RECENT DEVELOPMENTS IN SOME CHILDHOOD INFECTIONS.

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I have had the opportunity in recent years of witnessing the results of our increasing knowledge as it applies particularly to the field of disease in childhood. Inevitably enough, many of these advances are largely attributable to the introduction of sulphonamides and penicillin ; and the importance of these two agents are duly noted in this paper.

I have chosen three main topics which I have had every opportunity of studying closely, and have accordingly divided the paper into three sections.

The first section is an outline of my experience in the treatment of influenzal meningitis in children. A slightly shorter account of this work was first published by me in the "Clinical Reports of the Adelaide Children's Hospital (Number 1, Volume 1, May, 1947.)

The second section of the paper deals with three separate outbreaks of the skin infection known as "Kaposi's Varicelliform Eruption", with which I have been confronted, and describes the clinical features and virus aetiology.

The third section of the paper is an account of my experience in treating acute laryngo-tracheo-bronchitis during an epidemic in 1944. The substance of this was previously reported in the Medical Journal of Australia, in that year.

All the cases discussed in these three sections were under my personal supervision at the Adelaide Children's Hospital, and all work was my own unless otherwise indicated. The virus investigation in the second section was carried out for me by Miss Jessica Mawson and Mr. Eric French, of the Institute of Medical and Veterinary Science, Adelaide.

THE TREATMENT OF INFLUENZAL MENINGITIS.

Meningitis due to infection with the Haemophilus influenzae was until recently a most unhappy disease to treat. During the years from 1941 to 1943 (inclusive) in this hospital, the only benefit derived from establishing this diagnosis was the rather doubtful one of being able to give the parents an invariably hopeless prognosis. Nine children admitted to the wards in those years were proved to have influenzal meningitis. All received courses of sulphapyridine or sulphathiazole, without any response - a mortality of 100 per cent. Two children lingered on for over a month in a comatose state, a prolongation of dying which may have been attributable to a very slight effect of the drug on the germ. Of these children five were under 1 year in age, three were 13, 14, and 16 months, and the remaining child was 3½ years.

These results were in accord with the general experience in this disease as reported by various workers. Although Knouf, Mitchell and Hamilton (1), in a ten year survey which they published in 1942, had apparently cured nine out of twelve cases with sulphapyridine, this was not the usual result.

Davies (2), in 1943, reported twentyfour cases of the disease, twenty of which had been treated by either sulphanilamide, sulphapyridine, or sulphathiazole. The mortality in the children under 2 years of age was 100%. He quoted Aleman (3) who in 1940 had reviewed 90 cases which had been treated with the sulphonamides then available, and had concluded that these drugs had little if any favourable effect.

In 1942, Alexander, Ellis & Leidy (4) of the Department of Pediatrics, Columbia University, described their results in the treatment of Influenzal Meningitis by means of a specific antiserum prepared in rabbits against Haemophilus influenzae, combined with the administration of various sulphonamides. This paper is not available to me, but in 1943 Alexander (5) (6) summarized in two papers some of the experimental work on which this treatment was based, and her results in 75 cases. She said: "Four years ago at Babies Hospital there was adopted for treatment

of type b Haemophilus influenzae meningitis a combination of a sulphonamide compound with type specific rabbit serum. This decision was taken for the following reasons: The pioneer work of Pittman (7) had demonstrated a striking biologic similarity between the pneumococcus and Haemophilus influenzae, suggesting that in infection with the influenza bacillus, as well as with the pneumococcus, type- specific antibody is an essential part of the recovery mechanism.

The sulphonamide compound was used in addition to rabbit antibody on the grounds that the high fatality rate justified a combination of all potentially effective agents." She showed that sulphadiazine had a high protective capacity for mice against Haemophilus influenzae infection - as high, in fact, as the specific rabbit antibody - and when used together, this protection appeared to be enhanced.

In the 75 cases reported by her, there were 57 recoveries, 26 of them under 2 years of age. She urged that the antiserum be given intravenously.

Alexander's work thus indicated that the newly introduced sulphadiazine had a definite effect on Haemophilus influenzae both experimentally and clinically, and later in the same year Hall & Spink (8) showed that sulphamerazine, the methyl derivative of sulphadiazine, might also be useful. They reported 116 cases of a varied nature in which sulphamerazine had been used. Two infants suffering from Influenzal Meningitis, both under one year, had been treated with antiserum and this sulphonamide, with recovery.

In March 1944, Birdsong, Waddell & Whitehead (9) of the Department of Pediatrics, University of Virginia Hospital, reported the recovery of 7 out of 8 cases treated with a specific antiserum and sulphadiazine, along the lines laid down by Alexander et al. Only two of these children who recovered were under two years of age.

In April, 1944, Nicholson (1), from the Melbourne Children's Hospital published a report of 4 cases treated by the intravenous

administration of antiserum and an unspecified "sulphonamide," with two recoveries. In March 1945 Turner (11), from the same hospital, reported a further twenty cases of influenzal meningitis treated by the antiserum and either sulphadiazine or sulphapyridine, with ten recoveries. She also favoured the intravenous administration of the antiserum.

It is considered that the routine treatment for this disease which has been developed at the Adelaide Children's Hospital, under the personal supervision of myself, since 1944, although differing in some respects from the above is amply justified by the results as reported in this paper.

It is not the purpose of this paper to discuss the diagnosis of the disease. The main point to stress is that the Haemophilus influenzae is the commonest single cause of non-epidemic purulent meningitis in this hospital, and that in the absence of clinical criteria (such as petechiae) suggestive of other organisms, or laboratory facilities for immediate identification, any sick baby with purulent cerebrospinal fluid should be regarded as suffering from this disease, and treated by a comprehensive routine treatment as outlined below. It should be noted that the great majority of patients seen in this series with influenzal meningitis are under the age of 2 years. This fact, and the other remarks so far will savour strongly of the obvious to the pediatrician, but our experience would indicate that these points are still not sufficiently appreciated by many medical practitioners. Now that we have a very useful treatment for the disease it has become exceedingly important to receive the cases early. Lumbar puncture in a baby is a minor procedure very much more simple to perform than in the average adult. The standard technique at the Adelaide Children's Hospital for several years has been to sit the baby up leaning over a pillow, and to use for the puncture a serum needle (22 S.W.G.), preferably with a slightly shortened bevel and without a stillette. Not infrequently a diagnosis of meningitis has been established by a routine lumbar puncture in a sick baby who has no gross bulging of the fontanelle or neck rigidity, when

no other satisfactory cause for the illness or fever can be found on examination. Certainly, all babies admitted with convulsions who do not respond quickly to the usual measures or remain sick should be submitted to a lumbar puncture.

During the first half of 1944, only two cases of influenzal meningitis were treated in the Adelaide Children's Hospital, The first child was aged 4 years and was treated in another hospital for the first week, receiving 8 grammes sulphapyridine and 24 grammes sulphathiazole. Sulphathiazole was continued after admission here in a dose of 0.5 grammes four hourly for 17 more days. On the fourteenth day after admission Haemophilus influenzae reappeared in the cerebrospinal fluid, and when gross haematuria occurred on the seventeenth day, it was decided to change immediately to sulphadiazine. This was given in a dose of 0.75 grammes four hourly for a further 29 days, and was well tolerated. The sulphathiazole haematuria which was present when the sulphadiazine was commenced, rapidly cleared when the sulphathiazole was stopped, and the child made an uninterrupted recovery without sequelae.

The second child treated with sulphadiazine alone also recovered. This was an infant aged 8 months, who was admitted with a fractured skull and haematoma of the scalp which became infected. The organism in the pus from this haematoma was found to be Haemophilus influenzae, and a lumbar puncture revealed a purulent cerebrospinal fluid also containing the same organism. The haematoma was drained, and sulphadiazine commenced with an initial dose of 3 grammes, followed by 1 gramme six hourly. This was continued for 16 days, a total of 64 grammes being administered. She appeared well, but three days after discontinuing the drug her temperature rose to 104°, she commenced vomiting, and her neck stiffness returned. Sulphadiazine in the same dosage as before was recommenced and continued for 20 more days. She settled again rapidly, and was discharged well without any apparent sequelae.

Late in 1944 the specific Haemophilus influenzae antibacterial serum (prepared in rabbits) was made available to the hospital for

clinical investigation by courtesy of the Commonwealth Serum Laboratories. This serum was estimated by the manufacturers to contain not less than 1 mgm. of antibody nitrogen per c.c.

At that time there seemed to be no great unanimity as to dosage or route of administration, but most writers were agreed that the serum should be given in conjunction with sulphonamide therapy. By now sulphadiazine had become my sulphonamide of choice for most purposes, and these two cases described above (as well as the authorities quoted) were considered to indicate the possible advantages of this drug over previous sulpha drugs in Haemophilus influenzae infections also. The need for prolonged administration of the drug was also realised.

Accordingly the next five cases of influenzal meningitis were treated by the administration of the anti-influenzal rabbit serum intramuscularly in a total dosage of from 60 to 120 c.cs., usually in two or three injections, into the thighs, on the first two or three days after diagnosis; and sulphadiazine by mouth continuously for four weeks, in a gradually decreasing dosage. Only one urticarial reaction to the serum was observed (on the eighth day) although the thighs in the smaller infants inevitably became rather tense for a few days after the injection of such a large volume of fluid. No sulpha-sensitivities developed, although the white blood count usually dropped to 6,000 or less per cubic mm. as the acute stage passed, and remained constant in spite of continuation of the sulphadiazine. The infants' ages were 6½ months, 8 months, 11 months, 12 months, and 23 months, and confirmation of the identification of the organism as Haemophilus influenzae (Pittman Type b) was obtained by sending cultures to the Commonwealth Serum Laboratories. Striking improvement in the clinical condition and in the cerebrospinal fluid findings occurred in all five cases of this first series during the first week of treatment. No relapses occurred, and all five were discharged as completely cured after an average observation period of 10 days following the completion of the month's course of sulphadiazine.

Four of these children have had no further troubles referrable

to the meningitis, and have developed normally. The fifth child (aged 23 months at the time of her first attack) was well for 11 months after discharge when she developed meningitic signs again following a mild upper respiratory infection, and was readmitted with a second attack of influenzal meningitis. She was given a course of treatment similar to her first one, receiving 90 c.cs. of the specific antiserum (intramuscularly in two doses on the first and third days), and a total of 69.5 grammes of sulphadiazine spread over four weeks. She recovered completely, and has remained well for a further 11 months, without any sequelae.

Whether this was an example of a small loculus of infection remaining latent for 11 months during apparent good health, with a subsequent relapse, or whether it was a re-infection from without is a matter of opinion. In any case she responded to treatment just as promptly in the second attack as in the first.

The sixth case marked a slight turning point in my attitude to treatment. A child of 2 years was admitted to the hospital on 7/9/45 with purulent meningitis from which for several days no organism could be isolated. He, accordingly, was started on sulphadiazine orally in our usual dosage of 2.0 grammes, followed by 1.0 gramme six hourly, and penicillin 15,000 units intramuscularly three hourly, and intrathecally one dose of 15,000 units on each of the first two days. On the sixth day, when he was remarkably well clinically and his cerebrospinal fluid was macroscopically clear (containing only 48 cells /c.mm.) the bacteriologist at last succeeded in isolating Haemophilus influenzae from the fluid sent down on the first day. He was so well that it was resolved not to give him any specific anti-serum, but to continue with the sulphadiazine and penicillin. He made a complete recovery, and has remained well. Penicillin-sensitivity tests on the strain of organism isolated showed that growth of the organism in culture was inhibited by one drop of a five-unit/c.c. solution of penicillin (see appendix). It was at this time that penicillin-sensitive strains of the organism were reported by Forgacs, Hutchinson, and Rewell (12) and it was resolved to add penicillin to our armamentarium for our future attacks on the disease.

The next case was a female child aged 11 months who was admitted to the hospital on 28/10/45. Her cerebrospinal fluid was so purulent that it could be aspirated with a syringe through the lumbar puncture needle only with difficulty, and it clung to the sides of the test tube into which it was squirted, and had to be shaken down to the bottom. Penicillin in a dosage of 36,000 units in 5 c.cs. of physiological saline was injected intrathecally, and was also continued intramuscularly in a dosage of 20,000 units three hourly. The intrathecal injection was repeated on the four following days. A dose of 30 c.cs. of the anti-serum was injected on the first day intramuscularly and repeated the following day; and sulphadiazine was administered in an initial dose of 2 grammes, followed by 1 gramme six hourly for two weeks, and then reduced to 0.5 gramme for a further two weeks - a total of 84 grammes. Recovery was complete.

A similar routine using these three drugs - sulphadiazine, specific anti-serum, and penicillin - has also been employed in the last seven cases admitted during 1946. The patients' ages were 8 months, 4 months,2 months, 17 months, 13 months, 4 months, and 11 months. One other child, aged 15 months, who was treated for purulent meningitis by the same routine responded satisfactorily and is believed to have been a case of the influenzal type. However, as we were unsuccessful in isolating any organisms from the cerebrospinal fluid he is not included in the series of seven.

Five children out of these seven made satisfactory recoveries, and at the time of writing (February 1947), with one reservation, have no obvious sequelae. The reservation is one of the 4 months-old babies (case 13) in this group, who received a total of 90 c.cs of anti-serum into the thighs in three equal doses on the first, third, and fourth days of treatment; and sulphadiazine in a total dosage of 60 grammes in the first three weeks. Also, penicillin was given intrathecally in a dosage of 15,000, 30,000, 30,000, and 15,000 units once on each of four days early in the illness, as well as intramuscularly in the usual dosage of 15,000 units three hourly. In spite of all these therapeutic measures, her general condition deteriorated, and her meningitic signs returned

on the twenty-first day, with a re-appearance of the Haemophilus influenzae in the cerebrospinal fluid. She was given a further 60 c.cs. of anti-serum, several more daily intrathecal injections of penicillin, and the sulphadiazine by mouth was continued. In addition, penicillin intramuscularly was increased to 50,000 units three hourly. She slowly recovered, and was discharged 44 days after the relapse. Twenty c.cs. of air were injected intrathecally during this period, and the subsequent encephalogram showed dilated ventricles. Although she now seems alert and normal for her age (10 months) she is still not sitting unsupported, and her head circumference is 18 in. - an increase of 1½in. in four months. This is the only recovery about which I am doubtful of the ultimate result, and, as she had been ill for 10 days before specific treatment in hospital was commenced, it can be taken as support for my plea for earlier diagnosis.

