previous history of illness are suggestive of the presence of histoplasmosis infection, particularly in the riverine areas. Though no definite conclusions can be drawn about the extent of the incidence of histoplasmosis in Delhi and in other parts of the country from the present study, it undoubtedly emphasizes the urgent need for a more comprehensive survey which will provide further information about the epidemiology of the disease in this country.

Summary

A pilot histoplasmin survey was carried out in the Delhi area. Skin tests were performed on 747 people from different places representing rural, urban, and riverine areas of Delhi.

12.3% positive reactors were found in the riverine area, 2.9% in the rural area, and 4.9% in the urban area.

Cultural and serological examinations of histoplasmin-positive reactors were all negative.

Our thanks are due to Dr. Hans F. Smetana, who suggested the pilot study, to Dr. M. L. Passi and his staff of the Delhi Municipality for their valuable assistance, to Mrs. L. Gamer for her valuable help during the survey, and to Mr. Amar Nath for the technical assistance. This work was undertaken with the aid of a grant from the Indian Council of Medical Research.

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PUERPERAL ERYTHEMA NODOSUM AFTER LIVER EXTRACT INJECTIONS TREATMENT WITH PREDNISONE

BY

F. D. C. FORD, B.M., B.Ch., D.Obst.R.C.O.G.
General Practitioner, near Guildford, Surrey

In 1958 a trial was instituted by the South-East England Faculty of the College of General Practitioners into the prevention of early puerperal depression by injections of liver extract. Alternate cases were to be given two intramuscular injections of 4 ml. of "anahaemin" on successive days after confinement. The only two patients in this practice who were given these injections developed erythema nodosum within a month of confinement.

Previous Reports

It is known that some patients have an allergic tendency to react to all forms of liver injections, but such reactions are thought less likely to occur with anahaemin because of the refined nature of the product. It has not previously been reported as causing erythema nodosum.

Favour and Sosman (1947) found erythema nodosum associated with respiratory infection in 80% of their

patients. Half the throat swabs taken grew haemolytic streptococci, but rheumatic fever was rare and tuberculosis was uncommon. They noted that 80% of their adult patients had accompanying arthritis and that many of those treated with penicillin or sulphonamides recovered no more rapidly than otherwise expected. Most reports of drug-induced erythema nodosum concern sulphathiazole, this being bound to serum proteins more than other sulphonamides. Doxiadis and McLean (1948) found that in children with sulphathiazole-provoked erythema nodosum it began within seven days of the start of treatment and faded within nine days. Histologically it appeared the same as spontaneous erythema nodosum. Lemaire *et al.* (1948), reporting two adult cases of active early tuberculosis, found that the erythema nodosum provoked by sulphathiazole disappeared in spite of continued use of the drug.

A detailed study by Rollof (1950) of the erythema nodosum provoked by sulphathiazole in children showed 81% associated with tuberculosis; the more recent the infection the more commonly was erythema nodosum provoked. He concluded that it is not a specific disease, but that, whether spontaneous or sulphathiazole-induced, it is a manifestation of an allergic phenomenon due to some kind of infection. Added weight is given to this theory by the remarkably prompt response to cortisone recorded in four separate cases (without active tuberculosis) treated in the U.S.A. (Allbright and Kuffel, 1951; Ureleş and Kalmansohn, 1951; Farber and Mandelbaum, 1951; Schneerson, 1952). But, as in the following two cases, there is often no obvious source of infection.

Case 1

The patient, aged 42, was a gravida-6, including three abortions. Blood group A Rh+; Hb, 95%; W.R. and Kahn negative. Previous obstetric and general history without note. Her general health during pregnancy was good except for varicose veins and one day's slight vaginal loss of blood (and epistaxis) at the 27th week.

She had a normal confinement at home on July 6, 1958. Blood loss was 10 oz. (280 ml.). Ergometrine 0.5 mg. was given intramuscularly after the third stage into the outer side of one thigh. On the first two days of the puerperium anahaemin 4 ml. was given into each outer thigh. On the 10th and 19th days she developed mild superficial phlebitis of the right long saphenous vein in the calf and above the knee. Breast-feeding was established and maintained throughout the forthcoming illness.

31st Day.—She now developed "cellulitis" of the outer side of the right thigh at the site of an anahaemin or ergometrine injection. This appeared gradually over four days and was accompanied by an inguinal adenitis. Twice-daily injections of penicillin were started. During the next two days tender erythema occurred in old scars on the left knee and buttock and the right shin, and she complained of backache.

33rd Day.—Admitted to hospital with her baby as a case of septicaemia not responding to penicillin. Throat swab and high vaginal swab: no pathogens isolated. Catheter specimen of urine—nothing abnormal. E.S.R. (Westergren), 100 mm./hour, Hb 89%; W.B.C., 11,000/c.mm. (neutrophils 80%, eosinophils 5%, lymphocytes 9%, monocytes 6%). Penicillin was continued without effect on the fever or patches of erythema which remained confined to the legs. Three days later the area of cellulitis on the thigh was incised but no pus obtained. A swab gave no growth. Skin biopsy: erythema nodosum with giant cells and no caseation. Mantoux 1/1,000, negative. Chest x-ray film normal.

