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VITAMIN A AS AN ANTI-INFECTIVE AGENT.

*ITS USE IN THE TREATMENT OF PUERPERAL
SEPTICAEMIA.*

BY

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AND

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(Preliminary Communication.)

LAST year we published an account of an experimental investigation on animals, which suggested that an important function of vitamin A was to raise the resistance—either local or general, or both—to bacterial infection.¹ Animals deprived only of this vitamin died ultimately with multiple foci of infection, whereas control animals receiving vitamin A remained in good health, free from infection. Animals which had developed infective lesions, if given in time abundant vitamin A, usually recovered completely. In the publication referred to we dealt with the work of other investigators on the subject, and this will not be repeated here. Reference may, however, be made to one fact which has been described since that date. A discussion has ranged round the question of whether in animals deprived of vitamin A the epithelial hyperplasia precedes the local infection in the same position or vice versa. Tyson and Smith have found histological evidence of infection preceding the epithelial changes in the tongue and kidney.²

THE BASIS OF THE INVESTIGATION.

The results of our animal experiments seemed to be sufficiently impressive to warrant an investigation to determine whether vitamin A had any specific action in human infection. Some general clinical evidence in various types of infection, and particularly in pneumonia, lent support to the idea that preparations rich in vitamin A had a definite effect in increasing the general resistance and

in promoting recovery, but we were met with the usual difficulty in clinical work of assessing the value of the remedy in diseases which often have a low mortality rate whatever the treatment given.

In the publication referred to above we suggested specially that a deficiency of vitamin A in the body might play an important part in the etiology of puerperal sepsis. It is generally recognized that many sections of the community, and, indeed, many individuals of all classes, receive an allowance of fat-soluble vitamins in their diet well below the optimal. The pregnant woman is in still greater danger of a deficiency of this nature, for she has not only to supply her own body but also that of a rapidly growing organism. The growing animal, whose metabolic rate is relatively much greater than that of the adult, is known to make greater demands on its stores and supplies of vitamin A than is the slow-growing or adult animal. It is probable, therefore, that, unless her intake of vitamin A is high, the liver stores of the substance in a woman are gradually diminished during pregnancy, so that, if vitamin A plays the part in raising the resistance to infection indicated by the animal experimental results, she might be expected to be more susceptible to sepsis at this time. A somewhat analogous phenomenon is seen in the increased dental caries experienced by women during pregnancy, due most probably to the sacrifice of vitamin D, the calcifying vitamin, to the developing foetus. In any case, it was obviously possible to test this hypothesis of the relationship of puerperal sepsis to a deficiency of vitamin A. We are at present engaged upon such a test at the Jessop Hospital, Sheffield, with the assistance of the registrar, Miss Pindar. Out-patients attending the hospital in the prenatal period are being given a supply of a preparation rich in vitamin A two weeks prior to and one week after confinement, and the results are compared as regards the development of sepsis with those in an equal number of patients not receiving this addition. It is obvious that work of this type must involve large numbers of patients, and at the present time the numbers are not sufficiently large to warrant publication, although it may be stated that the results obtained are definitely in favour of the hypothesis that vitamin A has a prophylactic anti-infective action when given under these conditions.

In the meantime we thought we could get evidence on this point more rapidly, and possibly more dramatically, by studying the action of vitamin A in puerperal septicaemia. For if the deficiency of vitamin A in the body is responsible for the lowered resistance to infective organisms seen in puerperal septicaemia, then the exhibition of large doses of the same vitamin to patients suffering from this condition would be expected to have some curative effect. This prophylactic and curative relationship of small and larger doses is seen in the case of vitamin C in scurvy and vitamin D in rickets, and the same would be expected of

vitamin A in infective conditions if the hypothesis of its anti-infective function were sound. The choice of puerperal septicaemia, where the blood infection is usually due to a haemolytic streptococcus, had the advantage that the mortality rate is so high that the series of cases in which complete cure is brought about need not be large in order to allow a decision as to whether the remedy tested is having a beneficial effect. In the present communication, which is of a preliminary nature, the number of cases treated only allows the claim that the administration of preparations rich in vitamin A has had some beneficial result. Whether this form of treatment is specific for septicaemia, and possibly bacterial infections in general, can only be decided after the subject has been investigated on a much larger scale.