Two more striking cases in support of this are the two outright failures in this series of seven treated by the combined use of serum, sulphadiazine, and penicillin. Of these two children, one was age 2 months, and was admitted after the illness had been in progress for 14 days. This child made no response to treatment, including penicillin intraventricularly, although growth of the organism cultured from the cerebrospinal fluid was inhibited by one drop of a five-units solution of penicillin on a chocolate-agar plate, and died with extensive hydrocephalus 28 days after admission.

The other child was aged 13 months and had been under treatment elsewhere without a definite diagnosis of the type of meningitis for two months. On admission she was found to have a left hemiplegia, and Haemophilus influenzae was isolated from the cerebrospinal fluid. She received in all 150 c.cs. antiserum, 56 grammes sulphadiazine, three doses of 20,000 units of penicillin intrathecally, and a total of 1,140,000 units intramuscularly. She went steadily downhill, and died 14 days after admission. At post-mortem her brain was extensively destroyed by hydrocephalus, and the right hemisphere was densely adherent to the overlying dura and skull. Haemohilus influenzae

was cultured from swabs of the ventricular and subarachnoid fluids. No ventricular punctures for penicillin injections were attempted, and would obviously not have helped.

DISCUSSION.

Seventeen cases of meningitis due to the Haemophilus influenzae (Pittman type b) have thus been treated in the three years 1944-1946, in 16 infants with 15 cures. There were two deaths, but one child was apparently cured twice.

SULPHADIAZINE.

The main factor in these good results is considered to be the use of sulphadiazine in full dosage for the first two weeks, and the continuation of the drug for at least a further two weeks in a reduced dosage. The course of this drug varied a little in detail from case to case, but was never less than a month in duration. The dosage was sometimes reduced after the first week from 1.0 gramme to 0,5 gramme six hourly, if the condition of the child was sufficiently encouraging, but no child received less than a total of 60 grammes, and one child received 99 grammes.

Routine white blood counts and microscopic examinations of the urine were carried out every other day after the first week, but no case of haematuria attributable to the sulphadiazine occurred, and no toxic blood effects were encountered to force us to discontinue sulpha-therapy. The W.B. C. count in one case fell to 4,800 /c. mm. on the thirteenth day of treatment, but the sulphadiazine was continued in spite of this. The W. B. C. rose next day to 5,300, and then to 7,600 four days later, without any untoward incidents.

ANTI-SERUM.

The second line of attack with the specific Haemophilus influenzae anti-serum (prepared in rabbits) is also considered to be of definite value, particularly in babies who were shown by Fothergill & Wright (13) to have no natural immune bodies against this organism between the ages of 2 months and 3 years.
It was used in 12 cases, and was always given intramuscularly. Although some workers favour giving some or all of the dose intravenously, I have been quite satisfied with the thigh injection, and was sometimes glad the veins had been saved for blood

transfusions which occasionally became necessary.

North, Wilson, and Anderson (14) in their analysis published from the Commonwealth Serum Laboratories, seemed to favour the intramuscular route also, although this conclusion is possibly based on figures that include some of our cases as we supplied reports on our use of the serum to them in our earlier cases. It was always administered over the first two or three days after diagnosis, in a dosage of from 60-120 c.cs. except in the one case already mentioned in which there was a clinical relapse and the organisms re-appeared in the cerebrospinal fluid on the twenty-first day, necessitating a further dose of 60 c.cs. of anti-serum; and also one other who received a further injection of 30 c.cs. on the eleventh day. The usual procedure was to give 30 or 60 c.cs. as an initial dose, either immediately if gram-negative bacilli were seen on a direct smear of the centrifuged cerebrospinal fluid deposit, or the next day when the culture result was known; and to repeat this over the next two days to a maximum of 120 c.cs. if the clinical condition did not show a definite improvement, or if the pus cells and organisms did not disappear promptly from the cerebrospinal fluid. It was not unusual for the cerebrospinal fluid to change from a grossly turbid to a macroscopically clear appearance in a few days (e.g. case 15: 25/11/46, 30,800 pus cells /c.mm. cerebrospinal fluid; 30/11/46, 210 pus cells /c.mm. cerebrospinal fluid).

In the last three cases the sugar content in the cerebrospinal fluid was estimated by the method of Alexander (5), and the serum dosage varied accordingly. If the sugar content of the cerebrospinal fluid is less than 15 mgms. per centum, 120 c.cs. of serum is given; if the sugar content is from 18-25 mgms. per centum, 90 c.cs. is given; if between 25-40 mgms. per centum, 60 c.cs. is given, and if over 40 mgms. per centum, 30 c.cs. is given. Urticarial reactions were infrequent and never alarming.

PENICILLIN.

As already mentioned, after we had discovered a penicillin-sensitive strain of the Haemophilus influenzae this possibility received confirmation in a published report elsewhere. Our use of

penicillin in treatment subsequently received further support in the laboratory report of Gordon and Zinnemann (15), and in a case report by McIntosh and Drysdale (16). Penicillin sensitivity tests were carried out as a routine on the strains of Haemophilus influenzae isolated in the last seven cases, and growth of the organism was found to be completely inhibited by one drop of a solution containing 5 units per ml in 4 cases, 10 units in two cases and 25 units in one case. These results, like those of North et al (17), suggest that penicillin could not be regarded as a complete substitute for other therapy.

The usual intrathecal dose varied from 15,000 - 45,000 units in 3-5 c.c. of physiological saline. This was given at least twice in the first two days of treatment, and usually several further injections were given during the first week or so when lumbar punctures were repeated to follow the response to treatment. Unfortunately the case records do not adequately record the number of such further intrathecal injections. The first injection was done as a routine through the original lumbar puncture when turbid fluid was found. It has been shown by Cairns, Duthie, Lewis, and Smith (18) (in a study on pneumococcal meningitis) that penicillin diffuses along the cerebrospinal pathways with great facility, often reaching the lateral ventricles from the lumbar region, and only in one forlorn case did we consider it necessary to attempt ventricular puncture.

Intrathecal penicillin has been shown to maintain a high concentration in the cerebrospinal fluid for 12 or more hours, and in view of the proven sensitivity of the organism in this series of cases, its use is considered justifiable. Although penicillin was also given intramuscularly in these seven cases, this is possibly not so necessary. It has always been accepted that penicillin does not normally pass into the cerebrospinal fluid through the healthy meninges in any great concentration, but some authorities have stated that in meningitis some penicillin injected intramuscularly did find its way through the choroidal plexus. This view has been challenged by Kinsman and

d'Alonzo (19) whose work in cerebrospinal fever suggests that after the initial septicaemic stage is past, penicillin by intrathecal administration might be adequate by itself. They failed to find any considerable concentration of the drug in the cerebrospinal fluid from intramuscular injection at all. This is in agreement with Smith, Duthie, and Cairns (20) who, in a further paper on pneumococcal meningitis, stressed the importance of intrathecal penicillin and the doubtful spinal fluid concentrations of the drug obtained by intramuscular injections. Nevertheless, even with the purer preparations of penicillin that were available in 1946, these workers still discouraged using a dose higher than 20,000 units intrathecally at any one time.

These views, however, are at variance with the attitude of Erickson, Masten, and Suckle (21) who adhere apparently to an American Army wartime directive in advocating considerable caution in administering penicillin intrathecally in the treatment of any meningitis for fear of adhesions, transverse myelopathies, etc., with the conclusion that intraspinal injections should be avoided as much as possible. With this we cannot agree.

We have exceeded 45,000 units in a single dose intrathecally in one case only (during the relapse in Case 13), and this child admittedly developed a urinary retention that required catheterization for three days. This was the only immediate ill effect seen in the whole series, and no late sequelae attributable to the intrathecal penicillin injections have been observed. Perhaps the purer penicillin now available (some of it is from 1,400 to 1,500 units per mgm.), and our adherence to physiological saline as the diluent, have been factors in this, although it must be confessed that the tonicity of various strengths of penicillin solutions is somewhat obscure, and will obviously vary with the impurities present as well. Asepsis, of course, is also rigidly observed.

Heparin (5,000 units) was injected intrathecally in four cases to minimise adhesion formation, but has been abandoned. Occasionally 5-10 c.cs. of air were injected intrathecally with the same intention. This, at least, is safe, although its effect is

doubtful.

We realize that when three substances are used to treat a disease, it is difficult to apportion the credit for the cure that is obtained. This may be unscientific, but in fighting influenzal meningitis in infants we intend to continue with any agent which has a reasonable justification and is found to be of use.

Zinnemann (22), in a review of twenty cases from various English hospitals (from whom he had been sent specimens of cerebrospinal fluid) strongly supported the combined use of sulphadiazine, penicillin, and specific antiserum. The English experience with the antiserum, however, appears to have been somewhat limited up to that time.

We have not yet used streptomycin in the treatment of influenzal meningitis. This newer antibiotic apparently is useful, but it has yet to be shown that it will improve on the results obtained in this series. Alexander, Leidy, Rake, and Donovick (23), in reviewing a series of 25 cases treated by streptomycin, concluded that the value of this drug is limited in severe cases, and suggest the use of all three agents - rabbit anti-serum, sulphadiazine, and streptomycin.

SUMMARY.

(1) Seventeen cases of purulent meningitis due to Haemophilus influenzae were treated at the Adelaide Children's Hospital in the three years 1944-46.

(2) Two of these cases were in the one child who had a second attack (or a recrudescence) 11 months after an apparently complete recovery.

(3) In these 17 cases (in 16 children) 15 recoveries were obtained and two deaths occurred.

(4) The two infants who died (aged 2 months and 13 months) had been severely ill for two weeks and two months respectively before specific treatment was instituted, and it is doubtful whether our therapy should be judged in these two cases.

(5) Of the 15 recoveries, two were attributable to sulphadiazine alone; in five cases sulphadiazine was combined with the

use of specific anti-serum; in one case sulphadiazine and penicillin were employed; and seven patients were treated with sulphadiazine, specific anti-serum, and penicillin. Thirteen of these cases were under the age of 2 years.

(6) One other case believed to be influenzal meningitis, and treated by these three agents recovered, but is not included in the figures because the organism was not isolated.

(7) The frequency of the disease in infants, and the importance of prolonging the administration of sulphadiazine for a period of approximately one month to minimize the risks of relapse, is stressed.

SUMMARIES OF CEREBROSPINAL FLUID FINDINGS AND TREATMENT.

CASE 1.

F.O'M., aged 4 years. Admitted 7/1/44 after treatment elsewhere with 8 grammes sulphapyridine and 24 grammes sulphathiazole. Sulphathiazole continued in Adelaide Children's Hospital until 24/1/44 when changed to sulphadiazine 4 grammes daily because of haematuria. Continued until 15/2/44. Total sulphadiazine dosage, 80 grammes.

c.s.f. (11/1/44): 51 cells /c.mm. (all pmns.). Protein, 35 mgms./100 c.cs. Sugar present (not estimated). Sterile.
(14/1/44): 2,000 cells /c.mm. (all pmns.). Protein, 60 mgms. No sugar detected. Sterile on culture.
(16/1/44): 110 cells /c.mm. No sugar detected. Sterile on culture.
(21/1/44): 1,700 cells /c.mm. (all pmns.). Protein, 95 mgms. /100 c.c. No sugar detected. Haemophilus influenzae on culture.
(9/2/44): 135 cells/ c.mm. (65 per cent lymphocytes). Sugar present. Protein normal. Sterile. Discharged well on 22/2/44.

CASE 2.

S.D.L., aged 8 months. Admitted 26/6/44. Fractured skull. Haemophilus influenzae infection of scalp haematoma drained surgically on 1/7/44. Lumbar puncture 12/7/44:

c.s.f. 210 cells /c.mm. (90 per cent polymorphs). Haemophilus influenzae on smear and culture. Protein, 40 mgms. /100 c.cs. Sugar not estimated.

TREATMENT: Sulphadiazine, 3 grammes, followed by 4 grammes daily; commenced 12/7/44, discontinued 28/7/44: total, 64 grammes. Recommenced 31/7/44; discontinued 20/8/44 - a further 52 grammes.

c.s.f. (24/7/44): 78 cells /c.mm. (all pmns.). Sterile Recovery complete. Discharged 5/9/44.

CASE 3.

J.B.G., aged 8 months. Admitted 31/10/44.

c.s.f. (31/10/44): Numerous pus cells. Haemophilus influenzae on smear and culture. Sugar not estimated.
(6/11/44): 175 cells /c.mm. Protein, 40 mgms. Sterile.
(8/11/44): 56 cells /c.mm. (all pmns.). Sterile.
(11/11/44): 280 cells/ c.mm. (all pmns.). Protein, 70 mgms. Sugar present. Sterile.
(30/11/44); 32 cells /c.mm. (70 per cent lymphocytes). Otherwise normal.

TREATMENT: Sulphadiazine, 2 grammes, followed by 4 grammes daily, commenced on admission.
(13/11/44): Reduced to 2 grammes daily.
(6/12/44): Discontinued. Total 99 grammes.
Specific anti-serum -
(2/11/44): 50 c.cs. intramuscularly.
(3/11/44): 40 c.cs. intramuscularly.
(4/11/44): 30 c.cs. intramuscularly.
Discharged well, 14/12/44. No sequelae.

CASE 4.
C.N., aged 1 year. Admitted 6/12/44 with pneumonia. Developed meningitis one week later.

c.s.f. (15/12/44): 1,100 cells /c.mm. Protein 40 mgms. Sugar present (not estimated quantitatively). Haemophilus influenzae on culture.
(16/12/44): 6,700 cells /c.mm. (98 per cent pmns.). Haemophilus influenzae on culture.
(21/12/44): 95 cells /c.mm. (64 per cent lymphocytes). Protein, 45 mgms. Sugar present. Sterile.
(11/1/45): 70 cells /c.mm. (96 per cent lymphocytes).
(26/1/45): 170 cells /c.mm. (54 per cent lymphocytes). Protein, 45 mgms. Sterile.

TREATMENT: (16/12/44): Sulphadiazine, 2 grammes at once, then 4 grammes daily.
(29/12/44): Reduced to 2 grammes daily.
(11/1/45): Discontinued. Total, 78 grammes.
Specific anti-serum -
(15/12/44): 60 c.cs. intramuscularly.
(16/12/44): 60 c.cs. intramuscularly.
Discharged well, 27/1/45, in spite of persistently raised cell count in c.s.f. No sequelae.

