

## THE ACTION OF VITAMIN D IN PREVENTING THE SPREAD AND PROMOTING THE ARREST OF CARIES IN CHILDREN.

BY

MAY MELLANBY AND C. LEE PATTISON, M.B., B.S.,

(Pharmacology Department, University of Sheffield, and King Edward VII Hospital, Sheffield.)

In papers published in 1924 and 1926 respectively,<sup>1 2</sup> we recorded investigations showing that the dietetic factors which control the structure of teeth in puppies also influence the initiation and spread of caries in children. Animal experiments<sup>3 4 5</sup> had proved that food substances which contained the antirachitic or calcifying vitamin, now called vitamin D, greatly stimulated the calcification of teeth, while cereals, and especially oatmeal, inhibited perfect calcification of the teeth when this vitamin was deficient in the diet. In the investigations on children referred to above we found that diets favourable to calcification limited the initiation and spread of caries, while diets of lower vitamin content, and containing oatmeal, had no such effect. In many cases also diets rich in vitamin D caused "hardening" of teeth in which caries had started, and thus tended to suppress the active carious process. On the other hand, diets with low calcifying properties had no such retarding influence. In both investigations caries was extensive at the beginning, and an attempt was made to group the children in such a way as to start with approximately equal amounts of caries in each group.

In the first series of cases (1924) we attempted in one group to raise the calcifying properties of the ordinary hospital diet by adding extra milk and eggs and by giving cod-liver oil. In another group these extras were omitted and oatmeal was added. It may be stated that all the diets were good, and contained a fair amount of milk and other wholesome foods; in fact, from any nutritional standpoint they were probably much better than those eaten by the average child in this country. Table I gives a summary of the results obtained.

TABLE I.

Main differences in diet.	No. of patients in group.	Average No. of teeth per child showing initiation or spread of caries.	Average No. of teeth per child in which caries showed hardening.	Average No. of teeth per child in which caries showed softening.
A1. Abundant fat-soluble vitamins and calcium; diminished cereal	9	1.4	1.5	0.0
B1. Much less fat-soluble vitamins and calcium than A1; more cereal, including oatmeal	10	5.1	0.7	0.4
C1. Intermediate between A1 and B1 as regards fat-soluble vitamins and calcium and cereal	13	2.9	1.0	0.1

In the second series of cases (1926) an attempt was made to keep the protein, carbohydrate, and fat intake as constant as possible, and to vary only the extras whose effect was being tested. The total energy of the diets, the calcium and phosphorus intake, and the acid-base ratios were also fairly constant. It was not possible to attain absolute accuracy, but a fair equality in most of these respects was brought about. The main variables in the diets A<sub>2</sub>, B<sub>2</sub>, and C<sub>2</sub> were (a) the fat-soluble vitamins and (b) the anti-calcifying factor of cereals. Fuller details of the diets can be obtained from the original publication (*British Dental Journal*, October 1st, 1926). Below (Table II) is summarized the effect of these diets as regards caries in the children of the different groups. Column 4, describing the "degree" of caries, requires some explanation. Each carious area was numbered according to its extent at the first and last inspection; the figures thus obtained were, of course, quite arbitrary; but were comparable one with the other.

TABLE II.

Main differences in diet.	No. of children in group.	Average No. of teeth per child showing initiation or spread of caries.	Average degree of spread of caries per child.	Average No. of teeth per child in which caries showed hardening.	Average No. of teeth per child in which caries showed softening.
A2. Abundant fat-soluble vitamins	23	1.8	2.0	2.0	0.3
B2. Much less fat-soluble vitamins than A2; oatmeal in place of some of bread of A2	24	5.8	6.7	0.0	0.5
C2. Intermediate quantity of fat-soluble vitamins; no oatmeal	24	3.0	4.0	1.2	0.1

