TABLE IV.—*Crude Death Rates per* 100,000 (*Both Sexes*, 1954) *from Bronchitis* (500–502) *by Residence*

England and Wales			Denmark		
Regions	Population in 1,000's	Death Rate	Regions	Population in 1,000's	Death Rate
Conurbations ..	16,894	65			
Urban area with population of 100,000 and over	5,851	61	Copenhagen ..	776	6
Urban area with population of 50,000 and under 100,000	3,391	58	Provincial towns, including Frederiksberg	1,292	5
Rural districts ..	8,610	42	Rural districts, including Gentofte	2,357	7

Tobacco Consumption.—A comparison of the average weight of tobacco consumed per head per year in England and Wales and in Denmark, and the proportion of this that is smoked as cigarettes, are given in Fig. 2. The total annual

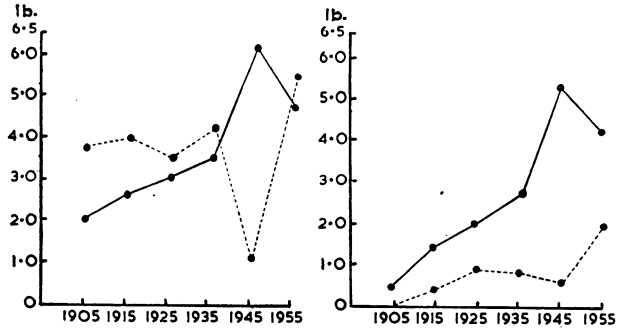

FIG. 2.—Tobacco consumption in England and Wales (———) and Denmark (- - - -), 1905–55. Left: Total annual consumption of tobacco (unmanufactured) per person, in pounds. Right: annual tobacco consumption as cigarettes per person, in pounds.

consumption per head has been lower in this country than in Denmark except for the war years. However, the amount smoked as cigarettes has always been more than twice the Danish figures. Oswald *et al.* (1953), Palmer (1954), and Ogilvie and Newell (1957) have shown that the prevalence of bronchitic symptoms is related to cigarette-smoking. The national smoking habits may therefore contribute to the bronchitis mortality excess recorded in England and Wales.

Climatic Conditions.—In England and Wales the mean annual rainfall is a little greater than in Denmark and the winter temperatures are a little higher. However, both countries lie in the same belts of mean annual temperature (7.22–10.00° C.), mean atmospheric pressure (754.4–759.5 mm.), and wind direction. Thus climate alone cannot directly contribute to the excess in England and Wales.

Summary and Conclusion

A fifteenfold excess of mortality from bronchitis is recorded in England and Wales compared with Denmark. Both countries use the International Certificate of Cause of Death and the International Statistical Classification of Diseases, Injuries, and Causes of Death. However, differences in the method of selecting causes of death for statistical purposes, when multiple causes are given, still occur: these could account for as much as half the excess mortality in England and Wales. Possible differences in diagnostic habits may contribute to the remaining excess but do not appear to explain it. The cigarette consumption of England and Wales is twice that of Denmark and might also contribute to this excess; but when considered separately the differences in the age distribution, social class, climate, and atmosphere pollution of the two countries do not appear to be important factors.

Within the strict limits imposed by differences in method of compiling the death rates, it would appear that there is a real excess of the disease labelled bronchitis in England and Wales, compared with Denmark; but the confirmation of this difference and the elucidation of its causes are likely to result only from comparative field surveys in the two countries.

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ANTIBODY RESPONSES TO BRITISH POLIOMYELITIS VACCINE OF CHILDREN WITH NATURALLY OCCURRING ANTIBODY

BY

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The results have already been reported of a study of the antigenic activity of British poliomyelitis vaccine in a group of children who, at the time of their first injection of vaccine, had no antibodies to any of the three types of poliomyelitis virus (Medical Research Council, 1957a). In selecting this group the sera of a number of children in five different areas were tested, and, although those who were shown to have antibodies to one or more types were excluded from the Council's study, they were nevertheless injected with poliomyelitis vaccine. The antibody responses of some of these children were investigated and the results are reported here.