The Method Adopted.

The treatment consisted, so far as we are concerned, of the administration of preparations containing vitamin A. Two preparations were used, X and Y. In order to give some idea of their content of vitamin A, it may be said that, using the colorimetric method of Carr and Price,³ preparation X gave a dilution test of 1 in 20,000 to 1 in 30,000, and preparation Y of 1 in 300,000. An average specimen of cod-liver oil will give a corresponding figure of 1 in 2,000, so that X, on the average, was about 10 times and preparation Y about 150 times as rich in vitamin A as cod-liver oil. (It has not yet been definitely proved that the antimony colour reaction is specific for vitamin A, but all evidence tends to show that this is the case.)

When the condition of the patient was such that X could be administered it was usual to give 2 drachms (about 7 c.cm.) twice daily. On the basis of the above colour test figures this is equivalent to about 5 ounces of cod-liver oil. In some cases (vide Cases iv and v later) it was impossible to give X by mouth owing to vomiting, and it was necessary to give preparation Y in doses of 2 minims hourly in a teaspoonful of orange juice for twelve doses daily. When Y was thus given, about 1½ c.cm. was the total daily dose. This is equivalent, on the above reckoning, to 225 c.cm. of cod-liver oil—namely, 8 ounces. In another case, treated before Y was obtainable, the preparation X, since it could not be taken by mouth, was injected subcutaneously in 1-drachm doses for two days. This procedure was not continued, however, for although the injected doses were apparently absorbed fairly rapidly, and gave rise to no local sepsis, we did not think this mode of administration desirable.

It may be well to add that, since the patients were not under our direct charge, the treatment in some cases was not confined to the administration of vitamin A preparations. In one case (Case ii) the patient received quinine; another case (Case v) received a course of intramuscular

metarsenobillon. It is difficult to appraise the value of these additional forms of treatment, but in view of the fact that they had been used on similar cases over a number of years at the same hospital with results which cannot be considered good, it is possible that, as curative agents, they are not of great value, and did not influence the course of the disease to any great extent. Except for local applications, Cases i, iii, and iv received only the vitamin A treatment recorded above.

Preparation X is radiostoleum, kindly supplied for this investigation by British Drug Houses Ltd. Preparation Y, the very potent concentrate of vitamin A, was placed at our disposal by Lever Brothers, Port Sunlight. To both of these firms we wish to express our thanks.

Analysis of Results.

At the Jessop Hospital, Sheffield, and its annexe for septic cases at Norton, the results obtained in puerperal cases of haemolytic streptococcal septicaemia during the past two years are as follows:

	Prior to Vitamin A Treatment.		Vitamin A Treatment.
	1927.	1928.	1929 (3 months).
Number of cases... ..	8	16	5
Number of recoveries	2	0	5

Of the 24 cases not receiving the vitamin A treatment, 22 died, giving a mortality of 92 per cent. In the 5 cases receiving vitamin A there were no deaths, and all made a complete recovery.

Reference to the case notes given below will show how the different cases responded to the treatment. It would appear that the effect of vitamin A is rather to increase gradually the general resistance than to act suddenly, as might be expected in the case of a substance having a specific bactericidal or antitoxic effect. It will be noted that blood cultures in all cases became sterile, and although the number of cultures made in each case were too few to allow the determination of the exact time required for this development, it was usually found that about a fortnight after the beginning of administration of vitamin A no organisms could be grown from the blood. Nothing immediate and dramatic in the effect of this form of treatment has been noticed. It may be added that we have also treated a number of other cases of severe puerperal sepsis by the same means, but since their blood cultures were negative we have not considered them in this publication. Of all these cases the only failures were two of severe peritonitis.