51st Day.—More nodules developed, with pain in the knee-joints and minimal effusions. After this the fever settled slowly. *58th Day.*—E.S.R., 76 mm./hour; Hb, 70%; W.B.C., 9,000/c.mm. *63rd Day.*—The patient returned home, the erythema subsiding slowly but completely during the next two months. On the 71st day after confinement the E.S.R. was 40 mm./hour; Hb, 98%; W.B.C., 6,000/c.mm.

Case 2

The patient, aged 34, was a gravida-4. Blood group O Rh+; Hb, 77%; W.R. and Kahn negative. Previous obstetric history was as follows. First pregnancy: twins; severe pre-eclamptic toxæmia; induction at 34 weeks (one baby died. Second pregnancy and confinement normal. Third confinement normal after threatened abortion; 20-oz. (570-ml.) post-partum haemorrhage. Her general health was fair, with recurrent anaemia due to menorrhagia said to be caused by metropathia haemorrhagica.

Fourth Pregnancy.—Slight vaginal bleeding at 8th and 14 weeks; repeated epistaxes in middle trimester; labour induced at 42nd week by membrane sweep. Normal confinement at home on October 29, 1958. Ergometrine 0.5 mg. given intravenously, with birth of the anterior shoulder. Blood loss minimal.

Puerperium

On the second and third days anahaemin 4 ml. was given into the outer side of each thigh. On the 7th day mild right pyelitis was treated with "sulphatriad" (total 25 g.). On the 16th day lochia were still red, unaffected by ergometrine, and probably due to a lacerated cervix. Breast-feeding established.

21st Day.—She had no further loss, but developed bilateral "cellulitis" of outer thighs at sites of both anahaemin injections. In the next few days she developed erythema nodosum—multiple tender dusky-red patches over the legs and, later, the arms. The areas of cellulitis remained unaltered and acutely tender. She ran a fever which was uninfluenced by twice-daily injections of penicillin.

33rd Day.—The nodules remained the same, but she now had arthritis of the left elbow and a few days later of both wrists and ankles. This was only partially relieved by aspirin 10 gr. (0.65 g.) four-hourly.

48th Day.—Hb, 76%; W.B.C., 7,000 (neutrophils 65%, lymphocytes 24%, monocytes 11%).

51st Day.—She was able to get up for an hour or two, but the nodules and joints remained very painful. A course of prednisone was started—40 mg. the first day, 30 mg. the second, 20 mg. the third, 15 mg. the fourth, and 10 mg. the fifth and following days. In the first 48 hours there was considerable improvement of both the nodules and the joints.

62nd Day.—Lactation failing. Tab. stilboestrol 5 mg. given twice daily for five days.

69th Day.—Prednisone decreased to 5 mg. daily. She had slight oestrogen-withdrawal bleeding, but all the nodules and the arthritis had now vanished except for a residual tender indurated area on the left outer thigh.

75th Day.—Prednisone decreased to 2.5 mg. daily.

83rd Day.—Prednisone withdrawn though the left thigh remained the same. This gradually became normal over the next two months. Chest x-ray examination on June 5, 1959, revealed no abnormality.

Discussion

The first of these patients was thoroughly investigated in hospital. No definite cause for the erythema nodosum was found, but it was presumed to be connected in some way with the intramuscular injections, either of ergometrine or of anahaemin, since the presenting signs were localized to the site of injection. The same

syndrome presented in the second case, and the illness took the same protracted and, at first, alarming course. This time the ergometrine had been given intravenously and the evidence therefore appeared to point to the anahaemin injections.

Analysis was made by the makers of the 25-ml. rubber-capped bottle from which three of these four injections were given. It was sterile and contained less than 1 µg. of histamine acid phosphate per ml. In view of the serious illness produced in these two patients, no further injections of anahaemin have been made in other patients during the puerperium, but 1-ml. doses from the same bottle were given as maintenance therapy to a patient with pernicious anaemia and she suffered no ill effects. I have information on nearly 200 other cases treated in the puerperium without mishap (private communication).

After the experience gained from the first case, the second case was treated at home and therefore did not undergo such searching tests to exclude other possible causes. But, excepting mild pyelitis, in neither patient was any infection found; the other members of their families, including the newborn babies, remained perfectly well.

On the assumption that this was an allergic phenomenon, the second patient was given a short course of prednisone lasting 32 days. Admittedly this was started 30 days after the onset of erythema, when the patient was already a little better, but she improved much more strikingly in the next 48 hours. The improvement, though not complete, was maintained as the dose was decreased, and there was no relapse when the drug was withdrawn. Neither patient appears to have suffered any permanent harm. The conclusion seems well founded that these two patients had erythema nodosum induced by injections of liver extract, and that in one of them the course of the disease was shortened by steroid therapy.

Summary

Two cases of erythema nodosum are reported. Both occurred in multigravidae within a month of confinement, in one case 30 days and in the other 19 days after intramuscular injections of anahaemin.

It is suggested that the erythema nodosum was an allergic reaction induced by this substance.

In the second case prednisone appeared to hasten recovery.

I am grateful to my principal, Dr. J. F. Stent, whose patients I was attending; to Dr. T. B. Oswald, who instituted the trial; to Dr. G. A. MacGregor, who investigated the first patient in hospital; and to Dr. J. L. Hunt, of British Drug Houses Ltd., who arranged the analysis of the "anahaemin."

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