Titration of Sera

Sera from 254 London and Manchester children, aged from 1 to 9 years, were obtained before giving two intramuscular injections of formalinized poliomyelitis vaccine (Glaxo) four weeks apart. Samples of sera were also obtained 14 days after the second injection. All sera were titrated for neutralizing antibody to the three types of poliomyelitis virus by the method used routinely in the Biological Standards Control Laboratory (Medical Research Council, 1957a). In this method, serum-virus mixtures are held at 37° C. for three hours before being added to cultures of monkey-kidney cells, and the titres (PD_{50}) expressed as the dilution of serum in the serum-virus mixture and not as the initial serum dilution. The three virus strains used in the neutralization tests were the same as those employed in the manufacture of British vaccine—namely, the attenuated Brunenders for type 1, MEF-1 for type 2, and Saukett for type 3. In three cases one type was omitted because of insufficient serum. Children whose serum at a dilution of 1/8 did not inhibit any one of the poliomyelitis viruses were regarded as negative so far as that type was concerned. The sera of those who did not produce this titre after vaccination were also tested at a dilution of 1/4.

Results

Of the 254 sera taken before vaccination, 68 had no antibodies to any of the three types, and 64 of these were included in the triple-negative study already reported (Medical Research Council, 1957a). Of the remaining 186 sera, 55 contained antibodies to one type only, 67 to two types, and 64 to three types. The types were fairly evenly distributed throughout the group, 120 having antibodies to type 1, 122 to type 2, and 141 to type 3.

The response of the children with pre-existing antibody to each component of the poliomyelitis vaccine is given in the chart with reference to the level of pre-existing homologous antibody. It is compared with the response of the 68 triple-negative children whose sera were titrated in the same laboratory and by the same method. As can be seen, there was a great variation in the antibody titre produced in children without initial homologous antibody both in those who were triple negative and in those with heterologous antibody. Two children in the triple-negative and one in the heterologous antibody group failed to produce antibody to type 1. None of the children in either group failed to produce some detectable antibody to types 2 and 3.

In those children with pre-existing homologous antibody to the type being investigated, the levels produced were very much higher, only one failing to produce a titre of 512 to type 1 and two to each of the other types.

The effect of heterologous antibody on the response is given in the Table. As an epidemic of type 1 poliomyelitis was occurring in the Manchester area during the vaccination programme, it was concluded that the high titres (8,192 and over)—all of which were in children from that area—were due to infection, and these were excluded from the analysis, as was done in the Medical Research Council report. The geometric mean titres of the children with heterologous antibody to the types indicated are compared with those obtained in triple-negative children. Although the groups were small, it would appear that with type 1 virus the presence of type 2 antibody, but not type 3, increased the level of antibody produced; with type 2, pre-existing antibody to either type 1 or type 3 produced this effect, whereas with type 3 enhancement was evident only when both heterologous antibodies were present.

Effect of Pre-existing Heterologous Antibody on the Response to Poliomyelitis Vaccine of Children with No Homologous Antibody

Type of Test Virus	Geometric Mean Titre after Vaccination of Sera from Children with Pre-existing Antibody to:				
	No Type	Type 1	Type 2	Type 3	Both Heterologous Types
1	79 (68)	—	575 (13)	68 (25)	132 (24)
2	245 (67)	818 (15)	—	682 (25)	960 (24)
3	113 (68)	94 (15)	120 (13)	—	224 (17)

Figures in parentheses indicate number of children in each group.