In the present investigation an attempt has been made to vary only one factor in the diet—namely, the vitamin D intake. In the previous investigations cod-liver oil, egg yolk, and extra milk were added to the diet of one group. Now these substances are rich in both vitamin A and vitamin D. Vitamin D is undoubtedly responsible for promoting normal calcification, whether of the developing teeth or of the secondary dentine in erupted teeth, and therefore it might be expected to play an important role in the arrest of dental caries. On the other hand, it is now probable that vitamin A is an anti-infective agent, so that it might also be expected that this vitamin would tend to inhibit the initiation and spread of the infective carious process. Evidence of the susceptibility of animals fed on diets deficient in vitamin A to infective and pyogenic processes has recently been given by H. N. Green and E. Mellanby.<sup>6</sup> They found that young rats brought up on diets containing abundant vitamin D, but deficient in vitamin A, died with infective and pyogenic lesions, including infections of the eye, alimentary tract, renal tract, and broncho-pneumonia, and pus formation in the middle ear, nasal sinuses, base of tongue, and many other positions. The limitation of growth which has usually been regarded as the chief characteristic of vitamin A deficiency they suggest may be due to the development of the above-mentioned infective conditions, in which case this vitamin should no longer be designated the "growth-promoting" vitamin, but rather the "anti-infective" vitamin. It seemed likely, therefore, that in the case of the teeth also vitamin A would play a part in the prevention of caries, which is essentially an infective lesion.

Tests are now being made of adding, on the one hand, extra vitamin A, on the other, vitamin D to the constant diets of children and observing the effect of these vitamins respectively on the initiation, spread, and arrest of dental caries. The results so far suggest that vitamin A has little or no effect on the progress of caries, but as the data are not yet sufficiently complete to allow the statement that this vitamin plays no part in preventing or curing dental caries, they will not be recorded here. The tests with vitamin D, however, have given results sufficiently striking to warrant their preliminary publication, and are given below.

The average daily diet of the 21 children in this series (Group A<sub>2</sub>) was roughly as follows:

1½ pints milk	½ lb. meat (as purchased)
10 oz. bread	1 oz. bacon (as purchased)
1 oz. butter	5 oz. potatoes (as purchased)
½ oz. cooking fat	5 oz. other vegetables (as purchased)
1 oz. sugar (including cooking)	½ oz. cocoa
1 oz. jam or syrup (including cooking)	½ egg
½ oz. rice, etc.	Fruit (four times a week)

The source of vitamin D used was irradiated ergosterol in the form of radiostol. The majority of children in Group A<sub>2</sub> received 2 c.cm., some 1 c.cm., and some 4 c.cm. The investigation lasted twenty-eight weeks; the average number of carious teeth per child at the beginning was 8.8.

The methods of appraising the results were the same as those used in the previous investigations, details of which can be seen in the earlier publications.<sup>1 2</sup> The mouth of each child was charted before the feeding test; the

amount and extent and also the "degree" of hardness or softness of each carious area were noted. The main results are summarized in Table III and are compared with the

TABLE III.

	GROUP A <sub>3</sub> .	Groups.		
		A <sub>2</sub> .	B <sub>2</sub> .	C <sub>2</sub> .
Number of children in group ... ..	21	23	24	24
Number of weeks on diet ... ..	28	28	25	28
Average age (years) of children at beginning	5.4	8.7	9.0	8.8
Average number of new carious teeth per child at end	0.2	0.5	2.4	0.6
Average number of teeth per child showing increase of old caries	0.8	1.3	3.4	2.4
Average number of teeth per child showing initiation or spread of caries	1.0	1.8	5.8	3.0
Average "degree" of increase of caries per child	1.1	2.0	6.7	4.0
Average number of teeth per child in which caries showed hardening	3.9	2.0	less than 0.1	1.2
Average number of teeth per child in which caries showed softening	0.0	0.3	0.5	0.1

figures for the second investigation. It must be noted that the results given in this table are not necessarily strictly comparable, partly because of the difference in the average ages of the groups; in Group A<sub>3</sub> the average age was 5½ years, and in Groups A<sub>2</sub>, B<sub>2</sub>, and C<sub>2</sub> it was nearly 9 years. Now the arrest of caries might be expected to take place more readily in the deciduous teeth of children under 6 years of age, since there is presumably at this time less interference with the pulp tissue of the teeth by the natural processes of root absorption than is the case in the older children.

