were reported but none with tetanus toxoid. However, only 19 per cent of the Army were aged over 35. Brigadier England had concluded that there was no evidence to suggest the occurrence of hyper-sensitivity from repeated injections but experience was mainly related to intradermal TATB in which the dose of tetanus toxoid is small (2 Lf).

8.4.2 The Sub-Committee felt that these papers were most useful and considered a number of measures that might lead to a reduction of adverse reactions associated with vaccination. The antigen dose could be reduced since it was clearly associated with reactivity. However there was concern that
the immunogenic response might then not be sufficient. Reduction of adjuvant content would also reduce local reactivity but then it would be necessary to increase the dose of the antigen. Another possibility was further purification of the vaccine. The fourth possibility was to reduce the number of booster doses. However, the Sub-Committee considered it would be a formidable task to establish the ideal vaccine composition and schedule in view of the numerous variables, which included not only those referred to above but also age, sex and social factors, individual variation and, possibly, differences in vaccine batches.

8.5 Review of Neurological Adverse Reactions (Tabled Paper)

8.5.1 Professor Gilliatt introduced this paper in which he had reviewed the literature of neurological syndromes after tetanus toxoid. Reports of transverse myelitis and encephalitis were rare. There had been several accounts of peripheral nerve involvement in the form of a generalised or local polyneuropathy or a mononeuropathy either affecting a cranial or peripheral nerve. The frequency of peripheral nerve involvement in one study had been calculated to be 0.4 cases per million doses distributed. Whilst it was unclear whether these reports were due to chance association, there were two patients who had either a recurrence or an exacerbation of their polyneuropathy after receiving further doses of tetanus toxoid.
8.5.2 In response to the question of whether there was any
association between the site of injection and distribution of
the neuropathy, Professor Gilliatt said that since cases were
uncommon, no clear association was detectable.

8.6 After consideration of these papers, members were reassured that
serious adverse reactions suspected of being associated with
diphtheria and/or tetanus immunisation were rare events. There did
not appear to be any evidence for the Joint Committee to change its
current advice regarding diphtheria and tetanus immunisation.

3.7 It was agreed that a drafting Committee consisting of
Professor Gilliatt, Professor Miller, Dr Pollock, Dr Smith and/or
Dr Sheffield, Dr Barnes and Dr Zutshi, should prepare a paper for the
JCVI and GSM on suspected adverse reactions associated with
diphtheria or tetanus. It should include consideration of local
reactions, the risk/benefit ratio in relation to levels of immunity
and booster doses, and the more serious adverse reactions reported in
the NCES and PHLS studies and also in Professor Gilliatt's review.
It should also advise whether it was safe to administer DT when DTP
was contra-indicated.

9. **Adverse Reactions to Tetanus Vaccination: Presentation by Dr G F Sheffield**

9.1 This presentation was given immediately prior to item 8 on the
agenda.
Dr Sheffield said that dramatic and serious adverse reactions such as angioneurotic oedema, anaphylactic shock and the occasional sudden death had occurred with the early use of tetanus vaccine. These were now rare due to the elimination of Witte's peptone from the production process of the vaccine. The adverse reactions which currently occurred were much less serious and in the main consisted of local reactions.

Dr Sheffield reminded members that there had been a number of studies on the incidence of local reactions. White (Lancet 1980; 1:42) in a series of some 18,000 workers at British Leyland had found an incidence of 9 per cent following the administration of plain tetanus toxoid and 2 per cent following the use of adsorbed toxoid, Griffith (Proceedings of 2nd International Conference on tetanus, Berne: Huber, 1967: 299-306) in a series of 900 oil workers found the adverse reaction rate varied from 10 to 20 per cent according to the batch. Collier (Lancet 1979; 1:1364-1367), who was Director of the Lister vaccine production unit in 1979, reported a trial in some 260 schoolboys and girls in Hertfordshire. He compared semiquantitatively the local reactions that occurred after routine reinforcement tetanus immunisation with adsorbed and plain formol toxoid. The adsorbed vaccine caused more severe and more frequent local reactions than did the plain formol toxoid and also a higher incidence of pyrexia. Dr Sheffield considered it was probably because of these findings that he was asked by the Department to undertake a similar trial.
Dr Sheffield said that he had carried out his trial with Dr E Jones in Manchester. They had adopted the same trial design as Collier and compared the three commercially available vaccines. However, they failed to obtain the same results as Collier. They found that the two adsorbed vaccines were slightly less reactogenic than the plain vaccine. If the mild reactions were not considered then the adsorbed vaccine "2" caused considerably less local reactions.

