is generally accepted that if kinaesthetic sensation is lost owing to a parietal lobe lesion, then this phantom limb will disappear. Such a case is quoted by Head (1920), and I will describe another in the second lecture, though for a different purpose. On the other hand, phantom limbs can exist without loss of the limb if the sensory pathway from the limb is destroyed. Cases of this sort have been described at every level of the sensory pathway. Whether such a phantom would disappear in a parietal lesion is probable, but I am not familiar with any such case in the literature. The suggestion, however, that such phantom limbs disappear because the post-central region is no longer functioning is rendered invalid by the evidence of the "third phantom." Such cases have been briefly mentioned by Macdonald Critchley (1953), and I would like to offer another such.

Case 5

A young man received a left parietal wound which resulted in a right hemiplegia with complete loss of postural sensation in the right limbs. After recovery from the initial dysphasia he felt that the paralysed hand was making piano-playing movements (he was a pianist), and only by looking at it could he convince himself that it was lying immobile across his chest or under his bedclothes. When sitting up in a chair and wanting to reach a glass of water or to turn a door-knob he often apparently put out his paralysed arm, and the feeling of movement was complete until nothing happened and he looked down at the limb with the immediate disappearance of the phantom. The tendency to try to use the paralysed limb was increased because he was definitely dyspraxic with the good left arm. He could never work out why he couldn't do things with the left hand such as use a comb, blow a kiss, or use a pair of scissors. He always tried to excuse the failure by saying it was because he was very right-handed and this was the cause of the clumsy left hand. He also said that if he shut his eyes he could easily feel his right arm doing all the things at which the left was bad. He never said I can see the right arm doing all these things. With the partial recovery of postural sensation the phantom third limb disappeared permanently.

Comment.—Cases such as this would suggest that a parietal lobe lesion causing the disappearance of a phantom limb is massive and includes more than the post-central cortex and subcortex. It would suggest that the mechanism for the third phantom, the maintenance of posture, and the orientation of the body not only can take place outside consciousness but can remain efficient even when the conscious appreciation of movement is lost; further, that orientation of the body as a whole when sitting or standing can fail even though normal sensation is present.

Mechanism of Body Image

The concept of the body schema as put forward by Head indicates that it is conveniently on the edge of consciousness—usually outside it, but capable of being drawn into it and thus reaching our awareness. This use of words is unfortunate, for it creates a curiously solid picture of a body-image mechanism which may, even on this hypothesis, have a definite localization. Perhaps such a view is superficially useful to explain how one loses awareness of parts of the body in terms of disappearance or damage to the body image. Yet this concretization cannot but impede progress in determining the real mechanism.

From his studies of memory and its breakdown, Ritchie Russell (1957) suggests that the memory of movement patterns is due to constant activity within the cerebrum of neuronal circuits. These are established by constant repetition and reinforced by activity. With non-physical memory, reinforcement can take place even during sleep, indicating that a voluntary drive need play no part. The circuits producing postural tone control must be widespread, including cerebellum and brain stem, and must be capable of modification by the afferent information the body can

provide. It is clear from our personal experience that this mechanism exists outside our awareness once the neuronal circuits have been well established, but it must never be accepted as fixed but rather as a dynamic state. This is capable of constant change, as will be shown in the next lecture for the much simpler spinal circuits.

If the body-image mechanism is considered as a series of neuronal circuits, then at points where these circuits are narrowly confined, as in the reticular substance in the brain stem, physical change will produce the widest alterations in the pre-existing state of the individual. This may account for the ascendancy the brain stem has acquired in the neurophysiology of to-day.

This concept of neuronal circuits which are constantly active makes the difficulties of anatomical localization clear and must mean the abandoning of mosaics of function in the hemispheres. It will account also for the widespread area in which lesions may occur with the production of similar alteration in function.

The body image therefore must be regarded as a series of long-standing well-established neuronal circuits or loops which are constantly reinforced because the circuit is self-propagating. Superimposed are the modifying influences produced by streams of afferent impulses from eyes, muscles, and joints. Spreading from this are the impulses which will affect posture and movement, both of which will be considered in more detail in the second lecture.

[The second lecture, with a list of references, will appear in our next issue.]

SEROLOGICAL RESPONSE OF INFANTS TO POLIOMYELITIS VACCINE

BY

F. T. PERKINS, M.Sc., Ph.D.

RISHA YETTS, B.Sc.

From the Biological Standards Control Laboratory, Medical Research Council Laboratories, London, N.W.3

AND

WILFRID GAISFORD, M.D., M.Sc., F.R.C.P.

