received in addition a sprue diet and additional vitamins. When ethyl biscoumacetate was discontinued and phenindione substituted, the diarrhoea returned within a few days, this time as a bloody dysentery (possibly because the patient was now having a sprue diet). When the anticoagulant was changed back to ethyl biscoumacetate the condition improved after four to five days, although the sprue regime was abandoned. No clinical or laboratory findings to suggest any other cause for the diarrhoea were elicited. At no stage was there any fever, blood dyscrasia, or jaundice. The liver-function tests were not grossly deranged, although the plasma albumin (3.7 g. per 100 ml.) was a trifle low. Burns and Desmond (1958), summarizing the day of first appearance of other observed sensitivity reactions to phenindione, found that these occurred at a variable time, from 2 to 38 days after administration had begun. In the present case six weeks elapsed before the onset of any certain symptom.

Summary

A severe drug-sensitivity reaction manifesting itself by frank steatorrhoea developed in the seventh week of phenindione administration to a 67-year-old male patient suffering from peripheral vascular disease. The steatorrhoea cleared after ethyl biscoumacetate was substituted. On recommencing phenindione the diarrhoea returned, this time as a bloody dysentery, only to disappear again when ethyl biscoumacetate was substituted.

My thanks are due to Dr. John Badenoch for his help in the investigation of this unusual problem, to Dr. R. Biggs, Dr. R. G. Macfarlane, Professor P. R. Allison, and Professor Sir George Pickering for their valuable suggestions.

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WHOOPIING-COUGH IMMUNIZATION CLINICAL FOLLOW-UP OF FIRST BARKING FIELD TRIAL, 1955

BY

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In our original work (Spiller *et al.*, 1955) we stated that we were following up clinically the immunized children and that we would give the results at a later date.

Two groups of children were immunized against diphtheria and whooping-cough, the one group by the combined method—that is, three injections of 1 ml. of diphtheria-pertussis prophylactic W.D.P. (red) Wright-Fleming, at monthly intervals; the other by the separate method—that is, three injections of 1 ml. of suspended whooping-cough vaccine (Glaxo), followed by two injections of 0.5 ml. P.T.A.P. The first injections were given between the ages of 2 and 5 months inclusive, and blood samples were taken at the age of 15 months in the case of 160 of these children so as to assess their antibody level. This was the original work on which we reported, and, furthermore, 52 of these children have recently been bled again, 4–4½ years after the end of

primary immunization in infancy. The main object of these long-deferred bleedings was to determine the diphtheria antitoxin titres at pre-school entry age.

The Investigation

A careful clinical follow-up has been carried out on the whole 714 children who were originally incorporated in the research, so as to ascertain the number of those who did actually develop whooping-cough during the years that have followed. It may be interesting to mention here that over 300 of the children changed addresses at least once or twice during the course of the follow-up, and it required the assistance of rent offices, electoral registers, as well as health visitors, relatives, and neighbours in tracing them, as the families rarely notified a change of address. Because the blood results (agglutination titres) appeared to indicate an eminently satisfactory protection level, it may be thought that the clinical result is disappointing. It should be remembered, however, that we have not merely relied on whooping-cough notifications but have followed up individually each case by careful questioning. Many cases of doubtful cough that were not notified were accepted as whooping-cough because of various factors—for example, other simultaneous cases of suspicious cough in the family; an unusually prolonged and violent cough with no other obvious cause, and no previous history; other whooping-cough contacts, etc.

Whooping-cough Incidence.—Of the original 714 children incorporated in the scheme, 64 either lapsed in their attendance for injections or left the country and could not be followed up. Of the remaining 650 (315 in the “separate” group and 335 in the “combined”) it appears that 22 almost certainly had whooping-cough, mostly in a mild form (but some were severe); and 11 were reported as doubtful cases, and may have had it very mildly. This gives a maximum frequency of 5.07% or a minimum of 3.38%, over a total period of three years.

Separate Versus Combined Injections.—Of the 22 confirmed cases, 8 had separate injections and 14 had combined injections. Of the 11 doubtful cases, 4 had separate injections and 7 had combined injections. Although it seems at first that the separate method of injection gives better protection, analysis of the figures gives $\chi^2=2.1$, $P=0.1$, indicating no significant difference.

Severe Attacks Analysed.—There were 4 children who had severe attacks, and 3 of these were immunized by the combined method; 2 of them had nearly a three-months gap between two of their whooping-cough injections and developed the disease respectively five months and one year after the last injection. The other 2 children developed whooping-cough 35 and 30 months after the last injection, so that one can assume that they were losing their artificial immunity.

Gaps.—Of the remaining 18 confirmed cases, 6 had gaps of two to three months during the course of their injections; the other 12 appeared to have attended at regular monthly intervals for injections. In the doubtful group all 11 children had attended for injections at monthly intervals—that is, there were no gaps. If we take the 33 children who had (or may have had) whooping-cough and assess the number of “gaps” of two to three months and over in their attendance we find there were eight gaps—that is, 24%. In the 617 remaining children there were attendance “gaps” in 9.7%. This difference does seem somewhat significant.

It should perhaps be explained that many of the "gaps" were due to interruption of immunization during a polio season.