CASE I.

The patient, a primipara aged 30, was delivered at her own home by means of forceps on January 6th, 1929. Two days later she had a temperature of 100° F., and, on January 12th, perineal sutures were removed owing to sepsis. On the 13th she was admitted to hospital with a history of delirium.

On admission she was pale and had an anxious expression; the temperature was 100.6° F., pulse rate 126, respiration rate 26.

The edges of a large perineal tear, extending almost to the sphincter, were sloughing. On January 15th she had tenderness and rigidity on the left side of the abdomen, and swabs from the perineum and cervix showed pus and Gram-positive diplococci. On the 17th her temperature was 101.6° F., pulse rate 120, and on the following day she received the first of a series of intrauterine injections of glycerin and glauramine.

On the 21st her temperature was 102.4° F., pulse rate 120, and the administration of preparation X by mouth, in 2-drachm doses twice daily, was started. In a blood culture made on the 22nd *Streptococcus haemolyticus* was grown in twenty-four hours; on the other hand, the perineum was much cleaner and the abdomen less tender. On the 23rd the temperature was 104° F., and the pulse rate 122. On the 24th she had pain and tenderness in the right loin, but the perineum was healing. Fever continued on the 26th, the temperature being 102° F., the pulse rate 124; but on the 28th the temperature subsided slightly and the abdomen felt less tender. On the 30th and on February 1st the temperature was 100° F., and the pulse rate about 120; tenderness developed in the gall-bladder region. On February 6th the temperature was down to 99° F., though the pulse rate remained at 120; she was tender in the left iliac fossa, but less tender over the gall-bladder.

From this time on the temperature and the pulse came down to normal; the blood culture became sterile, and by the 16th the perineum was healed, the uterus involuted, and the patient felt well. Administration of preparation X was discontinued and the patient was discharged on February 22nd. The total quantity of X, at the rate of 2 drachms given twice daily for twenty-seven days, was 13½ oz.

CASE II.

The patient, a primipara aged 24, had a normal labour at her own home on January 15th, 1929; there was a perineal tear. The next day her temperature was 100° F., and on the 17th the perineal sutures were removed owing to sepsis.

She was admitted to hospital on the 18th, her temperature then being 102.6° F., her pulse rate 124, respiration rate 26; she was very thin, with flushed cheeks, had diarrhoea, and complained of a dull ache in the lumbar region. A perineal swab showed the presence of *Staphylococcus albus* and *Streptococcus haemolyticus*; a swab from the cervix showed *Streptococcus haemolyticus*, and *Streptococcus haemolyticus* appeared in a blood culture in twenty-four hours. Quinine hydrochloride (5 grains in 10 c.cm.) was administered intravenously every other day for three doses, and 5 grains in 1 c.cm. intramuscularly on four alternate days.

Administration of preparation X by mouth in 2-drachm doses twice daily was started on the 21st; on the 22nd the patient had a rigor followed by drowsiness; she was tender in the right iliac fossa. On the 24th the temperature was 102° F.; the right wrist, the dorsum of the right hand, and the right elbow were swollen and tender. On the 29th an abscess over the right wrist was incised and thin yellow pus was evacuated. Shortly after, tenderness was noted over the right thigh, and though the wrist healed the pulse remained rapid and the temperature at about 102° F. On February 11th there was a swinging temperature from 99° F. to 103° F., the pulse rate being 120. Blood cultures were sterile on the 12th, but on the 18th an abscess over the right hip was aspirated and thin yellow pus was obtained. On the 20th the abscess was incised and a large quantity of pus was evacuated. The patient's temperature was still swinging, and on the 24th it rose to 104° F., the pulse rate being 140. She began to have pain in the left hip and swelling over the left buttock. On the 28th this swelling began to subside, but the temperature still swung from 98° F. to 102° F.

On March 2nd the temperature was normal for twenty-four hours. The wound over the right hip started to heal rapidly and was healed on the 15th, when the temperature had been normal since March 1st. On March 16th the patient was discharged, having taken in all 21½ oz. of preparation X.