It is clear from these results that the addition of this one factor—vitamin D—has had a pronounced effect in (a) preventing the initiation of new carious foci, (b) limiting the spread of caries, and (c) apparently arresting the carious process in many cases. The results at first sight seem, indeed, to be better than those obtained in former tests when cod-liver oil, egg yolk, and extra milk were used as the main sources of vitamin D. This is not necessarily the case, however, for it was not possible to gauge exactly the relative strengths of vitamin D in the cod-liver oil, egg-yolk, and extra milk and in the radiostol respectively. Moreover, the average age of the children in the third investigation was less than in the previous two. Evidence which supports the view that the better results procured with irradiated ergosterol than with the natural vitamin D-containing foods may be due partly to the age factor, is obtained if children under 6 years of age be chosen from each of the groups and the effect of the diet on caries be compared. The comparison is made in Table IV.

It will be seen that with an average age of under 6 years the addition of vitamin D to the diet of group A<sub>3</sub> gives a result somewhat similar to, though rather better than, that obtained in Groups A<sub>1</sub> and A<sub>2</sub>, which had fat-soluble vitamins in the forms of cod-liver oil, extra eggs, and milk; but, as already mentioned, it is not easy to calculate how much vitamin D was present in the diets of Groups A<sub>1</sub> and A<sub>2</sub> in comparison with Group A<sub>3</sub>.

The following reports of individual cases give some indications of the observed effect of vitamin D. The first

two cases reacted especially well to the treatment, whereas in the third case the reaction was very slight. It is to be noted that in the first two instances the children were 3½

TABLE IV.  
(Average Age of Children under 6 Years.)

Main differences in diet.	No. of children in group.	Average No. of teeth per child showing initiation or increase of caries.	Average degree of increase of caries per child.	Average amount of hardening or arresting of caries per child.
A <sub>3</sub> . Institutional diet plus vitamin D (radiostol)	21	1.0	1.1	3.9
A <sub>1</sub> and A <sub>2</sub> . Abundant fat-soluble vitamins	18	1.4	1.7	3.7
B <sub>1</sub> and B <sub>2</sub> . Much less fat-soluble vitamins than A <sub>1</sub> and A <sub>2</sub> ; oatmeal in place of some of bread of A <sub>1</sub> and A <sub>2</sub>	19	5.0	6.0	0.2
C <sub>1</sub> and C <sub>2</sub> . Intermediate quantity of fat-soluble vitamins; no oatmeal	20	3.3	4.5	1.2

and 4 years old respectively, whereas in the third instance the child was 7½ years old.

Case 1.—K. C., aged 3½ years. At the beginning of the test 17 out of 20 teeth were carious, 11 being in a bad condition. The "degree" of caries was 52. This child received 4 c.cm. of radiostol in addition to the ordinary institutional diet. After thirty-five weeks there was no extension of old carious areas and no new carious points; 12 teeth which showed active caries at the beginning were at the end of the period in a state of partial or complete arrest (see Fig. 2); 3 teeth which at the beginning showed a tendency to arrest had completely hardened up, and only 2 of the teeth showed no signs of arrest during the period. These may, of course, be dead teeth, but there appeared to be no spread of caries in them. After thirty-five weeks of diet one tooth in which arrest was taking place was extracted and divided into three parts. One piece was stained with fuchsin and another with carmine, and ground sections were made from both. The surface did not stain as in active decay, but was uneven (Fig. 2). In the pulp