CASE 5.
J.C., aged 11 months. Admitted 10/3/45.

c.s.f. (10/3/45): 2,100 cells /c.mm. Protein 90 mgms. No sugar detected. Haemophilus influenzae on culture.
(13/3/45): 540 cells /c.mm. Protein, 70 mgms. Sugar present. Sterile.
(17/3/45): 102 cells /c.mm. Protein, 45 mgms. Sugar present. Sterile.
(3/4/45): 7 cells /c.mm.

TREATMENT: Sulphadiazine, 4 grammes daily for 11 days, then 2 grammes daily for three days, and finally 1 gramme for 17 days - a total of 67 grammes.
Specific anti-serum -
(10/3/45): 60 c.cs. intramuscularly.
(12/3/45): 30 c.cs. intramuscularly.
Mild serum rash appeared 18/3/45; lasted four days.
Discharged well, 17/4/45.

CASE 6.
D. T., aged 6½ months. Admitted 22/7/45.

c.s.f. (25/7/45): 1,020 cells /c.mm. Protein, 50 mgms. No sugar detected. Haemophilus influenzae on direct smear.
(27/7/45): 83 cells /c.mm.
(3/8/45): 36 cells /c.mm.

TREATMENT: Sulphadiazine, 4 grammes daily; later reduced - a total of 68.5 grammes being given.
Specific anti-serum -
(25/7/45): 60 c.cs. intramuscularly.
(26/7/45): 30 c.cs. intramuscularly.
Discharged cured, 6/9/45.

CASE 7.
A. McN., aged 1 year 11 months. Admitted 2/3/45.

c.s.f. (2/3/45): 15,000 cells /c.mm. Protein, 120 mgms. No sugar detected. Haemophilus influenzae on culture.
(7/3/45): 70 cells /c.mm. (55 per cent pmns.). Sterile.
(16/3/45): 40 cells /c.mm. (60 per cent lymphocytes), otherwise normal.
(31/3/45): Normal.

TREATMENT: Sulphadiazine 4 grammes daily for 14 days, then 0.5 gramme for 14 days; total, 64 grammes.
Specific anti-serum -
(3.3.45): 60 c.cs. intramuscularly.
(5/3/45): 30 c.cs. intramuscularly.
Discharged well, 8/4/45: (See also case 10).

CASE 8.
R.C., aged 2 years. Admitted 7/9/45.

c.s.f. (7/9/45): Numerous pus cells. Sugar present. Protein, 130 mgms. Sterile.
(8/9/45): Numerous pus cells. Haemophilus influenzae on culture (report received on 13/9/45). Growth of the organism was inhibited by a drop of a solution of penicillin containing 10 units per c.c. on the culture plate.
(13/9/45): 48 cells /c.mm. Protein, 45 mgms. Sterile.
(5/10/45): Normal.

TREATMENT:
(1) Sulphadiazine, 4 grammes daily, commenced on 7/9/45. Later reduced, finally discontinued on 5/10/45. Total dosage uncertain.
(2) Penicillin -
(a) Intrathecally, 15,000 units on 7/9/45; repeated on 8/9/45;
(b) intramuscularly, 15,000 units three-hourly to a total of 2,160,000 units.
Discharged on 18/10/45 cured.

CASE 9.
P.W., aged 11 months. Admitted 28/10/45.

c.s.f. (28/10/45): Thick pus. Haemophilus influenzae on culture
(29/10/45): 2,400 cells /c.mm. Protein 80 mgms. No sugar detected. Haemophilus influenzae on smear and culture.
(30/10/45): 470 cells /c.mm. Sterile.
(7/11/45): 60 cells /c.mm. Growth of the organism was inhibited by a five unit solution of penicillin on the culture plate.

TREATMENT:
(1) Sulphadiazine, 4 grammes daily for 13 days, followed by 2 grammes daily for 14 days.
(2) Specific anti-serum, 30 c.cs. intramuscularly (28/10/45). Repeated 30 c.cs. intramuscularly (29/10/45).
(3) Penicillin -
(a) intrathecally -
(28/10/45): 36,000 units.
(29/10/45): 40,000 units.
(b) intramuscularly -
20,000 units three-hourly until 5/10/45.
Discharged cured on 26/11/45.

CASE 10.
A. McN., aged 2 years 11 months. Admitted 7/3/46.
(See Case 7.).

c.s.f. (8/3/46): 3,300 cells /c.mm. Sugar not estimated. Haemophilus influenzae on culture.
(11/3/46): 85 cells /c.mm. Growth of the organism was inhibited by five units per c.c. penicillin.

TREATMENT:
(1) Sulphadiazine commenced, 7/3/46; discontinued, 8/4/46; total, 69.5 grammes.
(2) Specific anti-serum -
(8/3/46): 60 c.cs. intramuscularly.
(11/3/46): 30 c.cs. intramuscularly.
(3) Penicillin -
(a) intrathecally -
(8/3/46): 45,000 units
(9/3/46): 45,000 units
(11/3/46): 30,000 units
(b) intramuscularly -
20,000 units three-hourly for eight days.
Discharged cured on 17/4/46.

CASE 11.
S.F., aged 8 months. Admitted 27/6/46.

c.s.f. (28/6/46): 628 cells /c.mm. (92 per cent pmns.). Haemophilus influenzae on smear and culture.
(1/7/46): 142 cells /c.mm. Protein, 40 mgms. Sugar present (not estimated quantitatively). Haemophilus influenzae present on culture.
(5/7/46): 61 cells /c.mm. (76 per cent pmns.). Protein, 60 mgms. Sugar present. Sterile.
(11/7/46): Haemoglobin, 5.5 grammes. W.B.C., 11,300. Growth of the organism was inhibited by 25 units of penicillin.

TREATMENT:
(1) Sulphadiazine commenced 27/6/46, 4 grammes daily for 68 grammes, then 1.0 gramme daily for 6 grammes.
(2) Specific anti-serum -
(28/6/46): 60 c.cs. intramuscularly.
(2/7/46): 30 c.cs. intramuscularly.
(3) Penicillin -
(a) intrathecally -
(28/6/46): 30,000 units.
(1/7/46): 30,000 units.
(b) intramuscularly -
15,000 units three-hourly for 14 days.

(11/7/46): Blood transfusion (400 c.cs.).
Discharged cured on 31/7/46.

CASE 12.
T.F.G., aged 2 months. Admitted 12/7/46.

c.s.f. (12/7/46): Numerous pus cells. Haemophilus influenzae on smear and culture.
(18/7/46): 9,100 cells /c.mm. (mostly pmns.). Sugar not estimated. Sterile on culture. Growth of Haemophilus influenzae strain was inhibited by five units penicillin.
(26/7/46): From ventricular puncture (blood-stained). A few pus cells. Sterile.

TREATMENT: Sulphadiazine, 4 grammes daily, commenced 12/7/46. Total course not recorded.
Specific anti-serum -
(12/7/46): 60 c.cs. intramuscularly.
(13/7/46): 30 c.cs. intramuscularly.
Penicillin -
(a) intrathecally -
(12/7/46): 30,000 units.
(13/7/46): 20,000 units.
(14/7/46): 20,000 units.

(15/7/46): 20,000 units.
(16/7/46): 20,000 units.
(17/7/46): 20,000 units.

(b) intraventricularly -
(18/7/46): 20,000 units.
(27/7/46): 20,000 units.

Death, 9/8/46.

CASE 13.

D.D., aged 4 months. Admitted 5/8/46.

c.s.f. (6/8/46): 2,400 pus cells /c.mm. Haemophilus influenzae on smear and culture.
(8/8/46): 550 cells /c.mm. Sterile on culture. Sugar not estimated.
(16/8/46): 1,300 cells /c.mm. Sterile on culture.
(23/8/46): 20 cells /c.mm. (65 per cent lymphocytes).
(26/8/46): 805 cells /c.mm. Sugar, 10 mgm/100 c.cs. Haemophilus influenzae on culture.
(28/8/46): 5,000 cells /c.mm. Sterile on culture.
(29/8/46): 2,080 cells /c.mm. Sterile.
(3/9/46): 320 cells /c.mm. Sterile.
(3/10/46): 35 cells /c.mm. (40 per cent lymphocytes). Growth of the organism inhibited by five units of penicillin.

TREATMENT:

(1) Sulphadiazine, commenced 5/8/46, 2 grammes, followed by 4 grammes daily; total course, 94 grammes.

(2) Specific anti-serum -
(6/8/46): 30 c.cs. intramuscularly.
(8/8/46): 30 c.cs. intramuscularly.
(9/8/46): 30 c.cs. intramuscularly.
(26/8/46): 30 c.cs. intramuscularly.
(27/8/46): 30 c.cs. intramuscularly.

(3) Penicillin -

(a) intrathecally -
(7/8/46): 15,000 units.
(8/8/46): 30,000 units.
(11/8/46): 30,000 units.
(14/8/46): 15,000 units.
(16/8/46): 35,000 units.
(26/8/46): 45,000 units.
(28/8/46): 100,000 units.
(29/8/46): 100,000 units.
(3/9/46): 30,000 units.

(b) intramuscularly -
(5/8/46): 100,000 units daily in seven divided doses.
(27/8/46): Increased to 350,000 units daily.
(4/9/46): Discontinued. Total, 6,145,000 units.

(4) Other treatment:
(13/8/46): Haemoglobin, 4.3 grammes. Blood transfusion, 400 c.cs.
(29/8/46): Blood transfusion, 250 c.cs.
(6/9/46): 25 c.cs. air injected intrathecally. Skull x-ray showed dilated ventricles.

Discharged 11/10/46 apparently well.

In February, 1947 (aged 10 months), still not sitting unsupported, and widening fronto-parietal sutures.

CASE 14.

R.L.L., aged 1 year 1 month. Admitted 3/11/46.

c.s.f. (4/11/46): 700 pus cells /c.mm. Haemophilus influenzae on culture.
(5/11/46): 7,900 cells /c.mm. Sugar not estimated. Haemophilus influenzae on smear and culture.
(8/11/46): 1,010 cells /c.mm. Protein, 80 mgms./100 c.cs. Sugar, 10 mgms./100 c.cs. Haemophilus influenzae on culture.

(12/11/46): 6,900 cells /c.mm. Haemophilus influenzae on culture.
Growth of the organism inhibited by 10 units of penicillin.

TREATMENT:
(1) Sulphadiazine commenced 3/11/46; 2 grammes daily. Total, 28 grammes.
(2) Specific anti-serum -
(5/11/46): 30 c.cs. intramuscularly.
(6/11/46): 30 c.cs. intramuscularly.
(9/11/46): 90 c.cs. intramuscularly.
(3) Penicillin -
(a) intrathecally -
(3/11/46): 20,000 units.
(5/11/46): 20,000 units.
(8/11/46): 20,000 units.
(b) intramuscularly -
100,000 units daily. Total, 1,140,000 units.
Other treatment:
(9/11/46): Blood transfusion, 600 c.cs.
Died 17/11/46. Haemophilus influenzae still present in brain at P.M.

CASE 15.
R.W., aged 1 year 5 months. Admitted 24/11/46.

c.s.f. (25/11/46): 30,800 cells /c.mm. Protein 110 mgms. per cent Sugar, 13 mgms. per cent. Haemophilus influenzae on smear and culture.
(26/11/46): 11,500 cells /c.mm. Protein, 60 mgms.per cent. Sugar, 60 mgms. per cent. A few Haemophilus influenzae on culture.
(28/11/46): 930 cells /c.mm. Sugar, 58 mgms. per cent. Sterile on culture.
(30/11/46): 210 cells /c.mm. Sterile on culture.
(10/12/46): 20 cells /c.mm.
Growth of the organism inhibited by 10 units of penicillin.

TREATMENT:
(1) Sulphadiazine commenced 24/11/46, 2 grammes at once, followed by 4 grammes daily for nine days; then 2 grammes daily for 14 days. Total, 60 grammes.
(2) Specific anti-serum -
(25/11/46): 60 c.cs. intramuscularly.
(26/11/46): 60 c.cs. intramuscularly.

(3) Penicillin -
(a) intrathecally -
(25/11/46): 30,000 units.
(26/11/46): 30,000 units.
(b) intramuscularly -
200,000 units daily. Total, 710,000 units.
Diffuse maculo-papular rash on face and body appeared on 13/12/46. ? Drug rash.
Discharged well on 5/1/47.

CASE 16.
B.E., aged 4 months. Admitted 26/11/46.

c.s.f. (26/11/46): 2,300 cells /c.mm. Sugar, 15 mgms. per cent. Haemophilus influenzae on smear and culture.
(27/11/46): 14,500 cells /c.mm. Sugar, 25 mgms. per cent. Haemophilus influenzae on culture.
(28/11/46): 1,760 cells /c.mm. Sugar, 50 mgms. per cent. Haemophilus influenzae on culture.
(29/11/46): 1,060 cells /c.mm. Sterile on culture.
(4/12/46): 210 cells /c.mm. Sugar, 55 mgms. per cent. Sterile.
(5/12/46): 440 cells /c.mm.
(7/12/46): 850 cells /c.mm. Protein, 90 mgms. per cent.
(13/12/46): 43 cells /c.mm.

(19/12/46): 690 cells /c.mm. Protein, 120 mgms. per cent.
(20/12/46): 116 cells /c.mm. Protein, 70 mgms. per cent.
(4/1/47): 57 cells /c.mm. (mostly lymphocytes)

Growth of the organism was inhibited by five units of penicillin.

TREATMENT:

(1) Sulphadiazine (commenced 26/11/46), 2 grammes initially, followed by 4 grammes daily for seven days; then 2 grammes daily for three days; then 4 grammes daily for five days; then 2 grammes daily for 13 days. Total, 80 grammes.
(2) Specific anti-serum -
(26/11/46): 60 c.cs. intramuscularly.
(27/11/46): 60 c.cs. intramuscularly.
(7/12/46): 30 c.cs. intramuscularly.
(3) Penicillin -
(a) intrathecally -
(26/11/46): 30,000 units.
(27/11/46): 30,000 units.
(b) intramuscularly -
140,000 units for one day only.
(4) Other treatment -
(9/12/46): Blood transfusion 300 c.cs.

Discharged well, 4/1/47.

CASE 17.