*Director of the Department of Child Health,
University of Manchester*

It is now recognized that satisfactory serological response to poliomyelitis vaccine occurs in children after the age of 1 year (Medical Research Council, 1957), but as yet little is known of the response of infants to this vaccine. However, as it has been shown that even newborn infants can be adequately immunized against tuberculosis (Gaisford and Griffiths, 1951), diphtheria (Butler, Barr, and Glenny, 1954), and—with a suitable triple antigen—diphtheria, pertussis, and tetanus together (Feldman, 1954), it seemed logical to try to ascertain how early in infancy immunization against poliomyelitis could be successfully undertaken. This was the purpose of the study here described.

An additional reason for this investigation was the incidence of precipitated paralytic poliomyelitis after the injection of diphtheria and other prophylactic antigens, particularly when combined (Medical Research Council, 1956), because it was felt that if successful immunization against poliomyelitis were possible in early infancy this could precede all the other protective inoculations and might thereby eliminate the risk of provoked paralysis.

In this study, 88 mothers and their infants have been investigated in respect of the relationship between maternal serum and umbilical cord levels of polio-

myelitis neutralizing antibodies, the rate of loss of maternally transmitted antibodies in the infants, and the response of the infants immunized at different ages with poliomyelitis vaccine.

Procedures

Immunization.—The 88 infants were divided into three groups, A, B, and C, containing 34, 29, and 25 subjects respectively. The first dose of 1 ml. of vaccine was given to the infants in group A when they were 1 week old, to those in group B when they were 6 weeks, and to those in group C at 10 weeks. The second dose, also of 1 ml., was given to all the infants four weeks after their first dose. The injections were given intramuscularly into the left and right buttock alternately. Two batches of Glaxo vaccine were used, Nos. 7 and 10, and each was distributed equally throughout the three groups. These batches had been used in other field studies with older age groups and been shown to have satisfactory antigenic activity (Medical Research Council, 1958).

Collection of Sera.—Serum was collected from the cord blood of all the infants and from the mothers within three days of delivery. Pre-immunization samples of sera were taken from the infants in groups B and C on the day the first dose of vaccine was given; in the case of group A the cord serum served as the pre-immunization sample. Post-immunization sera were taken from all infants between 14 and 21 days after the second dose of vaccine.

Titration of Sera.—The sera were titrated for poliomyelitis neutralizing antibodies to each of the three virus types by the method previously described (Biological Standards Control Laboratory, 1957) which has been shown to give reproducible results (Perkins, Sousa, and Tobin, 1958). Fourfold serial dilutions of sera were made and the test dose of virus consisted of approximately 100 TCID₅₀. Each serum-dilution/virus mixture was inoculated into two monkey-kidney-cell culture tubes.

The sera from the mother, umbilical cord, and infant were titrated strictly in parallel in the same test in order that a valid comparison of antibody levels could be made. All titres are given as the dilution of serum in the serum-virus mixture before the addition to cell cultures.

Antibody Levels in Mothers, and Umbilical Cord Blood

Table I gives the distribution of antibodies in the cord sera of the 88 infants. A relatively large number (55) had antibodies to all three types and only four were "triple negative," having no antibodies to any of the types. There

TABLE I.—*Distribution of Poliomyelitis Antibodies in the Cord Sera of 88 Infants*

No. of Sera	No. of Sera with Antibodies to:			
	No Type	One Type Only	Two Types Only	Three Types
88	4 (5%)	9 (10%)	20 (23%)	55 (62%)

was considerable variation in the antibody levels, which ranged from less than 8 to 16,000 for types 1 and 2 and from less than 8 to 4,000 for type 3. The numbers of infants with no detectable antibody to one particular type were similar, being 21 for type 1, 19 for type 2, and 17 for type 3.

A comparison of the antibody levels of the cord sera with those of the mothers' sera is given for each subject in Fig. 1. With all three types the titres of the cord and mothers' sera were similar—in a high proportion the titres were the same—and where differences occurred they were mostly either twofold or fourfold, although in the case of two subjects the

difference was as great as 32-fold. The geometric mean titres of the cord sera and mothers' sera were also similar for all three types.

FIG. 1.—Poliomyelitis neutralizing antibody levels in mothers' and cord sera.

Loss of Maternal Antibodies in Infants

The loss of maternal antibodies in the 6-weeks-old and the 10-weeks-old infants is shown in Table II, where, for each type, the mean titres of the sera obtained at the time

TABLE II.—*Loss of Maternal Antibody in Infants at 6 and 10 Weeks*

Age of Group (Weeks)	No. of Sera	Virus Type	Geometric Mean Antibody Titre of Sera of		Loss of Antibody
			Cord	Infant	
6	29	1	125	42	66%
		2	271	73	73%
		3	62	21	66%
10	25	1	411	37	91%
		2	667	52	87%
		3	271	25	89%

of giving the first dose of vaccine are compared with those of the cord sera. In each age group the loss of maternal antibodies was similar for each type, being approximately 70% in the 6-weeks-old and 90% in the 10-weeks-old infants. Such a decline would suggest that the maternal antibody level was halved every 21 days.