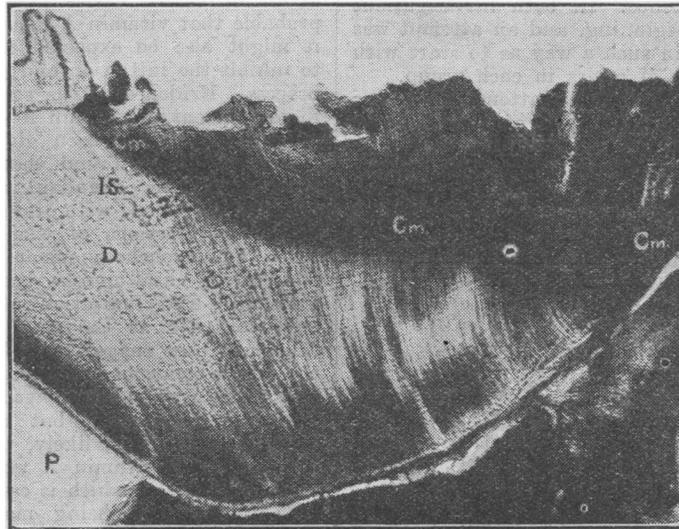


FIG. 1.—Showing active caries in a hypoplastic tooth from a dental clinic patient, aged 5 years. Surface soft and deeply stained with carmine; little or no pigmentation; no secondary dentine. (This figure and Figs. 2 and 3 are photomicrographs (×25) of carmine-stained ground sections of three children's molars.)

chamber, in a region corresponding to the injury, there was a mass of secondary dentine. A decalcified portion was sectioned and stained for organisms, and showed these to be still present in patches.

Case 2.—N. S., aged 4 years. At the beginning of the test 13 out of 20 teeth were carious, 9 being in a bad condition. The "degree" of caries was 46. This child received 2 c.cm. of radiostol daily, in addition to the ordinary institutional diet. After twenty-eight weeks there were no new carious points; 2 teeth showed apparent spread of caries, due to the breaking away of the weakened cusps. Using the criteria adopted in these investigations it was found that in 5 of the 13 carious teeth the caries was completely arrested, and in the remaining 8 there were definite signs of arrest.

The following case is mentioned as being the main exception in this series, for the reaction to the treatment was distinctly poor. This may be due partly to the greater age of the child and partly to the fact that too little irradiated ergosterol was given to allow the effect to be developed in the period of observation.

Case 3.—A. K., aged 7½ years. At the beginning of the test 11 out of 21 teeth were carious, 4 deciduous ones being in a bad condition and 3 out of the 4 permanent ones being also affected. The "degree" of caries was 23. This child received 1 c.cm. of radiostol in addition to the ordinary institutional diet. After twenty-nine weeks fresh new points of caries appeared in 2 teeth, and some spread of caries was found in 4 teeth. There were 11 "degrees" of increased caries. Six teeth showed some hardening.

In the whole series of 21 children to whom irradiated ergosterol was given a large proportion of the total increase

and spread of caries took place in Case 3 (A. K.), and if this patient is eliminated the results of this treatment on the remaining 20 children are exceptionally good. At the beginning of the investigation the 21 children had 185 carious teeth. In all the children at the end of the investigation there were 4 new points of caries, all very small. Of these 4, 2 were in Case 3. In the 185 carious teeth 16 showed some spread of the infective process or the breaking down of the enamel, and of these 4 were found in Case 3. In the majority of the teeth the soft and apparently active caries was in the course of arrest, and in many cases had actually been arrested, so far as could be ascertained.

The difficulties of an investigation of this type are obvious, and include that of appraising the amount or degree of caries in any tooth. Thus the apparent spread of caries may sometimes be due to the breaking down of a weak portion of the enamel, although such cases are classed as actual spread of the infective process. Again, it is often impossible to tell whether a tooth is already dead as the result of caries before the special feeding has begun, and it is probable that the absence of response to the vitamin in some of the teeth is due to this fact.

The question as to the effect of diet on the prevention and arrest of caries in adults is of great importance, but up to the present time only one patient (22 years of age) has been examined and charted carefully before and after treatment by an independent worker. In this case 2 c.cm. of radiostol were added daily to an ordinary diet. At the beginning of the period under review all the teeth were present in the mouth; there were no fillings, and the only caries present was in the two upper third molars, which were badly affected, and one lower third molar, in which the caries had started. After six months' treatment the upper molars were seen to be definitely hardening, and there was no visible increase in the carious patch in the lower molar. Other cases are being examined.