D.B., aged 11 months. Admitted 26/11/46.

c.s.f. (27/11/46): 1,500 cells /c.mm. Sugar, 40 mgms. per cent. Haemophilus influenzae on smear and culture.
(28/11/46): 1,260 cells /c.mm. Sugar, 72 mgms. per cent. Haemophilus influenzae on culture.
(29/11/46): 186 cells /c.mm. Sterile on culture.
(3/12/46): 91 cells /c.mm. Sterile on culture.
(9/12/46): 32 cells /c.mm.

Growth of the organism was inhibited by five units of penicillin.

TREATMENT:

(1) Sulphadiazine (commenced 26/11/46), 2 grammes initially, followed by 4 grammes daily for five days; then 2 grammes daily for 22 days. Total, 64 grammes.
(2) Specific anti-serum -
(26/11/46): 60 c.cs. intramuscularly.
(3) Penicillin -
(a) intrathecally -
(27/11/46): 30,000 units.
(28/11/46): 30,000 units.
(29/11/46): 30,000 units.
(b) intramuscularly -
None.

Discharged well, 31/12/46.

APPENDIX:

(1) The Culture Medium for Haemophilus influenzae.

Yeast extract blood-agar plates are prepared by boiling 0.5 gramme amounts of Difco Yeast Extract in 10 mls. tubes of nutrient agar in a water bath for 5 minutes, allowing the tubes to cool to 75° C. and then adding 1 ml. defibrinated horse blood to each tube, mixing, and cooling to 45° C. and pouring into four-inch petri dishes

(2) Determination of Penicillin Sensitivity of Haemophilus influenzae.

The Haemophilus influenzae culture is spread over the surface

of 2 of the above plates which are each divided into six parts by cutting troughs in the agar approximately 2-3 mms. wide with a sterile scalpel. Dilutions of penicillin containing, 1, 2.5, 5, 10, 25, 50 and 100 units per ml. are prepared and one drop of each is added to one portion of the agar. At least one portion is left on each plate as a control of the growth of the organism.

The penicillin sensitivity is determined by observing the least amount of penicillin required to prevent the growth of the organism after 24 hours' incubation at 37° C.

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KAPOSI'S VARICELLIFORM ERUPTION.

The dangers of secondary bacterial invasion of the affected skin in infantile eczema has always been fully appreciated, but only comparatively recently has the fact been realized that probably a number of viruses constitute a similar menace.

Kaposi (1), in 1887, drew attention to a severe, generalized pock-like eruption occurring as a complication of infantile eczema.

Here is a translation of his description of the disease, from the 1887 edition of his book:

"I have seen in a few cases a very alarming complication of infantile eczema of the face. It consisted of flat or indented small bullae, the size of lentils or slightly larger, transparent and filled with clear serum, numerous in number, partly disseminated, but in the majority of cases arranged in heaps and groups. They appear like varicella efflorescences but they are certainly not varicella. The affected skin of the face, previously swollen by the eczema, appears now to be more intensively raised, even tense, although more oedematous than indurated. The small patients show a high fever of 40 C. and more, and are restless. The eruption appears very acutely, even overnight. In a great number of cases it often continues for 3 to 4 days, even for a week, and fresh crops may appear while the rash of the first days regresses, either by drying, or in most cases, by bursting and exposing the corium, or by crusting and dropping off. The largest and densest masses of these varicella-like vesicles are found on the skin previously affected by the eczema. Single groups and smaller ones appear also on the previously intact skin of the neighbourhood; on the forehead, the ears, in the region of the neck, and even on the shoulders and arms. None were observed further down.

The course of this remarkable affection has a good prognosis, usually concluding with the healing of the bullae, the bare patches being covered with fresh skin within 2 - 3 weeks, the fever also receding in step with this.

In many cases, areas of pigmentation or flat scars remained.

The pre-existing eczema only altered so much as the necessary local therapy influenced it. In a case of a 6 months old child I witnessed death with convulsions on the sixth day of the illness when the eruptions were everywhere in the process of healing and a complete scabbing had taken place.

I am in a dilemma as to what I should call this varicella - like exanthem so dangerously complicating the facial eczema of infants. It had never been seen in these parts by very experienced pediatricians, although I have seen it some ten times, and it was without hesitation considered by the pediatricians to be not varicella but a specific condition.

The most suitable name would be eczema herpetiforme. Still less am I able to say anything about the aetiology of it. Nevertheless, I cannot resist the thought that we are dealing with the effect of a local contagion, indeed, of a fungus, which has found a suitable medium on the epidermis that has been made receptive by the eczema; and the growth of the fungus causes the characteristic efflorescence, which, by its considerable extent, causes the dermatitis As the cases are all of so alarming a nature, there has been no opportunity until now to take suitable specimens for microscopic examination from the sick infants.

The alarming fever is not to be considered as an indication of a blood infection, but according to its entire behaviour definitely only the effect of the local dermatitis and it is proportional to the intensity and course of this."

A similar condition was subsequently described by Juliusberg (2) who commented on the similarity of the lesions to vaccination pustules, but the details of his description are not available to me. Since that time, it has become increasingly recognised that generalized vaccinia as a complication of vaccination is a hazard to which the eczematous patient is more prone than one with a healthy integument, and also may ensue if a recently vaccinated person comes in contact with such a susceptible person (3) (4). This danger does not lie only in actual direct contact, for the

vaccine virus has been demonstrated in the nasopharynx on the fourth and fifth days after vaccination (5), thus making droplet infection a possibility.

In 1935 an epidemic of Kaposi's Varicelliform eruption occurred amongst the skin cases in the Stobhill Hospital, Glasgow. In reporting the sixteen cases concerned in this outbreak, McLachlan & Gillespie (6) admitted that "the decided resemblance to varicella and variola suggested a virus infection," but the material they obtained for virus studies proved to be unsuitable. They found a mixed bacterial flora in their cases, with a non-haemolytic streptococcus always predominating. This latter organism they regarded as the possible causal agent.

In 1944, Wenner (7) reported a series of three cases of infantile eczema which conformed closely to Kaposi's description, and from these he succeeded in isolating a virus closely resembling, if not identical with, that of Herpes simplex. The infective agent obtained was capable of provoking encephalitis and kerato-conjunctivitis in rabbits; and immunological studies provided evidence of a serological relationship between the four strains isolated and a classical strain of Herpes simplex virus.

FIRST SERIES:

During November - December 1943, three children were seen in the wards of the Adelaide Children's Hospital with an unusual generalized skin eruption, associated with severe toxaemia.

CASE 1. The first case was a male baby, aged 6 months, who was admitted on 15/11/43, with a history of having suffered from infantile eczema "since birth," with some extension recently before admission. On examination there was a generalized involvement of the face and body with typical eczematous lesions, but one week after admission a secondary infective process was noted on the face. The new lesions started as vesicles 1 - 2 mms. in diameter; these became pustules and then either crusts or ulcers. This process spread rapidly, involving most of the eczematous skin. The ulcers when close together coalesced to leave wide areas denuded of the epidermis. Swabs of the lesions yielded a growth of Staphylococcus aureus on ordinary culture. The child was severely ill during this time,

the temperature gradually rising during the first week until, in the second week, it swung from 101° F. to 105°F. each day. The baby's weight dropped in two weeks from 17 lbs 12ozs to 15 lbs 9 ozs.

A white blood cell count on 29/11/43 was 25000 /c. mm. the differential count being:

polymorphs (segmented)	48%
polymorphs (nonsegmented)	17%
myelocytes	3%
lymphocytes	27%
monocytes	5%

Death ensued on 2/12/43. A post-mortem examination revealed non-specific toxic changes in the spleen, liver and kidney. There was pus in the right mastoid. No virus investigation was carried out, but in retrospect the probable nature of the infection was realized; the opportunity to prove this in another case came shortly afterwards.

CASE 2. The second case was a female baby, aged 5 months, who was admitted to hospital on 11/12/43. There was a history of a rash that had first appeared eight weeks previously, and this was rapidly getting worse. On admission the head and limbs were extensively involved with weeping ulcers and crusts. The ulcers were small areas of epidermal destruction approximately 2 mms. in diameter, giving a punched-out appearance.

On 15/12/43, four days after admission, a new crop of small vesicles and pustules began to appear over the affected areas, and these rapidly broke down into ulcers, which, as in the previous case, in places became confluent, with wide loss of epidermis as a result. The white blood cell count at this time was 7,300 /c.mm. of which 50% were polymorphs, and 47% lymphocytes.

Sulphathiazole by mouth in a dosage of 0.25 grammes 4 hourly was commenced on 12/12/43 and discontinued on 16/12/43 after a total of 6.25 grammes had been administered without any obvious effect on the course of the disease. The temperature was sustained in the region of 102° F. until two days before death when it became sub-normal. Death occurred on 20/12/43. Ordinary cultures of the skin lesions in life yielded a growth of Staphylococcus aureus and Streptococcus pneumoniae. At post-mortem, again no specific

visceral lesions were found, but in this case swabs of the lesions were taken for virus investigation five days before death.

VIRUS INVESTIGATION: Swabs of the vesicles were taken on 15/12/43 and extracted with saline. This saline extract was filtered under positive pressure through a "Gradocol" membrane of average pore diameter of 600 millimicrons. The filtrate, which was sterile on bacteriological culture medium, was inoculated onto the chorio-allantoic membrane of 9- to 11-day-old chick embryos. After 5 days' incubation at 35° C. the chorio-allantoic membranes were removed aseptically, and found to have gross lesions typical of Herpes simplex (8) (see appendix). The virus was readily propagated by serial passage on the chorio-allantoic membrane, and infected membranes were used to infect mice and rabbits in an effort to establish the virus in these animals. After some little trouble, the virus was adapted to mouse and rabbit brains, where it produced a fatal encephalitis. Histologically, many of the nerve cells of the affected rabbits and mice contained eosinophilic intranuclear inclusions readily seen in paraffin sections stained with haematoxylin and eosin. A kerato-conjunctivitis was produced in rabbits by inoculating the scarified cornea with a suspension of the virus. The cells of the substantia propria were seen to contain eosinophilic intranuclear inclusions when stained by haemotoxylin and eosin. (See Appendix II, figures 1 and 2).

Similar lesions were produced by a strain of Herpes Simplex virus.

The serological relationship of the virus isolated from this case to Herpes simplex virus was investigated as follows:

Rabbits were immunized by intradermal, subcutaneous, and finally intramuscular injections of infected rabbit-brain suspensions of each of the two viruses. A virus neutralization test on the chorio-allantoic membrane using Burnet's technique (8) then gave the following results:

A suspension of the patient's virus when mixed with normal rabbit serum and titrated on the chorio-allantoic membrane produced 24,000 foci per ml. of suspension. When mixed with homologous

antiserum produced in a rabbit, the foci were reduced to 78 per ml. This represents a reduction of 99.68% due to the antiserum. An anti-Herpes serum reduced the foci from 24,000 to 30 per ml. of suspension representing a reduction of 99.86%.

CASE 3. The third patient case in this first series was a girl aged three years who was admitted to hospital on 6/12/43 with a history of dermatitis for the previous three months, affecting the head, face and groins, and lately becoming worse. Her scalp was covered with thick yellow crusts, and there was an erythemato-squamous eruption involving the whole of the body which was considered to be toxic in origin. Her condition remained unchanged for the first two weeks when her temperature suddenly commenced a daily swing from 100°F. to 104°F. and she became obviously ill (see appendix II, figure 3). The scalp condition during this time had been treated with applications of ammoniated mercury ointment and had not improved; it now was observed to have under the crusts a number of shallow, punched-out ulcers, which also extended down the face. A few vesicles and pocks appeared on the abdomen but death occurred on 26/12/43 before these had become extensive. A white blood count on 21/12/43 was 12,200 /c.mm. (91% polymorphs). Cultures of swabs of the ulcers on the abdomen and head were taken on 24/12/43 and yielded Staphylococcus aureus. Blood culture on the same day also produced a growth of the same organism.

No post-mortem examination was obtained. It is possible that the infecting agent present in the skin of the second child was transferred to this third case by cross infection as both children cases were present in the ward at the same time.

VIRUS INVESTIGATION: Swabs from the vesicles of this patient were treated in a manner similar to that described above. The virus was readily established on the chorio-allantoic membranes of chick embryos, and from here adapted to mouse and rabbit brains. It produced a kerato-conjunctivitis, and typical encephalitis with eosinophilic intranuclear inclusions in rabbits.

The virus was titrated with anti-Herpes serum on the chorio-allantoic membrane as above. This serum reduced the pock count by 99.6%. The antiserum prepared against the virus isolated in Case 2 reduced the pock count under similar conditions by 99.1%.

These results reveal a close immunological relationship between the viruses isolated from these two patients and that of Herpes simplex.

The lesions in the three cases in this first series were strikingly similar. A herpes-like virus was isolated from two of them. Although no claims can be made, it is reasonable to assume on clinical grounds a virus aetiology in the first case also.
No further cases were seen for three years, and, in the meantime, Wenner's work, which confirmed our findings, was published.
It was thought (and hoped) that such an apparently rare disease was not likely to be seen here again for a long time, if at all.
However, during the months of October - November 1946, five babies under treatment in the ward for infantile eczema developed the typical pock-like lesions as manifested in the small 1943 series, with evidence of a severe toxaemia. Three of these children died in spite of penicillin therapy. Virus investigations instituted on one of these cases showed that a filterable infective agent was present in the vesicles in that child.

SECOND SERIES:

CASE 1. The first child in this second series to contract the infection was a baby girl, aged 6 months, who was admitted to the hospital on 5/9/46 for treatment to eczema involving the scalp, face, neck, trunk and limbs. Her progress was typically slow for a month, but on 4/10/46 her temperature commenced to swing, reaching 104°F at nights, and she became severely ill (see appendix II, figure 4). Her face was raw and crusted, but for a while, diagnostic endeavours were concentrated on finding other causes for the fever. General examination was negative, chest X-ray (10/10/46) revealed no abnormality; the urine contained no cells or organisms; and the blood examination showed a haemaglobin value of 9.5 grammes % and

19,000 white blood cells /c. mm (66% polymorphonuclears).