CASE III.

The patient, a primipara aged 18, was delivered of an anencephalic monster at her own home on February 1st, 1929, and eight hours later admitted to hospital with a retained placenta. Immediately after the manual removal of the placenta her temperature rose to 101° F., and 30 c.cm. of anti-streptococcal serum were administered. On February 3rd her temperature had risen to 101.4° F., her pulse rate to 108, and the lochia were profuse and offensive. A perineal swab taken the following day showed on culture the presence of *Staphylococcus aureus*, *B. coli*, and *Streptococcus haemolyticus*, and *Streptococcus haemolyticus* was grown from a blood culture in twenty-four hours. Her temperature was now 103.6° F., pulse rate 126. On the 6th a course was started of intrauterine injections of glycerin and glauramine, but on the 10th the temperature and pulse rate were still rising, being 102.2° F. and 138 respectively.

Administration of preparation X in 2-drachm doses twice daily was begun on the 11th; on this day her temperature was 102° F., pulse rate 140, and respiration rate 30. The following day she had pain and tenderness on the left side of the abdomen, and on the 15th follicular tonsillitis, and complained of stiffness in the joints. The following and succeeding days the stiffness in the joints continued and she had a swinging temperature, rising as high as 103° F. On the 18th, however, the blood culture was sterile and she felt better. From now, moreover, the temperature came down, becoming normal on March 3rd. On March 6th the administration of X was discontinued, and on the 16th, the temperature and pulse having been normal for several days, the patient was discharged. The total quantity of X administered was 12 oz.

CASE IV.

The patient, a primipara aged 23, had normal labour at her own home on March 1st, 1929; there was a perineal tear which was sutured. The following day she complained of feeling cold and of abdominal pain, and these symptoms continued until the 4th, when she was sent to hospital. On admission she had a temperature of 104° F., pulse rate 120, respiration 22, flushed cheeks, shooting abdominal pains, abdominal tenderness, most marked in the iliac fossae, distension, and diarrhoea. The lochia were profuse and offensive. On March 6th the perineal swab culture showed the presence of *Streptococcus viridans*, *B. coli*, and diphtheroid organisms, and *Streptococcus haemolyticus* was grown in a blood culture after forty-eight hours. On the 8th she had diarrhoea, marked dyspnoea, a temperature swinging from 100° to 104° F., a pulse rate of 140, and respiration rate of 48. On the 10th, the oral administration of preparation X having failed through the patient vomiting, a drachm was injected subcutaneously into the buttock. The temperature now was 104° F., and the pulse rate 128; the following day the temperature was 101.4° F., the pulse rate had risen to 160, and the patient complained of pain in the right chest. On the 13th subcutaneous injection of 1 drachm X was repeated; on the following day the patient's pulse was very poor in volume; she had marked dyspnoea and her condition was critical. Preparation Y was given by mouth, 2 minims hourly for twelve hours. Examination of the sputum showed the presence of pus, pneumococci, and non-haemolytic streptococci. On the 15th the respiration rate was 62 and respirations were very shallow. She had a troublesome cough, and the temperature and pulse remained high. On the 20th there was still dyspnoea, the bases of both lungs were dull on percussion, there was bronchial breathing, and fine crepitations were heard at both bases. On the 22nd blood cultures were sterile, and the patient began to feel better, had no pain, and less dyspnoea. Signs of consolidation of both lungs persisted, and on the 28th there was absolute dullness at both bases, tubular breathing at the left base, and moist rales and faint breath sounds at the right base. On the 31st administration of preparation Y was discontinued and capsules each containing 2 minims

of X were given once hourly for twelve hours over a period of eight days. On April 2nd there was absolute dullness over the right base, and breath signs were very faint. The temperature ranged from 97° to 99°, the pulse rate was 90, and the respiration rate 20. On April 9th pus was aspirated from the right chest and a portion of rib was resected for an empyema. On the 12th and following days the empyema wound drained freely, and on the 15th the temperature was normal. On May 1st the temperature was still down, the wound was draining slightly, and the patient's general condition was good. Altogether she had 2 drachms of preparation X subcutaneously and 3½ by mouth. Of preparation Y she had approximately 24 minims daily for seventeen days.