The facts observed show that arrest of decay is essentially due to the presence of vitamin D in the diet, and that vitamin A (the anti-infective vitamin) possibly plays little or no part in this arrest. Whether, as seems possible, vitamin A is of importance in the general immunity of some mouths to caries cannot at present be stated. In any case, the arrest of caries involves some post-developmental calcification of the teeth, and is possibly due rather to this defensive agent than to the specific agents controlling resistance to infection in the case of other tissues.

It may be pointed out that in the series of children (A<sub>2</sub>) receiving vitamin D no effort was made to limit the

cereal intake of the diet. It has been shown that cereals specifically interfere with tooth calcification just as vitamin D specifically promotes calcification. It is probable that cereals also interfere with the arresting of caries, and that this effect is antagonized by vitamin D; on this point, however, there is but little direct evidence.

#### The Process of Arrest of Dental Caries.

Since the actual process of arrest of dental caries becomes, in consequence of these investigations, largely a problem of nutrition, it may be well to refer to the main changes that occur in the teeth during this process, as illustrated in some of the teeth of the subjects of these investigations.

In active caries the surface of the area attacked is usually more or less "soft." In the early stages of arrest it tends to harden and may appear rough; later the irregularities are gradually removed, probably mechanically; and the surface becomes still harder and smoother and

more pigmented, until finally it is hard, smooth, polished, and pigmented. Caries may, of course, recur in the arrested area when the conditions are again altered. In response to caries, changes, apart from pigmentation, may take place, not only in the primary dentine (Fig. 2), but also in the pulp; the odontoblasts, in an endeavour to protect the living tissues of the pulp, may lay down new dentine—the so-called secondary dentine—to form a protective barrier.

When arrest is about to take place it appears that these processes are generally exaggerated, and much well-calcified secondary dentine is formed,<sup>7,8</sup> and finally the bacterial onslaught is prevented. It is, however, more common for the reaction to caries to be poor, so that there is little or no secondary dentine formed, or that formed is poorly calcified and contains many interglobular spaces, and caries spreads. These facts are illustrated in Figs. 1 to 3, which are photomicrographs of carmine-stained ground sections. Unfortunately the photomicrographs do not differentiate between the pigmented and stained areas. Fig. 1 shows a tooth with active caries; the surface is irregular, a large area of the dentine is deeply stained, indicating decalcification, and there is no secondary dentine. In Fig. 2 the carious process is being arrested, as is evidenced by the reduced staining power and the slight brownish pigmentation of the dentine and the amount of well-calcified secondary dentine. (Note: The carious surface of this tooth felt hard in most parts when examined with a probe.) Fig. 3 shows almost complete arrest of caries. The dentine is unstained, but somewhat pigmented, and there is much well-calcified secondary

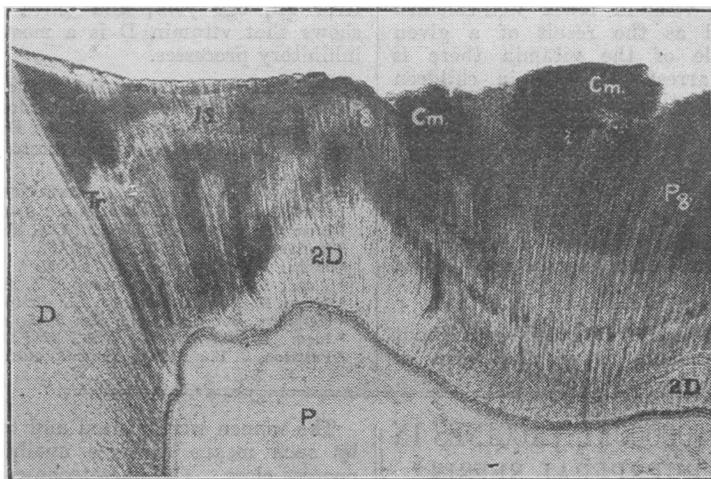


FIG. 2.—Showing "arresting" caries in a hypoplastic tooth from Case 1 mentioned in the paper. (Vitamin D was added to the hospital diet for thirty-five weeks prior to the extraction of this tooth.) The surface of the tooth was hard when tested with a fairly sharp probe, but was rough in places and had not the polished appearance of long-standing arrest. A few small areas are stained with carmine, and there is some general brownish pigmentation. There is much well-calcified secondary dentine coinciding with the carious area.