Effects of Maternal Antibody on the Response to Immunization

The antibody response to immunization of the 1-, 6-, and 10-weeks-old infants is shown for each type in Fig. 2, which gives the titres both before and after immunization for each infant. Considering all three groups together, it is seen that

only a small proportion of infants responded to the vaccine: 12.5% responded to type 1, 47% to type 2, and 36% to type 3. It is also evident from Fig. 2 that, for each type, the lower the maternal antibody level the greater the proportion

TABLE III.—*Response to Immunization of Infants with no Maternal Antibody at the Time of Giving the First Dose*

Virus Type	No. with No Maternal Antibody before Immunization	No. Responding	Geometric Mean Titre of Sera after Immunization
1	24	6 (25%)	3
2	22	21 (95%)	329
3	20	15 (75%)	47

TABLE IV.—*Proportion of Infants (a) With Maternal Antibody Titres of 64 or Less at the Time of Immunization, and (b) Responding to Immunization*

Virus Type	Age of Group (Weeks)	Total No. of Infants	No. with Antibody Titres of 64 or Less	No. Responding to Immunization
1	1	34	8 (23%)	1 (3%)
	6	29	14 (48%)	3 (10%)
	10	25	19 (76%)	7 (28%)
2	1	32	10 (31%)	11 (35%)
	6	28	13 (47%)	14 (50%)
	10	25	20 (80%)	15 (60%)
3	1	34	15 (44%)	5 (15%)
	6	29	22 (76%)	14 (48%)
	10	25	20 (80%)	13 (52%)

of infants who responded. The effect of maternal antibody, however, differed with the three types. With type 1 no infant with a maternal antibody titre of greater than 16 responded, whereas a response was given by 10 out of the 32 who had titres of 16 or less. With type 2 no infant with a titre of greater than 512 responded, but a response was

TABLE V.—*Effect of Age on Response to Vaccine*

Virus Type	Age of Group (Weeks)	No. of Infants with Antibody Titre of 16 or Less	No. of Infants Responding to Immunization
1	1	5	1 (20%)
	6	11	3 (27%)
	10	16	7 (44%)
2	1	8	8 (100%)
	6	6	6 (100%)
	10	12	11 (92%)
3	1	9	5 (56%)
	6	11	9 (82%)
	10	12	9 (75%)

obtained in one infant with a titre of 512, in three with titres of 256, and in 36 of the 45 with titres of 128 or less. With type 3 no infant with a titre of greater than 64 responded, but 32 of the 58 responded when the titre was 64 or less.

The results clearly indicate that, with the vaccines used, the type 2 antigen was the most effective in overcoming the inhibiting effect of the homologous maternal antibody, that the type 3 was not quite so effective, and that the type 1 was the least effective. The relative activities of the three antigens are also shown in Table III, which gives the responses obtained in those infants who had no detectable homologous maternal antibody at the time of inoculation. It is evident that the type 2 antigen was the most active, that the type 3 was less active, and that the type 1 was poor. A similar result was also reflected in the responses obtained with the four triple-negative infants. Although the number was small, it is of interest to note that all four responded to type 2, two to type 3, and one to type 1.

Antibody Response in Relation to Age

When the results in the three different age groups are considered separately it is seen that for all three virus types the older the infant the greater the number with lower maternal antibody levels at the time of vaccination. This increase is evident from the analysis in Table IV, which gives for each type and for each group the proportion of infants with maternal antibody titres of 64 or less. It is also seen from Table IV that as the proportion of infants with low maternal antibody levels increased there was a corresponding increase in the proportion responding to immunization. However, the increase in the proportion of those responding was not entirely due to the decline in maternal antibody but appeared to be dependent, to a small extent, on the age of the infant. This is

FIG. 2.—Serological response of 1-, 6-, and 10-weeks-old infants to poliomyelitis vaccine.

evident from Table V, where the results are given for those infants with maternal antibody levels of 16 or less—levels which produced little or no interference with antibody response. Although the numbers are small, it appears that, in the case of types 1 and 3, the older the infant the better the response to vaccination, although in the older groups there was still a high proportion who did not respond, especially to type 1. With type 2, however, the age of the infant had no effect on the response, because in all groups all the infants except one responded well to this type.