Her condition remained unimproved for the next month. The temperature continued to swing to 104°F. or more each day, and her white blood count rose to 44,800 /c.mm on 26/10/46. Staphylococcus aureus was isolated on culture from the eyes, ears, nose, throat and faeces on 17/10/46, and the growth of this strain of Staphylococcus was only partially inhibited by the addition to the culture of one drop of penicillin solution containing 100 units per c.c., and not at all by weaker solutions. In spite of this, penicillin therapy was commenced on 11/10/46 in a dosage of 20,000 units intramuscularly every three hours, and continued until 27/10/46 when the dosage was changed to 200,000 units every eight hours. The patient remained in a prostrated state throughout this period, merely rallying occasionally for a day or so. Intravenous saline was commenced on 30/10/46 and 200 cc of blood was also given by transfusion. Several short courses of Sulphadiazine by mouth were also given during this month. The skin of the face during this time was weeping serum and oozing blood from various areas, the whole visage being a more or less continuous superficial ulceration, extending from the scalp down to the neck, and involving the ears. Death occurred on 5/11/46 from bilateral broncho-pneumonia and mastoiditis when the skin lesions actually appeared to be improving. No virus investigation was instituted until after death, and the rather unsatisfactory material obtained then gave negative results. However, in the early stages when her illness was following this stormy and somewhat mysterious course, four other children were admitted to the same ward suffering from infantile eczema, and contracted severe secondary infections on their skins.

CASE 2. The first of these victims was a sixteen-months-old boy who had had typical infantile eczema since three months of age. He was admitted on 14/10/46 with excoriated areas of dermatitis on the face, scalp, arms and legs. His progress was uneventful until 18/10/46 when his temperature rose to 102° F. The following evening it was 103°F, and 105.6°F. the next. The rash on the face and knees was obviously inflamed, and small vesicles which burst

to leave small ulcers began to appear on the face and limbs on 25/10/46. He was now severely ill, with a daily temperature swing from normal to 102°F. and marked prostration. The vesicular eruption continued to extend along all limbs, with a few spots also on the trunk. At this time (28/10/46) scrapings of unbroken vesicles including both the skin and the underlying exudate were taken for virus investigation; and, as some of the vesicles appeared slightly umbilicated, a small blood transfusion with blood from a person recently vaccinated with vaccinia was given. Although there was no reason to believe that any person with an open vaccinia pock was in contact with the child, the possibility of a generalized vaccinia was considered, and the lesions were treated with local applications of potassium permanganate solution. Sulphadiazine by mouth was commenced on 21/10/46 and discontinued on 3/11/46, a total dosage of 28 grammes being administered; and penicillin intramuscularly was commenced on 22/10/46 in a dosage of 200,000 units six hourly. This was also discontinued on 3/11/46, after a total dosage of 6,490,000 units.

The boy's general condition improved steadily, and the ulcers gradually healed. On 11/11/46, he was largely back to his original condition of widespread eczema without complications.

Staphylococcus aureus was cultured by ordinary bacteriological methods from the skin, eye, ear, nose and throat at the commencement of the acute stage. The white blood count on 29/10/46 was 31,000 /c.mm. (polymorphs 59%, eosinophils 1%, lymphocytes 34%, monocytes 6%). On 4/11/46, this had dropped to 11,000 /c.mm; and the temperature on the same date was normal.

He has been seen on a number of occasions since this illness; he still has widespread eczema resistant to all treatment, but has had no recurrence of this pock-like eruption.

VIRUS INVESTIGATION: Fresh vesicle fluid was obtained on swabs during the evening of 28/10/46 and placed in a - 15° C refrigerator until the following day. The material was then filtered as described above, and inoculated onto the scarified cornea of a rabbit and the chorio-allantoic membrane of chick embryos. The

rabbit developed a kerato-conjunctivitis and the egg membranes were thickened. On serial passage of the egg membranes well defined lesions similar to those produced by Herpes virus were obtained. On inoculation of this egg material intracerebrally into two rabbits, a fatal encephalitis, histologically showing eosinophilic intranuclear inclusions in the nerve cells, ensued.

Another rabbit receiving the same material onto the scarified cornea developed in three days a kerato-conjunctivitis, showing eosinophilic intranuclear inclusions in the cells of the substantia propria. Both the brain and corneal lesions were similar to those produced by the virus from cases 2 and 3, Series 1, and by Herpes simplex virus.

CASE 3. The day after this boy was admitted to hospital, the third child of this second series, a baby boy aged six months, was admitted (on 15/10/46) to the same ward for treatment to a dermatitis affecting the face (the skin of which was "weeping"), the limbs, and to a lesser extent the trunk. This child became severely ill on 22/10/46, eight days after admission, with a sudden onset of the swinging temperature which we had learnt to dread, and with the rapid onset of vesicles and subsequent pocks. Many of the ulcerations coalesced. In this manner the face was soon largely denuded of its superficial epithelium, a destructive process which also involved the scalp, especially over the occipital region. Punched-out areas were also formed on the arms and chest, varying in size from a few millimetres up to several centimetres in diameter. These are well shown in the photographs taken immediately after the child's death on 5/11/46 (see appendix II, figures 5, 6 and 7). Attempts to find virus in the ulcers or brain at this stage were unsuccessful.

A small blood transfusion on 29/10/46, and a course of penicillin (200,000 units six hourly) had failed to influence the downward course of the disease.

CASE 4. The fourth child of the series was another six months old boy who was admitted on 18/10/46 suffering from mild infantile eczema of three months duration. Most of the body was affected

with a mild squamous dermatitis, with weeping areas on the legs, and right cheek. This child's temperature commenced to swing from normal to 101°F each night on 22/10/46, and a few vesicles followed by pocks appeared around the knees. Severe vomiting with diarrhoea commenced on 26/10/46, and the child died comparatively suddenly on 27/10/46. Attempts to isolate the virus from the skin and brain of this child at post-mortem were unsuccessful.

CASE 5. The fifth child, aged 18 months, was admitted to the ward on 9/10/46 with a longstanding eczematous eruption involving the legs and abdomen. His condition remained unchanged until 15/10/46 when his temperature commenced with characteristic abruptness to swing from 99°F to 104° F each day, and the affected areas were seen to be complicated with a number of the typical small pustules and pocks. A strain of Staphylococcus aureus was isolated from the pustules by ordinary bacteriological culture.

Sulphadiazine was administered for nineteen days (in a total dosage of 34.5 grammes) and penicillin intramuscularly for ten days (in a total dosage of 3,870,000 units). The temperature continued to swing for nine days, and then returned to normal on 24/10/46 (see appendix II, figure 8). The secondary skin infection improved rapidly during this time, and the child was discharged on 15/11/46 in good general health, with the dermatitis in a quiet phase.

We were thus confronted in this series with an epidemic involving all five eczematous children who were in the ward at the same time. The lesions varied in severity in the different cases but were strikingly similar in three, from one of whom a herpes-like virus was isolated. Although it is realized that no definite claim can be made about a common aetiology, it is considered strong presumptive evidence when, in the presence of an epidemic of clinically similar cases, an infective agent is isolated from one typical case. The isolation of a virus from this one case was probably due to the fact that the material for this work was obtained from fresh unbroken vesicles. The attempt was made in three other cases at post-mortem when only dry ulcers remained, but it was not surprising to us when no satisfactory results were obtained.

THIRD SERIES:

The third series consisted (no doubt significantly) of only one case. This was a baby girl, aged five months, who was admitted to the dermatology ward on 15/1/47 with a history of widespread eczema since she was six weeks of age, which had recently become acutely complicated by small pustules affecting to a gross extent the four limbs, and to a lesser extent the face and trunk. She was very irritable and toxaemic, her temperature being sustained between 102°F and 104° F for the first four days (see appendix II, figure 9). The photographs show graphically the nature of the eruption (see figures 10 and 11).

It was immediately recognised as a typical Kaposi's eruption and the patient was isolated in a room by herself at some distance from the ward where other eczematous children were being nursed. As previous experience had indicated the prevalence of the Staphylococcus aureus as a concomitant invader, penicillin cream was applied to the local lesions, and penicillin in a dosage of 15,000 units every three hours intramuscularly was commenced. The skin steadily improved, and the baby's general condition closely paralleled this. The temperature was normal on the seventh day (21/1/47), and remained normal thereafter, whilst the secondary infection was largely healed by 28/1/47. Material from fresh vesicles was taken on 16/1/47 for Virus investigation.

VIRUS INVESTIGATION:

Swabs from vesicles were collected on 16/1/47, treated as before, and inoculated onto the chorio-allantoic membrane of developing chick embryos. Well defined lesions similar to those produced by Herpes simplex virus were obtained, and one of the infected membranes was used to inoculate two rabbits intracerebrally. Both rabbits suffered a fatal encephalitis, and histologically eosinophilic intranuclear inclusions were found in the nerve cells. These inclusions were identical with those seen in the rabbits' brains infected by the viruses isolated from cases 2 and 3 (first series), and by the virus of herpes simplex. The virus of this third series is being further investigated to ascertain its serological relationship to Herpes simplex virus, and the three previously isolated viruses.

It is considered almost certain that a further epidemic of Kaposi's varicelliform eruption would have broken out amongst the other eczematous babies if this child had been allowed to remain in the dermatological ward. Early recognition and isolation from other "skin babies" of such a case is imperative.

The lesson of these three "series," however, has wider applications than this. It would appear that a virus which, in its ability to produce typical corneal and encephalitic lesions in rabbits closely resembles that of classical herpes simplex, is capable of causing a severe generalized pock-like eruption on the "prepared" skin of infantile eczema. From this it is reasonable to assert that people suffering from the typical vesicles of herpes simplex on the lips during an attack of coryza, etc. must be rigidly excluded from contact with such children. Secondary bacterial invasion no doubt contributes to the clinical picture, but it is considered that the primary and most important factor is the virus infection.

Treatment of the condition with penicillin and Sulphadiazine probably influences the course of the disease to a certain extent, by controlling this secondary bacterial infection. Staphylococcus aureus was isolated from the blood in the third case of the first series, and perhaps, if penicillin had been available to us in 1943, the outcome in that case may have been different. However, death can still occur in spite of the administration of penicillin, as was seen in three cases in the 1946 series. Nevertheless, it is considered that this drug offers the most hope of preventing an overwhelming bacterial infection whilst the body defences are being mobilized against the virus, and it should be administered as soon as the condition is recognized. A small blood transfusion from a donor who has suffered from Herpes simplex should also be considered.

In view of the doubtful outcome of treatment in the established disease, the prevention of its occurrence as stressed above must be the aim.

As far as can be ascertained, no member of the nursing staff in the ward was suffering from a herpes sore around the mouth at

the commencement of the 1946 epidemic. No check on this point, however, could be made in regard to visitors to the ward at this time.

According to Burnet (9) the herpes simplex virus becomes parasitic in the human individual usually in the early years of life. The incidence of infection in the community varies with the degree of hygiene exhibited in the individual's environment: in the poorer classes there may be nearly 100% incidence. When the child is first infected, a stomatitis may be produced, or the local lesions around the lips may be predominant. Thereafter the virus lives in the cells of the epidermis around the nose and mouth, only multiplying sufficiently to maintain itself as one skin cell replaces another. When the skin of this area is traumatized by an upper respiratory infection (or even by exposure to the sun or cold) the virus is enabled to multiply and produce the typical vesicular lesions around the nostrils and lips. At this stage the virus may be spread from person to person.

As the child is born free from infection with the virus, the first contact with the agent may produce a sharp reaction. The stomatitis may be quite severe; and this paper indicates that, should a child be eczematous, the virus at this critical time can invade the entire skin surface so affected. The interesting question arises as to whether in such a case the virus can continue to survive in the epidermal cells of the entire integument. This at the moment cannot be answered.

SUMMARY:

(1) Nine cases of Kaposi's Varicelliform Eruption, occurring in three series are described.

(2) Virus resembling that of classical herpes simplex was isolated from four cases.

(3) The dangers of this complication in Infantile Eczema, and the desirability of prevention, is stressed.

(4) It is believed that this is the first report of this disease in Australia; and the second occasion in which a herpes-like virus has been isolated from such an eruption in the English-speaking world.

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(8) W.B. BEVERIDGE & F.M. BURNET: "The Cultivation of Viruses and Rickettsiae in the Chick Embryo," M.R.C. Special Report, series 256, His Majesty's Stationery Office 1946, page 45-6.

(9) F.M. BURNET: "Epidemiology Today," Medical Journal of Australia, vol. 2, 1946, page 825.

APPENDIX I :

Extract from M. R. C. Special Report Series No. 256:

"The Cultivation of Viruses and Rickettsiae in the Chick Embryo," by W. I. B. Beveridge and F. M. Burnet, page 45.

D. - HERPES SIMPLEX.

1. Chorio-allantoic inoculation. Cultivation on the chorio-allantois has been used by a number of workers in the study of virus of herpes simplex (Saddington, 1932; Dawson, 1933; Shaffer and Enders, 1939; Anderson, 1940). According to Shaffer and Enders (1939), macroscopic lesions are developed if embryos are inoculated on the chorio-allantois at any time between the 9th and 17th days of incubation. In younger embryos, only insignificant lesions develop, and in older ones lesions fail to appear, probably because of the physiological atrophy of the chorio-allantois which sets in during the last stages of incubation. Twelve or thirteen-day

embryos provide the most satisfactory condition for general work.

Most workers have used the strain H. F., and in our experience this produces larger foci than most strains freshly isolated from human lesions. The foci are of typical proliferative necrotic structure, and as the strain becomes adapted by passage their average diameter increases and a central necrotic crater becomes more evident. Microscopically, well developed lesions show extensive necrosis of proliferated epithelium and marked accumulation of inflammatory cells in the mesoderm. Specific nuclear changes can nearly always be seen in the less severely damaged ectodermal cells. They rarely show a close resemblance to the classical changes seen in sections of the infected rabbit cornea. The commonest form is an enlargement of the nucleus with margination of the chromatin, the centre being occupied by lightly-staining acidophil material usually containing a few large vacuoles and sometimes fragments of chromatin (Burnet et al., 1939).

Herpes virus is particularly well adapted for chorio-allantoic titration, and for immunological work the method is more convenient than any current alternative.

Photomicrograph showing a section at the edge of a pock on the chorio-allantois of a chick embryo inoculated with virus from Case II, Series I. The ectodermal cell nucleus indicated is swollen, with margination of the chromatin. The central pale area was eosinophilic when stained with Giemsa.

APPENDIX II.

FIGURE I. A typical virus-infected nerve cell in the rabbit's brain showing margination of the chromatin and a large inclusion after intra-cerebral inoculation with the material. With haematoxylin and eosin staining, the inclusion is eosinophilic.