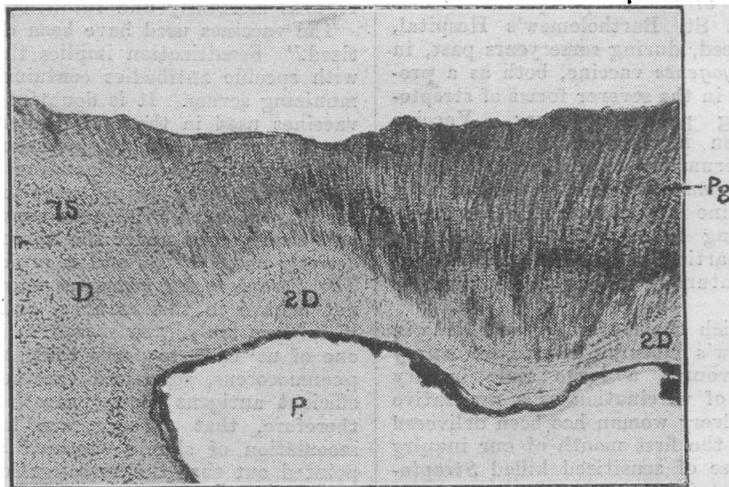


FIG. 3.—Showing arrested caries in a hypoplastic tooth from a hospital patient, aged 4 years, who had prior to the extraction received cod-liver oil for three years. The surface was hard and smooth, and appeared partly polished; no staining, slight brownish pigmentation; much well-formed secondary dentine. E=Enamel; D=dentine; P=pulp; IS=interglobular spaces; 2D=secondary dentine; Pg=pigmentation; Cm=carmine.

dentine. It is interesting to note that even in sections of teeth in which caries appears to be completely arrested the dentinal tubules may contain micro-organisms. These, however, are apparently inactive. For instance, some Gram-positive bacteria were found in the dentinal tubules of the teeth ground sections of which are seen in Figs. 2 and 3.

The production of secondary dentine in puppies by artificial stimuli has been related to the intake of vitamin D.<sup>8, 9</sup> With an abundance of this vitamin much well-calcified secondary dentine is formed as the result of a given stimulus, whereas with little of the vitamin there is little or no reaction. The arrest of caries in children obtained in the present investigation as the result of giving abundant vitamin D in the diet is, therefore, just what would be expected on the basis of the animal experiments.

That other factors play a part in the arrest of caries seems certain, but at present little is known concerning these. It has been shown by one of us<sup>9</sup> that calcifying diets which tend to assist the arrest of caries also result in a high calcium content of saliva, which may be of significance.

#### Summary.

In a batch of 21 children whose average age was about 5½ years the addition of vitamin D in the form of

irradiated ergosterol (radiostol) checked the initiation of new carious points, diminished the spread of old carious points, and arrested the infective process in many carious teeth.

This investigation corroborates those previously made, in which it was found that the carious process in the teeth of children could often be inhibited by increasing the intake of fat-soluble vitamins by the addition to the diet of cod-liver oil, egg yolk, and extra milk. The present work shows that vitamin D is a most powerful agent in these inhibitory processes.

Our thanks are due to the Medical Research Council and the Dental Board of the United Kingdom for their financial support of these investigations, and to the British Drug Houses, Ltd., for preparing and supplying the radiostol and the vitamin A oil used.

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## THE UTILITY OF STREPTOCOCCAL VACCINES IN THE TREATMENT OF PUERPERAL SEPSIS.

BY

RICHARD R. ARMSTRONG, M.D., F.R.C.P.,

AND

WILFRED SHAW, F.R.C.S.

THE following paper describes an investigation carried out (1) on clinical lines, (2) by laboratory experiments on animals, to decide the utility of vaccines in the treatment of puerperal sepsis.