Injection-Disease Time Lapse.—The lapse of time between the date of last whooping-cough injection and the development of whooping-cough was 1.7 years in the doubtful group and 1.6 years in the confirmed group. Actually the shortest time lapse in these cases was four months and the longest 35 months.

Age at First Injection.—The average age of the affected children at their first injection was 3.7 months in both the confirmed and the doubtful group, whereas the average age for the whole group was 3.9 months.

Blood Results.—Only 10 of the 33 children who developed whooping-cough had been bled at the age of 15 months and had had their pertussis agglutination titres measured. These varied from 1/20 to 1/1,280, from which it may be concluded that agglutination titre is no reliable index of protection against whooping-cough. This agrees with the findings of Horton and Standfast (1953).

Home Contacts.—In our follow-up questioning the parents of 35 infants reported that their child had been a home-contact with another suffering from whooping-cough; none of these 35 developed the disease. Unfortunately we have no information on the home-contact rate in respect of the 22 almost certain cases and 11 doubtful ones, although, of course, as they developed the disease they must have been in contact somewhere with an infected child.

Notification Rate.—Of the 22 definite cases, only 5 were notified in our area. Another 7 may have been notified out of the area, but this still leaves 10 definite cases not notified in their own area. One should be wary, therefore, of accepting notification incidence as a reliable measure of whooping-cough prevalence.

Summary

Two groups of infants were inoculated against diphtheria and pertussis in early infancy. One group received three doses of whooping-cough vaccine at monthly intervals, followed by two doses of P.T.A.P. The other group received three doses of combined formol-toxoid and whooping-cough vaccine. In the subsequent three years no significant difference was found in the frequency of undoubted whooping-cough in the two groups. Since, however, 22 children did develop the disease some 19 months after the end of primary immunization, a booster dose at the age of 15–18 months seems to be recommended. As whooping-cough is a more serious disease in very young babies, it might be thought advisable to give the first injection at 2 months or even younger in view of the fact that those immunized at 2 months appeared to be as well protected as those whose first injections were given at 3, 4, or 5 months.

Thanks must be accorded to Dr. G. Stewart, County Medical Officer, Essex, and to Dr. F. Groarke, Area Medical Officer, Barking, for permission to carry out the work. We gratefully acknowledge the assistance of colleagues, especially the invaluable help of Mr. Brian in the collection of blood samples, and of Mrs. Pratt, the nurse who assisted at these sessions. Thanks are also due to Mrs. Tidbury and Miss Valerie Harper for many hours of cheerful and willing clerical assistance.

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Medical Memoranda

Ehlers-Danlos Syndrome with Congenital Herniae and Pigeon Breast

The Ehlers-Danlos syndrome, described by Ehlers in 1900 and by Danlos in 1908, is rare. The classical features are: (1) hyperelasticity of skin; (2) friability of the skin and the blood vessels, with a tendency for wounds to gape and a susceptibility to intracutaneous or subcutaneous haemorrhages, even from trivial trauma, or occasionally to visceral haemorrhages; (3) profuse scarring, usually papyraceous in type; (4) hyperextensibility of joints; (5) frequent presence of tiny mobile subcutaneous nodules, probably of a lipomatous nature; and (6) familial incidence of one or more of the above features.

CASE REPORT

A 3-year-old French Canadian boy was admitted to Ottawa General Hospital on July 6, 1957, because of a lacerated injury over the right knee. Even minor injuries were apt to cause skin cuts, lacerations, bruises, and bumps, and he had numerous scars over his body. Since birth his skin had been very soft and elastic. He was born prematurely and had congenital umbilical and inguinal herniae. The umbilical hernia was repaired. At the age of 1 year he received multiple lacerated injuries in a car accident; the wounds gaped after the removal of only two stitches on the fifth day. His father's skin was soft, doughy, and slightly hyperelastic; his palms and soles were soft, his fingers could be slightly overextended, and his feet were flat. He had no scars or friability of skin. No abnormalities were found in other members of the family.

On physical examination the boy, though mentally alert, was seen to be somewhat underdeveloped, being 2 ft. 10 in. (86 cm.) in height, and weighing 27 lb. (12.2 kg.). His head circumference was 20 in. (51 cm.) and the fontanelles were closed. He could stand and walk normally. He had a pigeon breast (Fig. 1), and there were numerous scars all over his body, mostly on the face, head, left arm, knees, legs, and feet. Some of the scars appeared to be due to stitched or unstitched wounds. A few scars were papery, particularly over the lower abdomen and the forearms. There were a few bruises. A fresh lacerated gaping wound was seen across the front of the right knee.

The skin was doughy, soft, velvety, and elastic, and could be easily stretched for about 1 to 2½ in. (2.5 to 6.4 cm.) over the arms, forearms (Fig. 2), thighs, and legs. When let go the skin immediately returned to its position, like a piece of soft rubber, leaving no wrinkles or folds. No subcutaneous nodules were palpable. The mucus membrane was not elastic.

The child had large bilateral, reducible, indirect inguinal herniae, and the scar of the repaired umbilical hernia was visible.

FIG. 1.—Hyperextensible knee and pigeon breast.