FIGURE II. Section showing the substantia propia of an infected rabbit cornea. Several cells show granule formation in the nucleus. The nucleus of some cells is entirely replaced by granules, which, with haemotoxylin and eosin staining, are eosinophilic.

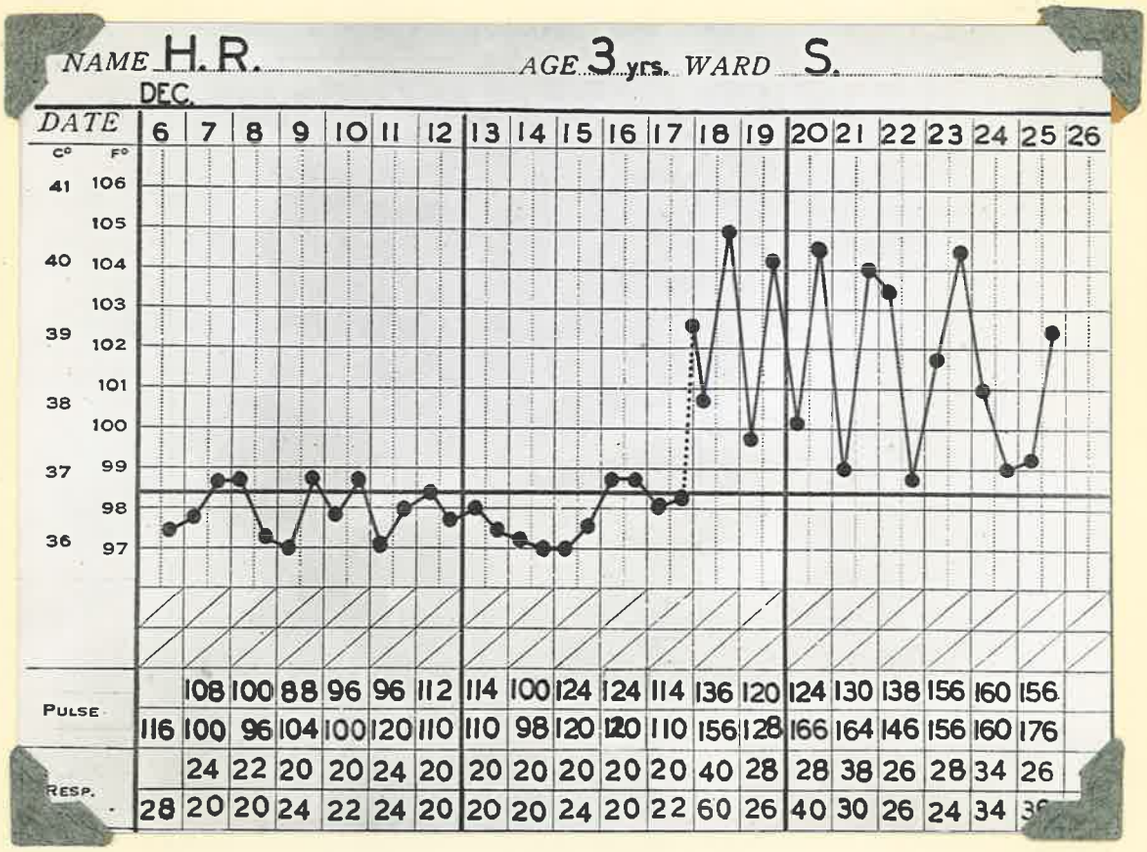
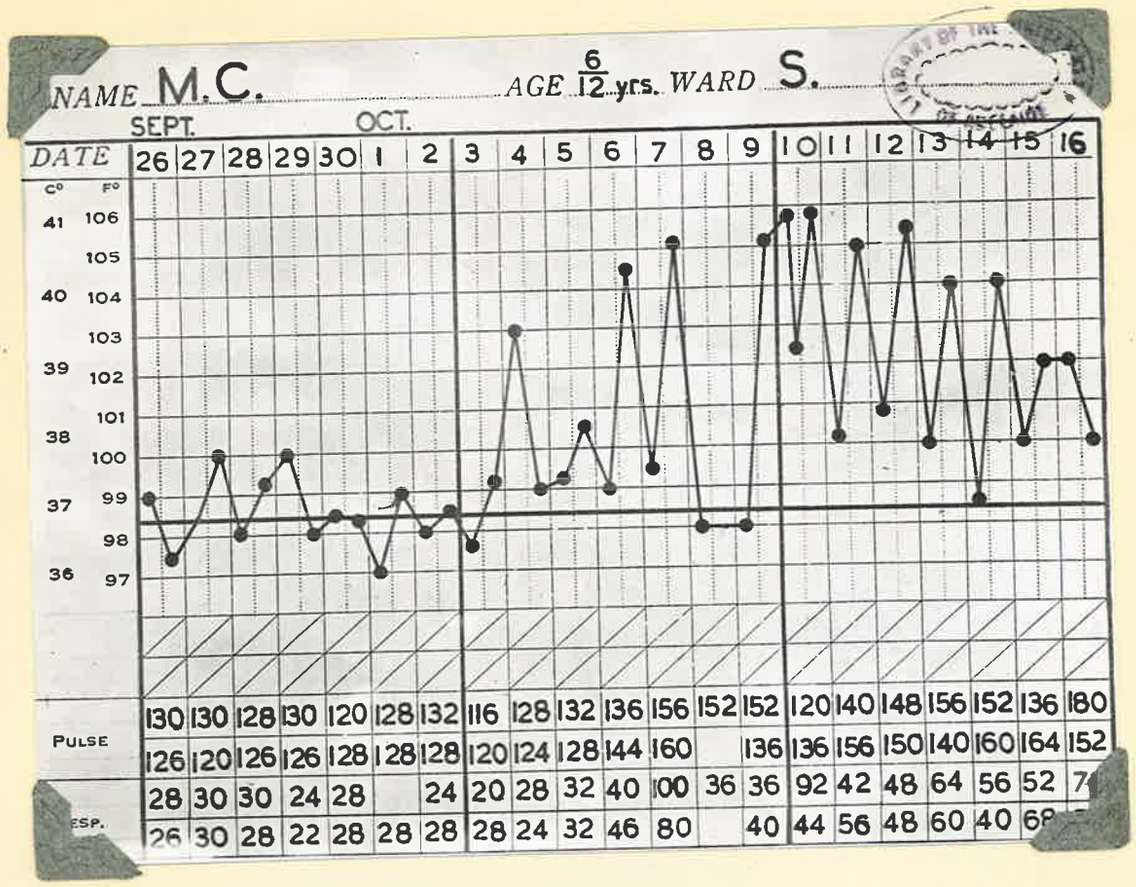


FIGURE III.

Temperature chart of Case III, Series I, who died on 25/12/43.



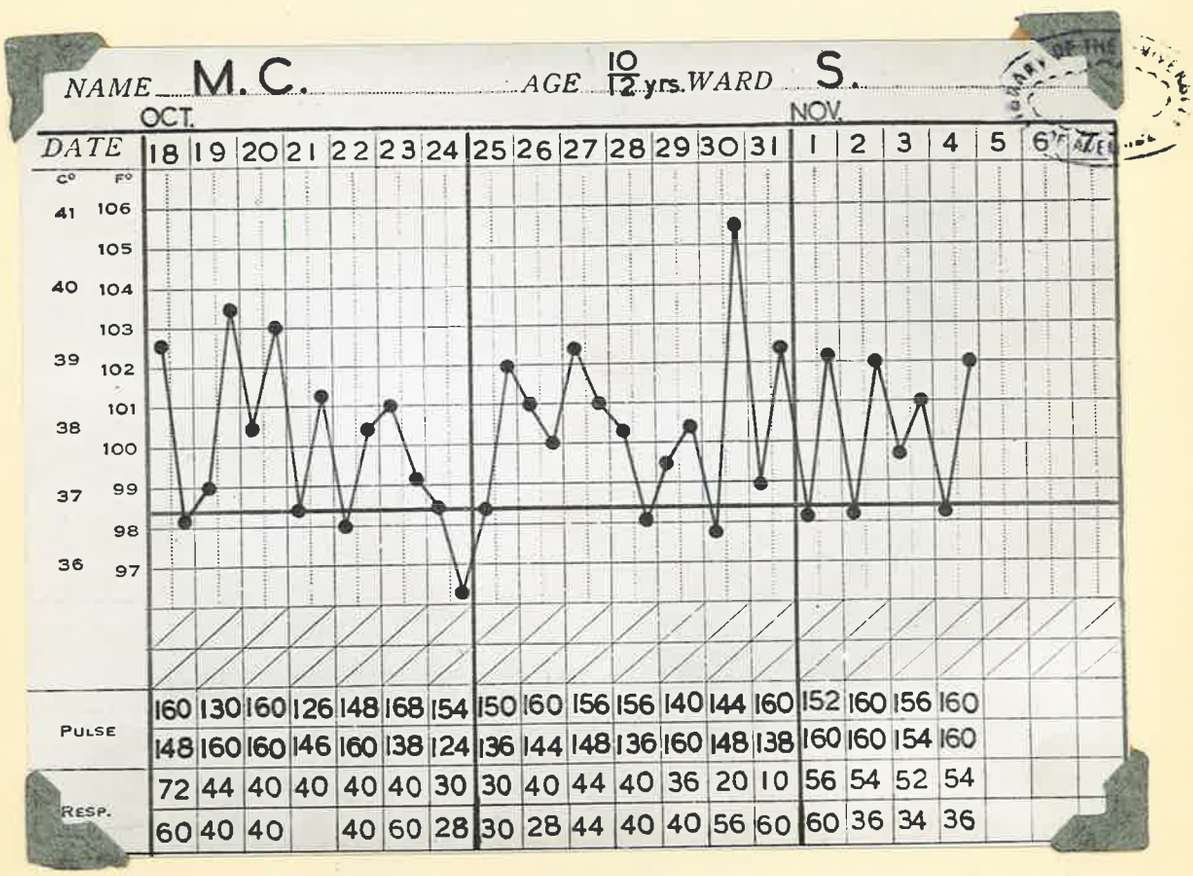
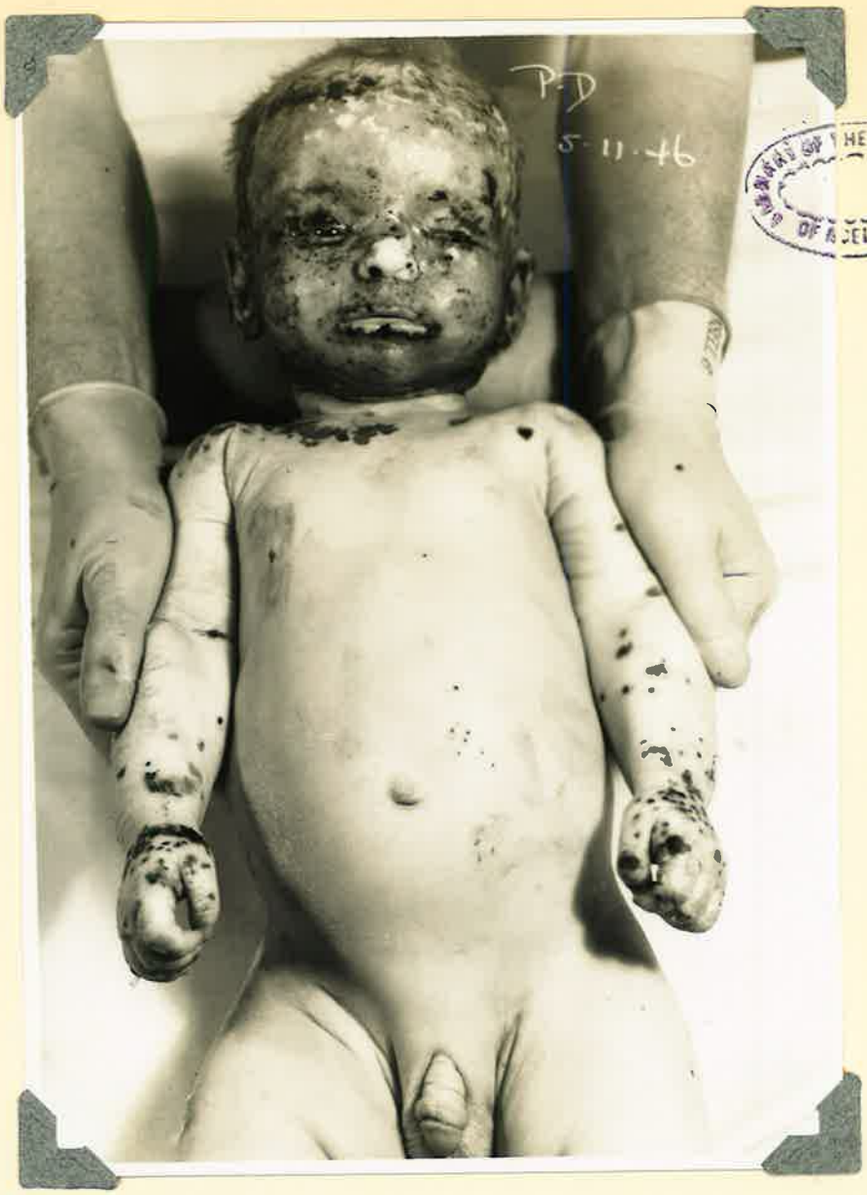
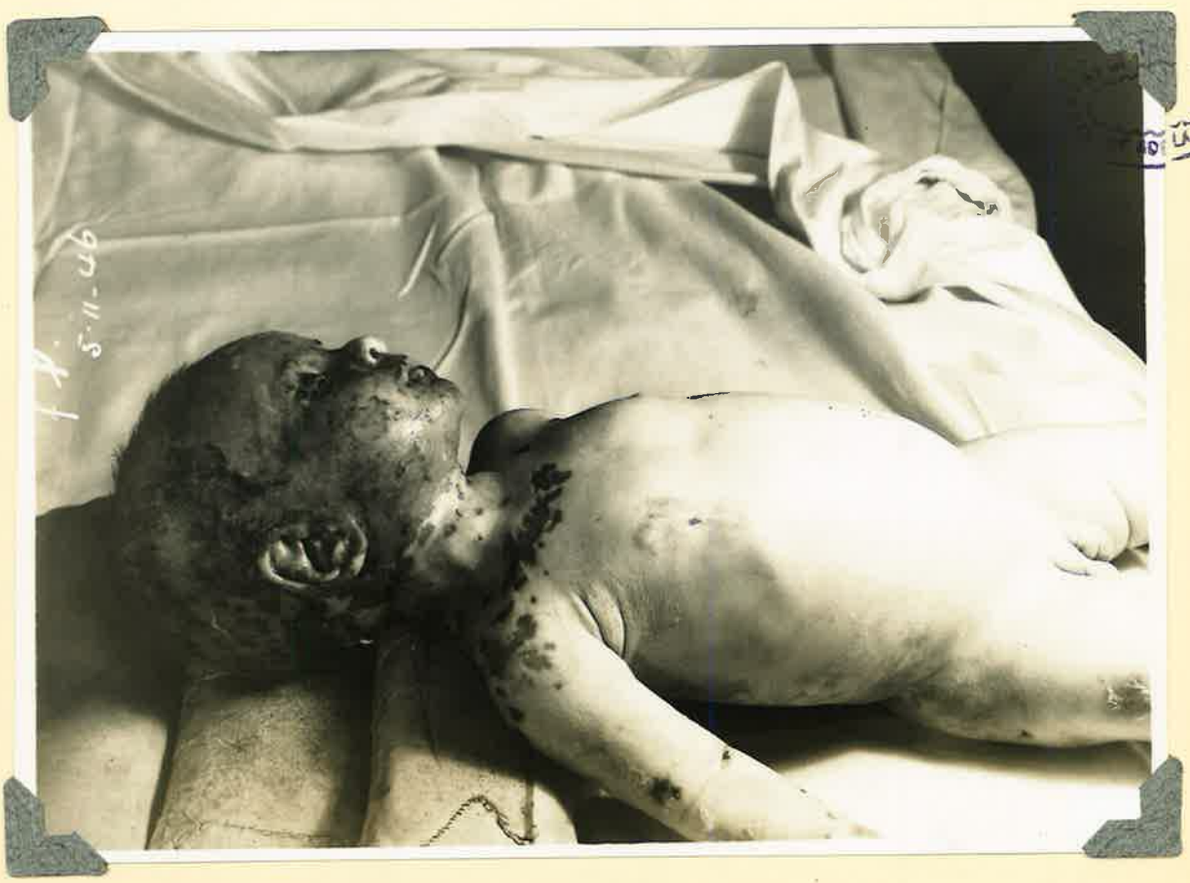