#### Clinical Investigation.

It is generally accepted that the *Streptococcus pyogenes haemolyticus* is by far the commonest cause of puerperal septicaemia. The majority of morbid puerperia are also due to this organism. At St. Bartholomew's Hospital, London, trust has been placed, during some years past, in the use of *Streptococcus pyogenes* vaccine, both as a prophylactic and for treatment in the severer forms of streptococcal infection, including puerperal fever. Vaccine "sensitized" by suspension in Pasteur Institute anti-streptococcal immunizing serum has been used. The mere fact that there has been constant demand over a long period of years for this vaccine implies a belief in its therapeutic value. But nothing is more difficult than to estimate the worth of a particular method of treatment in an infective disease naturally liable to spontaneous recovery.

The conditions under which the maternity and lying-in practice of St. Bartholomew's Hospital extern midwifery district are conducted favoured a large scale inquiry designed to test the value of vaccination as a preventive of morbid complications. Every woman has been delivered in her own home. During the first month of our inquiry each patient received a dose of sensitized killed *Streptococcus pyogenes* vaccine, containing 250 million organisms, on the day of delivery. If the patient's temperature rose, 500 million vaccine was given, followed the next day by 1,000 million vaccine, this latter dose being continued daily till the temperature fell. During the second month no prophylactic dose was given, but pyrexia was treated by 250 million vaccine on the day of onset, 500 million the next day, and then 1,000 million vaccine daily till the temperature fell. During the third month vaccine was not given in any circumstances, so that women confined during this month served as controls to the other cases. The same routine was observed in the following quarter, and so the changes were rung until, in the course of two years, the results of two thousand cases were available for analysis.

The women were visited and treated in their own homes by such means as were available in a district of the poorest class. The only technical refinement has been the consistent use by the midwifery clerks of sterilized rubber gloves and the employment at each case of a "drum" containing the following sterilized dressings, etc.: a sterilized gown, four small towels, two large pieces of wool, six small surgical wool swabs, two long strips of folded gauze, 1½ yards in length (for plugging the cervix if required), six gauze eye swabs; this in addition to the fully equipped midwifery bag such as is in universal use.

Such apparatus betokens more than an attempt at surgical cleanliness. It is to be considered an outward and visible sign of inward and spiritual grace, a recognition by the midwifery student, even in his novitiate, of the essential need to avoid contamination by employing cleanliness, care, and conservatism in the management of labour. We believe it is to this that the satisfactory results as regards morbidity and fatalities are due.

The vaccines used have been described above as "sensitized." Sensitization implies the conjugation of bacteria with specific antibodies contained in the homologous immunizing serum. It is doubtful whether the streptococcal vaccines used in the inquiry were truly sensitized in this sense. A suspension of pneumococci or typhoid bacilli, in contact with their corresponding antiserum, is agglutinated and precipitated in a coagulum consisting of bacteria surrounded by a gelatinous capsule; this may be stained and clearly seen under the microscope. Such a vaccine is actively chemotactic, and is rapidly ingested by leucocytes. The *Streptococcus pyogenes* vaccine supplied for use did not behave in this manner, and it is therefore doubtful if it were truly "sensitized." Experiments described by one of us<sup>1</sup> seem to prove that, at least in the case of the pneumococcus, sensitized vaccines are less rapid and less efficient antigens than "raw" vaccines. It is probable, therefore, that nothing was lost to treatment by the inoculation of simple vaccine. In any event it must be pointed out that the investigation here described was not so much a progressive and reasoned attempt to establish new treatment as a test of the validity of existing practice and beliefs.

In classifying the cases the British Medical Association standard of "morbidity" has been adopted—namely, a rise of temperature from any cause whatever, not necessarily streptococcal infection, to 100.4° F., on two occasions at least between the second and tenth days of the lying-in period. By "clinically septic" is meant the occurrence of offensive lochia, subinvolution of the uterus, and characteristic fever. The temperature shows a rise on the third day, a maximum on the fifth day, and fever persisting for an average of five days. "Septicaemia" indicates the severest form of infection with the demonstration of *Streptococcus pyogenes* in blood culture.