Dr Sheffield reminded members that it had been long known that repeated doses of tetanus vaccine tended to cause increasingly severe reactions. It had been suggested that this was due to Type III or IV or even Type III and IV hypersensitivity. Collier had assessed tetanus antitoxin titres and found that swelling and erythema increased significantly with the titre at the time of the inoculation but not with pain and tenderness. However, Dr Sheffield had found that swelling, erythema, pain and tenderness had all correlated with the antibody titre. Dr Sheffield concluded that the incidence of adverse reactions to tetanus vaccines may be also influenced by the assiduity of the search and also the attitude of mind of the vaccinator since the rate of adverse reactions fall with increasing age.

In the discussion of Dr Sheffield's presentation, Dr Pollock observed that Collier's study was very batch sensitive and adverse reactions could have been due to impurities in the Lister vaccinees. Dr Smith said that in White's study the delayed hypersensitivity was due to the toxoid antigen and not the impurities. These and other studies
provided evidence that levels of immunity were good and booster doses need not be given so frequently. Dr Badenoch said that accident prone children might be receiving an excessive number of tetanus immunisations.

The Chairman thanked Dr Sheffield for this most interesting presentation.

10. Summary of Suspected Adverse Reactions to Vaccine reported on Yellow Cards and Registered during the period 1 October 1982 to 31 January 1983

10.1 Dr Zutshi introduced this paper which included reports of 12 cases of convulsions and one of encephalitis following DTP vaccination and three cases of convulsions following the administration of monovalent pertussis vaccine.

10.2 The Sub-Committee discussed the adverse reaction report of a boy who developed a right sided foot drop without sensory loss 9 days after a pre-school booster dose of DT and polio. Dr Smith kindly offered, with Dr Sheffield's agreement, to arrange for tetanus antitoxin levels to be carried out if a sample of serum could be obtained from the boy. The general practitioner could be then advised whether tetanus toxoid should be given in the future. Dr Smith said this investigation should also be carried out on the patient who developed erythema multiforme following tetanus immunisation. Dr Zutshi undertook to write to the respective general practitioners.
10.3 The Sub-Committee agreed that a miscarriage, which occurred in a woman who was twelve weeks pregnant, following a tetanus and oral polio vaccination five weeks previously was unlikely to be related to the immunisation.

10.4 In the discussion on suspected adverse reactions associated with measles vaccination, Dr Smith drew attention to a recent report of two children hypersensitive to egg white protein who developed allergic reactions to measles vaccine. It was agreed that this paper should be placed before the Sub-Committee at its next meeting.

10.5 In the discussion on suspected adverse reactions following influenza vaccination it was noted that the four reports with a fatal outcome were due to coronary artery disease and/or myocardial infarction. The Sub-Committee agreed a causal relationship was unlikely in view of the time intervals between immunisation and death. Further, patients of their age group were particularly prone to death from heart disease.

10.6 Dr Sutshi informed the Sub-Committee that the backlog of reports of suspected adverse reactions associated with vaccine had been cleared. The follow-up of the recent more serious adverse reactions such as encephalitis, convulsions and arthropathy was underway. The Sub-Committee expressed its satisfaction with this improvement in the monitoring of suspected adverse reactions to vaccines.
11. Any other business

None.

12. Items for Information

MAL 36 was circulated for information.

13. Date of the next meeting

The date of the next meeting is Friday, 1 July 1983, at 11.00 a.m.

The last meeting of the year is on Friday, 28 October 1983.