FIGURE IV.

Temperature chart of Case I, Series II, who died on 5/11/46.





FIGURES V AND VI. Post mortem photographs of Case III, Series II, showing the punched-out nature of the skin ulcers, and the denudation of the face !

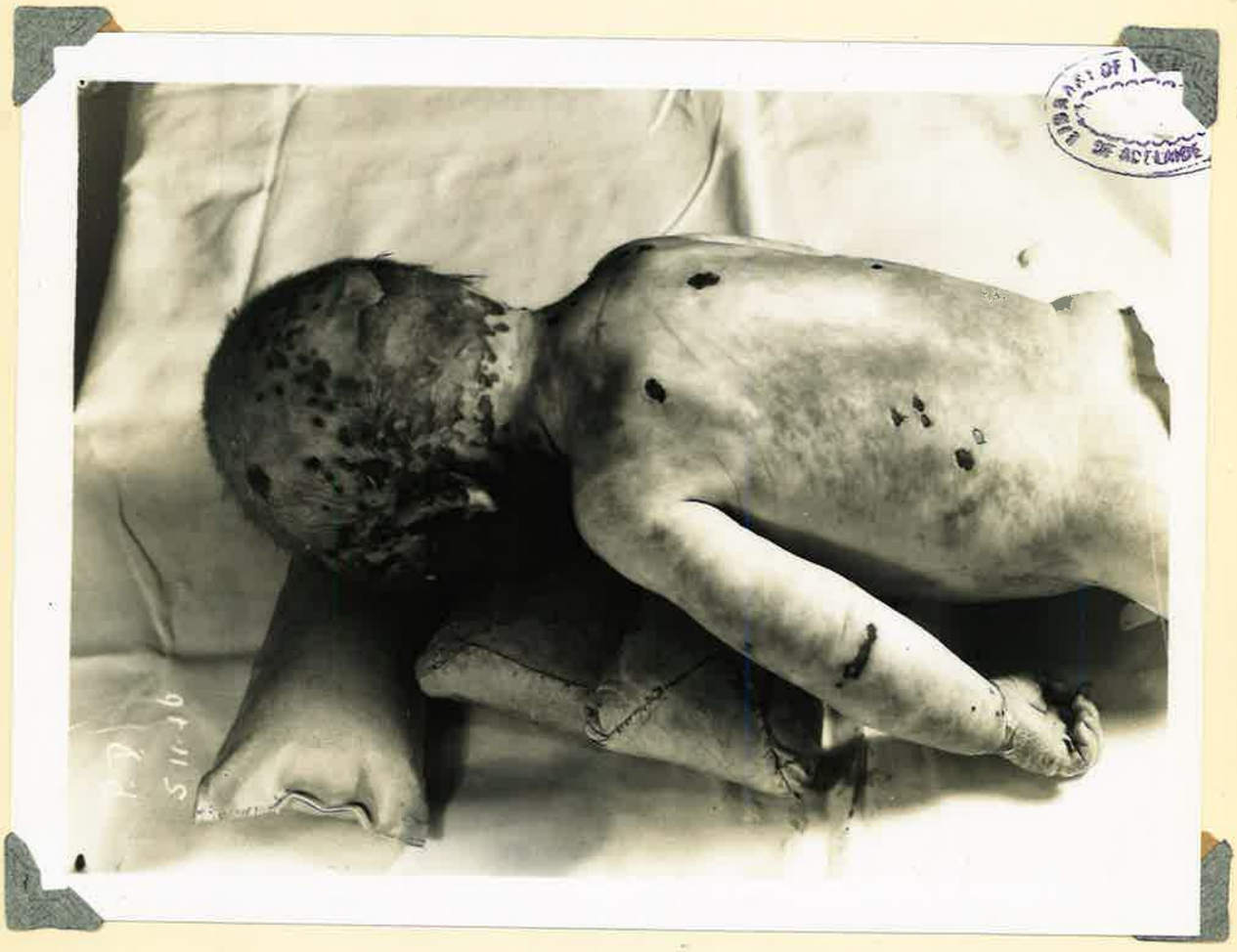


FIGURE VII.

CASE III, Series II, showing well the ulceration on head and back.

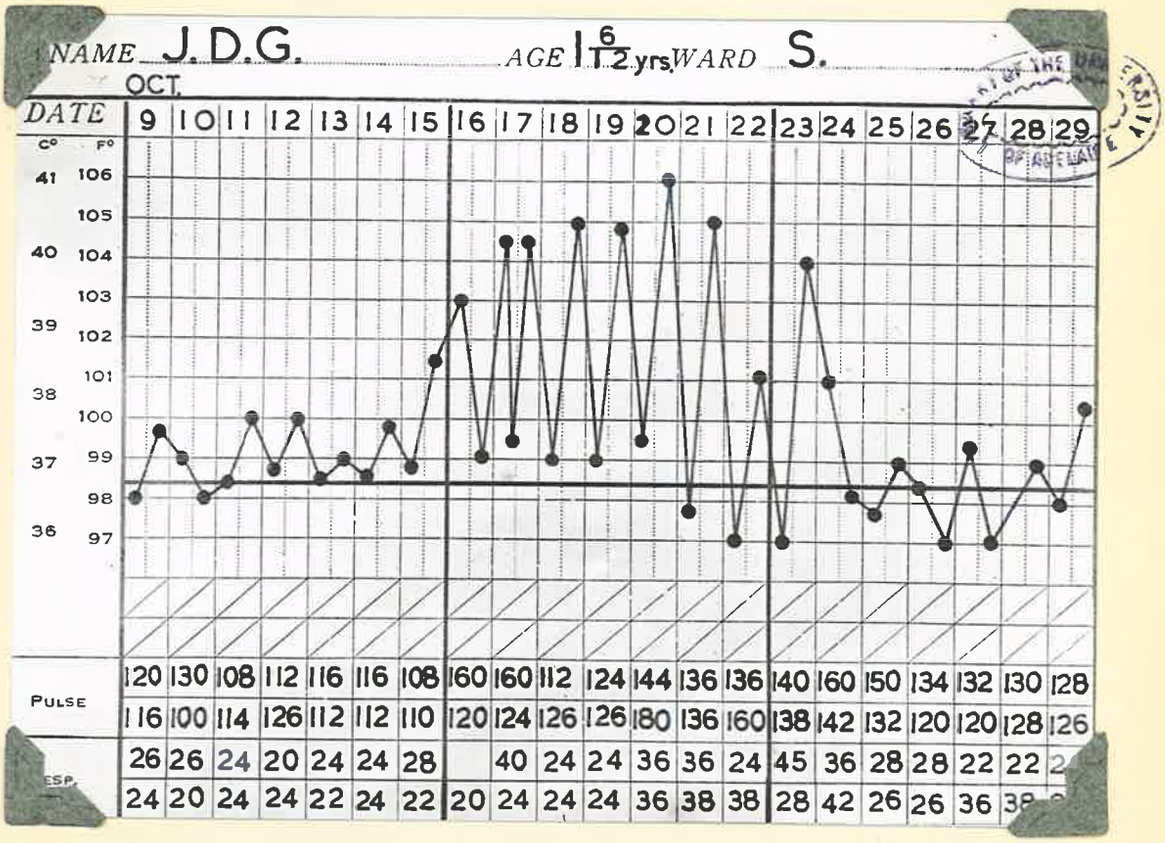


FIGURE VIII.

Temperature chart of Case V, Series II, who recovered.