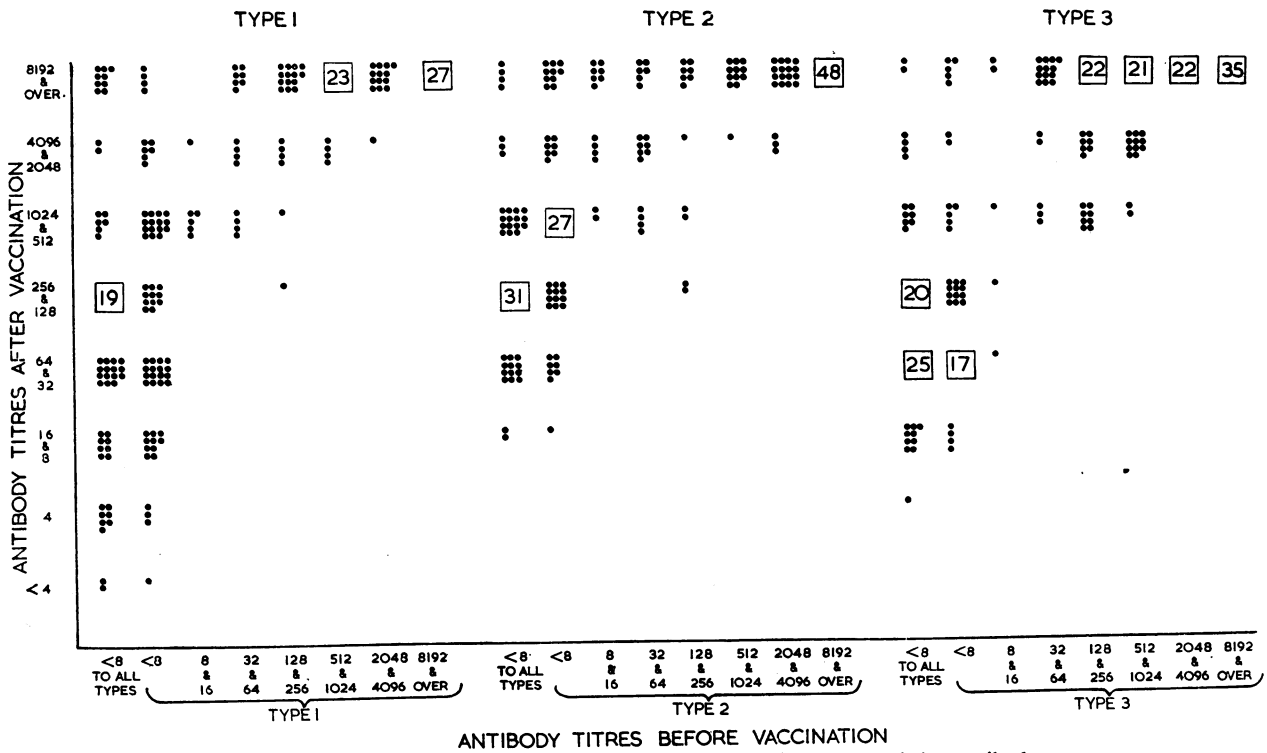
Conclusions

The results reported here follow the same pattern as those noted in triple-negative children, all except one child responding to all three components of the vaccine, including those types in which they were deficient before vaccination. In those with pre-existing homologous antibody a "booster" type of response was obtained similar to that which occurs in children with vaccine-induced antibody (Medical Research Council, 1957b).

The type 1 component of the British vaccine is prepared from the attenuated Brunenders strain instead of from the more virulent Mahoney strain preferred in North America. With the vaccine used in the United States, Salk (1956) has shown that the presence of pre-existing heterologous antibody may affect the response to any given virus types. The results noted here in children with different poliomyelitis antibody spectra before vaccination suggest that the Brunenders component of the British vaccine behaves in the same way, as the response to it is similarly enhanced by the presence of pre-existing type 2 antibody.

Summary

The response to the British poliomyelitis vaccine in 186 children with naturally occurring antibody was investigated. The results indicated that children with



Response to poliomyelitis vaccine of children with and without pre-existing antibody.

pre-existing heterologous antibody may show an increased response to a given type, while those with pre-existing homologous antibody give a "booster" response.

Thanks are due to Dr. J. A. Dudgeon, Dr. J. C. W. MacFarlane, Dr. D. O'Brien, and Dr. A. M. Peach (London), and to Dr. P. B. Stones and the medical staff of the Health Department (Manchester), who were responsible for immunizing and collecting sera from the children.

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HAEMOLYTIC ANAEMIA FOLLOWING THROMBOCYTOPENIC PURPURA

BY

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Primary thrombocytopenic purpura associated with red-cell sensitization was originally described by Evans *et al.* (1951). In their group of five patients presenting with primary thrombocytopenic purpura together with evidence of red-cell sensitization, one developed a haemolytic anaemia following splenectomy.

In the case described below an acute haemolytic anaemia developed after apparent spontaneous recovery from primary thrombocytopenic purpura.

Case Report

A 58-year-old man was referred to the dermatological out-patient department with varicose eczema, which had been present for 10 years. Four months later extensive purpura appeared on the legs, thighs, and trunk. Inquiry elicited that similar attacks with occasional epistaxis had occurred at irregular intervals over the preceding 10 years. He had taken no drugs likely to produce haematological effects.

Examination on January 3, 1956, revealed a heavily built man with healed varicose ulceration covering an extensive area of both legs. There was a purpuric eruption over the legs, thighs, and trunk. Neither the spleen nor the liver was palpable.

Investigation showed: Haemoglobin, 13.3 g./100 ml., red blood cells, 4,500,000/c.mm.; platelets, 15,000/c.mm.; white cells 7,000/c.mm., with a normal differential count. Reticulocytes were less than 1%, and the bleeding-time was nine minutes. Examination of the marrow showed some maturation arrest of the thrombocytic series. The tourniquet capillary fragility test was positive, and capillary microscopy showed tortuosity and varied calibre, with defective contractility of the capillaries on trauma. The patient was group O, rhesus negative. Serial dilution anti-human-globulin test was positive to a titre of 128, with pan- and auto-agglutinins in saline and albumin at 4° C. No rhesus, Kell, or platelet antibodies active at 37° C. were detected.