Discussion

The chief points which emerge from this study are that the titres of maternal and cord blood neutralizing antibodies are strikingly similar for all three virus types; that the loss of placentally transmitted antibodies in the infant is of the same order for all three types, the level being halved approximately every 21 days; that the response of the infants to the vaccine varies with the level of transmitted antibodies, which interfere with the response to the homologous type; that this inhibiting effect is most easily overcome by the type 2 antigen; and that the age of the infant also plays a part in determining the ability to respond to types 1 and 3.

It is clear, therefore, that the earliest age at which infants can be successfully immunized against poliomyelitis depends on a number of different factors, but if, for practical purposes, it is assumed that the majority of infants are born with antibody levels of the order of those observed in the present investigation, it is unlikely that these will have disappeared, or fallen to non-inhibitory levels, until the infants are between 6 and 9 months old. This unfortunately precludes the use of poliomyelitis immunization as the first protection to be offered routinely to infants and leaves the problem of overcoming the risk of provoked paralysis still unsolved.

Early protection against pertussis is particularly desirable and can most conveniently and efficiently be combined with diphtheria and tetanus prophylaxis. To be effective in earliest infancy, this demands an alum-containing antigen (Feldman, 1957), which experience has shown to be the most dangerous in producing provoked paralysis. Some method must therefore be evolved whereby this triple antigen may be given with safety. One solution would be to boost the levels of placentally transmitted poliomyelitis antibodies by immunizing all pregnant women. This would ensure that the infant would have sufficiently high titres against poliomyelitis to last at least for the first four months of life and—under cover of this protection—immunization could be started as soon as possible after birth with three doses of triple antigen and thereafter followed with poliomyelitis vaccine. A study of such a procedure is already in progress, and will be the subject of a further communication.

Considered solely from the point of view of the protection of infants against poliomyelitis, the earliest age for successful immunization is still undetermined; for, although our evidence suggests that all infants would respond adequately to type 2 by the age of 6 to 9 months, it is not yet known whether this would hold true for type 3 and, more particularly, for type 1. This is at present being investigated, as also is the effect of a third inoculation given a month after the primary course, the usual practice for diphtheria, pertussis, and tetanus prophylaxis. It is possible that those infants who have shown no obvious response to their two primary injections of poliomyelitis vaccine may nevertheless have developed a sufficient degree of basal immunity to enable them to respond to the third injection.

Summary

The levels of poliomyelitis neutralizing antibodies in sera from the mother and from the umbilical cord are similar. The loss of maternal antibody in the infant is similar for all three types, the level being halved approximately every 21 days.

The response of infants to poliomyelitis vaccine depends partly on the age of the infant, but chiefly on the level of maternal antibodies, which inhibit the response to the homologous type. This inhibiting effect is overcome most easily by the type 2 antigen, not quite so easily by the type 3, and hardly at all by the type 1.

In order to avoid the inhibiting effect of the placentally transmitted antibody, immunization should at present be delayed until six to nine months after birth, although even at this age it is not yet known whether the responses to types 1 and 3 will be adequate. Studies are proceeding to determine the earliest age at which the response to all types will prove satisfactory.

Investigations are also in progress of alternative methods of immunization in early infancy.

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ORAL TREATMENT OF DIABETES TRIAL OF PHENETHYLDIGUANIDE (D.B.I.)

BY

G. H. HALL, M.B., B.Sc., M.R.C.P.

Medical Registrar, Whittington Hospital, London

MARY F. CROWLEY, B.Sc.

Principal Biochemist, Whittington Hospital, London

AND

ARNOLD BLOOM, M.D., M.R.C.P.

Physician in Charge of Diabetic Unit, Whittington Hospital, London

In the treatment of diabetes insulin is irreplaceable: no satisfactory substitute has yet been discovered. However, the need for parenteral administration of insulin has stimulated the search for substances which will lower the blood sugar when given by mouth. Recently, certain sulphonylureas (notably carbutamide and tolbutamide) have been shown to do this. Unfortunately, sulphonylureas are effective only in mild diabetes, and this is in accord with the experimental finding that some functioning pancreatic islet tissue is necessary for them to exert full action (Levine, 1958).

Ungar *et al.* (1957) have investigated a series of compounds of different structure belonging to the diguanide group, and found that one of them, phenethyldiguanide, or N-beta-phenethylformamidinyl iminourae (D.B.I.), was able to produce hypoglycaemia even in eviscerated or alloxan-diabetic animals. Later workers have confirmed that this substance can lower the blood sugar in the absence of insulin (Nielsen *et al.*, 1958). Clinical trials of D.B.I. have been carried out by Pomeranec