CASE V.

The patient, a primipara aged 23, had a normal labour at her own home on March 4th, 1929. She was well until the third day, when her temperature rose to 104° F., after which it ranged from 99° to 103° F. until March 22nd, when she was admitted to hospital. On the 23rd her temperature was 103.6° F., and her pulse rate 128; preparation X, given by mouth, was vomited. On the 24th a swab from the cervix showed the presence of *Streptococcus haemolyticus* in pure culture, and *Streptococcus haemolyticus* was grown in a blood culture in twenty-four hours. Two minims of preparation Y were given hourly by mouth for twelve hours, and an arsenobillon course was started; she was very drowsy. On the 26th her condition was brighter; her temperature was 102°, and the pulse rate 100. On April 3rd a blood culture was sterile, but the temperature was still swinging from 98° to 103° F., and the pulse rate was 100; on the 11th the temperature ranged from 98° to 102° F., but on the 14th it came down to normal and administration of Y was discontinued. On the 24th the temperature and pulse were still normal, and the patient was discharged on the 27th. Preparation Y was given in 2-minim doses for twelve hours during twenty-nine days; the total amount being 1 oz. Arsenobillon was given intramuscularly in doses of 0.3 gram, three being given on the first day, two on the second, and one each on the third, fifth, and seventh days. The total quantity was 2.4 grams.

It is clear that, impressive as are the results described, they are too few in number to allow the deduction that this form of treatment is specific in its nature for septicæmia. They do, however, warrant the belief that the animal experiments pointed correctly to the hypothesis that vitamin A plays a part as an anti-infective agent to bacterial infection, and has the property of raising the resistance of the body to such infection. The fact, observed above, that the administration of these preparations does not produce an immediate beneficial effect, and that this only becomes obvious after a week to a fortnight, according to the severity of the case, from the beginning of treatment, suggests that the fulminating type of septicaemia, which proves fatal in a few days, may not benefit by this treatment in its present form. This view can only be tested, however, by further investigation. If vitamin A should ultimately prove, as the result of further tests, even to approach in efficacy the standard obtained in the present work, it is obviously of great value as a therapeutic agent. Nor is there reason to believe that this anti-infective action, if established clinically, would only be of importance in streptococcal infections, and it is most probable that the

same increase in bodily resistance would be found in many other types of infection. We think it desirable that clinical trials should be made in other bacterial infections. It is probable that the dosage of vitamin A and the mode of administration we have used can be improved upon by further trial.

Finally, if vitamin A should prove to have anti-infective qualities of a curative nature, as this work suggests, it must also be of inestimable value in its prophylactic effect. Indeed, it is possibly essential for the natural defence of the body against infective agencies, and, if so, it is incumbent to see that the body under all conditions, but especially in times of special stress, as in pregnancy, should receive an adequate and large supply of this substance by the inclusion in the diet of natural foods which contain it. Such foods include egg-yolk, green vegetables, milk, butter, and cheese. Cod-liver oil also contains vitamin A in abundance.

Summary.

On the basis of animal experiments which indicated that vitamin A is an anti-infective agent, we have treated five cases of puerperal septicaemia from whose blood haemolytic streptococci were grown, with preparations rich in vitamin A. All made complete recoveries, thus indicating that vitamin A, when given therapeutically, can raise the resistance of the human body against septic and infective micro-organisms.

The cases described were under the care of Mr. King, Mr. Chisholm, and Mr. Stacey, members of the honorary staff of the Jessop Hospital, Sheffield, and to them we wish to express our indebtedness. We wish also to thank Professor Miles Phillips for his interest in the work, and Miss Moore, the resident house-surgeon.

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