Five months later he was admitted to a medical ward with symptoms suggestive of coronary thrombosis. Examination showed that the purpura had cleared and there were no abnormal findings on examination of the cardiovascular system.

In view of the history of purpura the haematological investigations were repeated on June 6: haemoglobin, 12.6 g./100 ml.; red blood cells, 3,800,000/c.mm.; platelets, 200,000/c.mm.; white blood cells 2,000/c.mm. (band cells, 2%, neutrophil polymorphs 40%, eosinophil polymorphs 16%, basophils 0.1%, lymphocytes 20%, and monocytes 22%).

Over the next three weeks the haemoglobin fell to 9.8 g./100 ml., but the platelet and white-cell counts remained constant. As the patient was suspected of having sustained a small coronary thrombosis without electrocardiographic changes he was discharged home after three weeks' bed rest. In view of his apparent recovery from primary thrombocytopenic purpura and the leucopenia which had developed, it was decided to keep him under observation.

Three months later he was readmitted because of rapidly increasing anaemia. Examination showed marked pallor with mild icterus. The spleen was just palpable. Haemoglobin, 8 g./100 ml.; red blood cells, 2,420,000/c.mm.; platelets, 250,000/c.mm.; white blood cells 3,000/c.mm. (neutrophil polymorphs 54%, eosinophil polymorphs 2%, lymphocytes 40%, monocytes 4%). The reticulocyte count was 18% and the erythrocyte sedimentation rate was 138 mm. in the first hour (Westergren). The urine contained excess urobilin and urobilinogen, and the total faecal urobilinogen was 731 mg./100 g. of faeces.

Marrow examination showed greater activity of normoblasts and macronormoblasts than noted previously. Haemolysis continued, and three weeks later the haemoglobin was 5.6 g./100 ml. and the red cells numbered 1,670,000 per c.mm. The direct antiglobulin test was positive in serial dilution. The antibody coating of the erythrocytes appeared to be a mixture of gamma- and not-gamma-globulins. The acid haemolysin test was negative; there was a strong auto-agglutinin active at 37° C., 20° C., and 4° C., and a pan-agglutinin at 4° C. active in saline and albumin.

The direct antiglobulin test on the platelets was negative; platelet antibodies were not demonstrable by the methods of Stefanini *et al.* (1953) and Dausset *et al.* (1952), or by the indirect antiglobulin test. No antibodies could be eluted from the red cells after elution at 56° C. for 10 minutes. A preparation of stroma from three-times-washed red blood cells, eluted at 56° C. with 8% albumin, reacted with all group O cells tested.

At this point treatment with corticotrophin was begun, and was followed by a rapid rise in haemoglobin to 12.4 g./100 ml., and in red blood cells to 3,850,000/c.mm. The platelet count rose to 620,000/c.mm., and the white cell count to 8,000/c.mm. (see Table). Maintenance therapy with prednisone was continued until the time of report.

Date	Hb. (g. 100 ml.)	R.B.C. (10^6 c.mm.)	W.B.C. per c.mm.	Retics.	Platelets Lempert per c.mm.	Direct Anti-globulin Test
3/1/56	13·3	4·5	7,000	1%	15,000	+
6/6/56	12·6	3·8	2,000		200,000	
25/6/56 ..	10·4	3·01	2,000		200,000	
3/10/56 ..	8·0	2·42	3,000	18%	250,000	+
23/10/56 ..	5·6	1·67	3,400		570,000	
Corticotrophin, 120 u. daily						
29/10/56 ..	8·3	2·55	4,000	20%	620,000	+
7/11/56 ..	12·4	3·85	8,000	18%		
Prednisone, 30 mg. daily						
22/11/56 ..	13·9	4·25	7,000	2%	130,000	+
6/12/56 ..	13·3	3·8	8,000		280,000	+
Prednisone, 20 mg. daily						
20/12/56 ..	14·8	4·8	—	4%	280,000	+
3/1/57	15·0	5·0	9,000	4%	300,000	+
23/1/57	Prednisone, 10 mg. daily					
24/1/57 ..	14·5	4·4	8,000		340,000	+
Prednisone 5 mg. daily						
21/2/57 ..	14·8	4·5	6,000	3%	400,000	
29/12/57 ..	14·8	4·8	6,000	1%	190,000	+

The antiglobulin test in serial dilution remained strongly positive after treatment was started. Further attempts to demonstrate platelet antibodies were unsuccessful.

Discussion

The association of a low platelet count with evidence of red-cell sensitization led Evans *et al.* (1951) to suggest the existence of immuno-thrombocytopenic purpura. Dausset