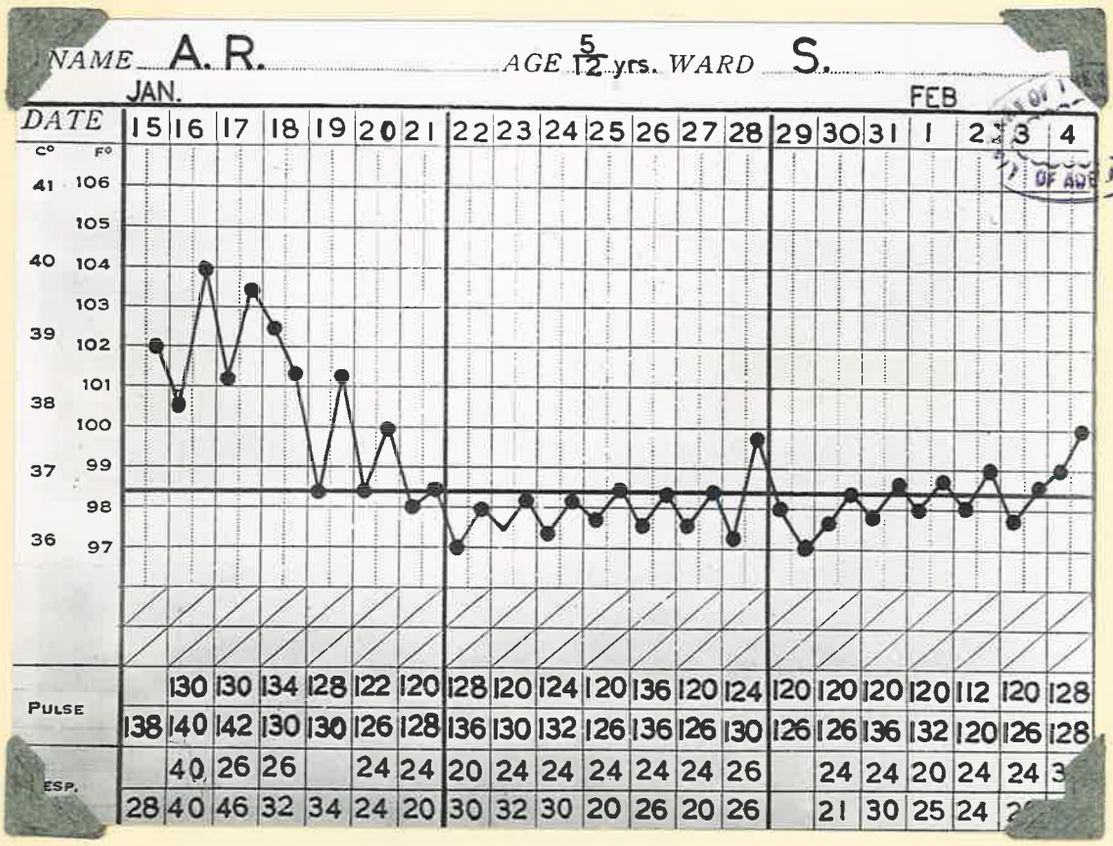
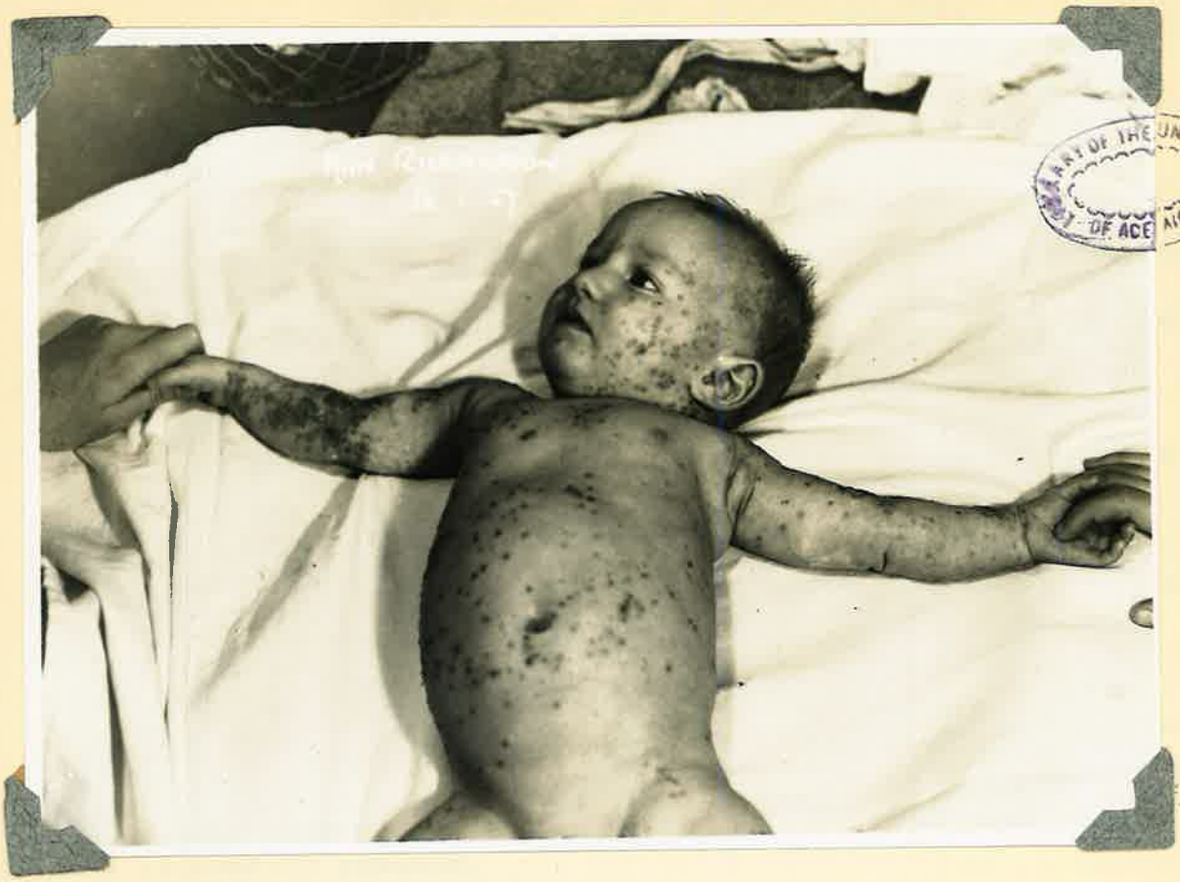
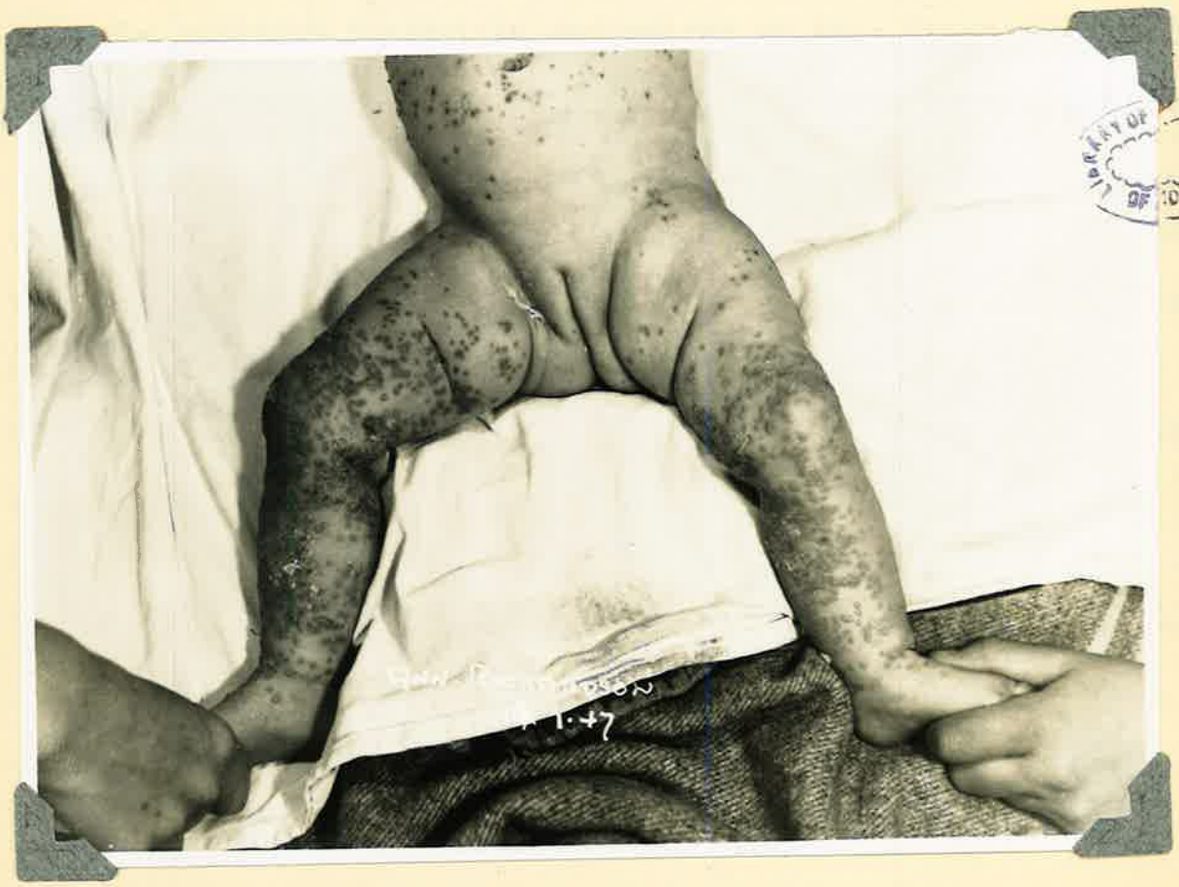


FIGURE IX.

Temperature chart of Case I, Series III, who recovered.





FIGURES X AND XI. Case I, Series III, in the acute stage. The vesicular nature of the eruption before coalesance and ulceration is well shown.

ACUTE LARYNGO-TRACHEO-BRONCHITIS TREATED BY PENICILLIN AND SULPHONAMIDES.

The familiar clinical picture of acute catarrhal laryngitis or "croup," with respiratory distress characterized by stridor and retraction of the lower ribs on each inspiratory effort, needs no elaborating. Occasionally, however, this condition assumes a malignant character with marked toxaemia, and respiratory obstruction sufficiently severe to require tracheotomy for its relief. After the tracheotomy, in a number of cases, the inflammatory obstruction may still descend the respiratory tract, and cause further distress by blocking the airway below the tracheotomy tube. Death may finally ensue as a result either of this respiratory obstruction, or from the intense intoxication which is usually present.

The earliest Australian references to this disease were those of Mathew (1) and Beare: (2) but in recent years papers by Arden (3) and Arden and Duhig (4) have clearly defined the clinical pictur and stressed the importance of the condition. The two firstnamed writers favoured the Staphylococcus aureus as the probable causative organism; but Arden, in his first paper, pointed out that the bacterial flora was by no means constant in the cases described by him, and suggested that "the only possible way out of this bacteriological tangle is to postulate a filter-passing virus as the infecting agent and to regard any bacteria found in the trachea as secondary invaders." In the later paper written by him in collaboration with Duhig, their further observations were considered by them to support this view. In this more recent series in Brisbane, the pathological investigations in two fatal cases failed to yield any evidence of inflammation in the larynx or trachea. Instead of inflammatory cell infiltration, necrosis of the mucosa of the upper portion of the respiratory tract was present; it was highly suggestive of a virus infection, but still no virus could be isolated.

In the first six months of 1944, the Adelaide Children's Hospital experienced a minor epidemic of acute laryngitis or "croup." Sixty patients were admitted (compared with nine in the same period of 1943), and of these, seven were sufficiently severely affected to require tracheotomy. This arbitrary gauge of severity - the necessity for tracheotomy - is regarded by most writers as the dividing line between the diagnosis of ordinary "acute catarrhal laryngitis" and the diagnosis of "acute laryngo-tracheo-bronchitis." It is not unusual to find several cases of "croup" in the one family, only one of which may be severe enough to require operative relief. This was observed in two of our severe cases; and one of the children more mildly affected with croup, who was admitted to hospital during the same period, had just lost a small sister from a more severe inflammation that required tracheotomy in a private hospital.

In seven of the cases now to be described, a dose of 20,000 units of diphtheria antiserum was administered as a routine measure, and throat and tracheotomy swabs were investigated for diphtheria organisms with uniformly negative results. Sedatives were given, a potassium bromide and chloral mixture being the usual choice, and the tracheotomy incision was always a low one, as near to the sternal notch as possible. All patients were treated in a steam tent after tracheotomy as well as before, and the mouth of the tube was kept moist by saline tampons.

The low tracheotomy in a small child enables the tracheotomy tube to be inserted down the trachea almost to its bifurcation (see figures 1&2)and renders endotracheal suction of viscid secretions most effective. The only technical difficulty of this approach is the frequency with which the thymus gland protrudes into the incision during the respiratory efforts whilst performing the operation, but this does not constitute a major hazard. The operation was always performed under local anaesthesia.
A powerful electric centrifugal pump was employed to keep the airway clear, and whenever necessary a soft rubber tube attached to this was pushed through the tracheotomy tube down into the bronchial tree.

An additional case is described which responded to treatment, but it was seen later in the year, and the tracheotomy was not performed by myself.

CASE REPORTS.

Case 1. J. D., aged nine months, was admitted to hospital on February 3, 1944, at 7 a.m., with a history of an acute onset of respiratory difficulty four hours before. On examination, the baby was cyanosed; laryngeal stridor was present, and recession of the lower ribs and sternum occurred with each respiratory effort. The temperature was 104° F., and the pulse rate above 160 per minute. Tracheotomy was performed and much mucopus was removed with considerable relief of the respiratory distress. Sulphathiazole therapy was commenced; but the pulse remained uncountable, and death occurred fourteen hours after the child's admission to hospital, apparently from toxaemia.

At the post-mortem examination of the respiratory tract, the lungs were found to be normal, but the region of the larynx was intensely congested; a number of scattered yellowish spots the size of pins' heads were present in the region of the aryepiglottic folds. There was a thick mucopurulent exudate in the larynx. Examination of sections (see figures 3&4) revealed an intense inflammatory reaction, associated in many places with shedding of the epithelium. The submucosa was packed with polymorphonuclear leucocytes, which in places formed miliary abscesses. In the trachea the lesions bore more resemblance to those described by Arden and Duhig - almost all the epithelium was lost and the submucosa was somewhat hyaline and eosinophilic. Ordinary cultures of tracheal swabs in life revealed Staphylococcus aureus as the predominating organism. After death, filtered washings of the lesion were inoculated onto the chorio-allantoic membranes of eleven-day chick embryos. In two passages there were no signs of a virus, and intranasal and intracerebral inoculations of mice (four of each) also gave negative results.

Case 11. A.K., aged seven years, was admitted to hospital on February 19, 1944, with a history of a sore throat of five days'

duration, and of difficulty in breathing for twenty-four hours before admission to hospital. On examination, his throat was inflamed, and a small patch of exudate was seen on the left tonsil; he had severe laryngeal stridor with chest recession. His temperature was 100° F. and his pulse rate 120 per minute. He was put in a steam tent, and treatment with sulphanilamide was begun; 1.5 gramme were given, followed by 1 gramme every four hours. Fourteen hours after his admission to hospital laryngeal obstruction became extreme, and tracheotomy afforded relief. The tracheal secretions were copious and viscid, but they remained sufficiently fluid to be sucked out, and no major incidents occurred in his subsequent care. He was still very ill after the tracheotomy was performed, and the sulphanilamide treatment was continued for five days, a total of 26.5 grammes being given. The tube was removed on the fourth day, and his subsequent convalescence was uneventful. Swabs from the tracheotomy tube and throat yielded a mixed flora, Streptococcus viridans being the predominating organism.

Case III. R.T., aged nine months, was admitted to hospital on March 27, 1944, with a history of a "croupy" cough and of difficulty in breathing, of three days' duration. On examination,he was found to have a reddened throat, laryngeal stridor and chest recession. The temperature was 103° F. and his pulse rate was 140 per minute. He was put in a steam tent, and treatment with sulphanilamide was begun; 1.5 grammes were given at once, followed by 0.5 grammes every four hours. The drug was changed to sulphadiazine in the same dosage after eighteen hours. His condition remained stationary until twenty-six hours after his admission to hospital, when it deteriorated alarmingly. There was a great increase in the respiratory embarrassment, his temperature rose to 104° F. and his pulse rate to 160 per minute. Tracheotomy was performed (March 28), and much mucopus was sucked out. His condition remained low the following day, the temperature being 105° F., the pulse uncountable, and the respirations 60 per minute in number. Frequent suction of thick secretion from the trachea was necessary. His condition slowly improved over the next two days. The sulphadiazine treatment was continued,0.5

grammes being given every four hours, until a total of 19.5 grammes had been administered. The tube was removed on the fifth day and his subsequent convalescence was uneventful.

Case IV. P.A., aged three and a half years, was admitted to hospital on April 26, 1944, with a history of "croup" for three days, growing progressively worse. One older brother had also just had croup. On examination, the child presented the usual appearance, with a reddened throat, laryngeal stridor and chest recession. Her temperature was 100° F. and her pulse rate 140 per minute. She was placed in a steam tent and sulphathiazole treatment was continued, 0.5 grammes being given every four hours (she had already received 2.5 grammes in the twelve hours before her admission to hospital). Twelve hours later her breathing became more difficult, the chest retraction greater, and her colour deteriorated. Tracheotomy was performed, and much mucopus was coughed up, with relief. Suction through a soft rubber tube down the tracheotomy tube was carried out whenever the tube became obstructed, and this was always sufficient to remove the viscid secretions. The sulphathiazole treatment was continued until a total of 18 grammes had been given. Her condition steadily improved, and the tube was removed after five days. Cultures from swabbings of the tracheotomy yielded no growth.

Case V. B.F., aged three and a half years, was admitted to hospital at 9.30 p.m. on May 6, 1944, with a history of "noisy breathing" and paroxysms of coughing, becoming progressively worse for two days. On examination, she had laryngeal stridor and chest recession; her temperature was 99° F. and her pulse rate 160 per minute. She was put in a steam tent and sulphathiazole treatment was begun, 2 grammes being given at once, followed by 1.0 grammes every four hours; but her condition rapidly deteriorated, and tracheotomy was performed at midnight. Copious mucopus was present in the trachea. The next day (May 7) she was profoundly toxaemic, her temperature was 101° F., her pulse rate was 160 per minute, and her respirations were irregular, averaging 70 per minute. Penicillin treatment was commenced at 3 p.m.,

10,000 units being given intramuscularly every two hours. That evening her temperature was 102° F. and her pulse and respiration rates were unchanged. On May 8 she had improved remarkably in her general appearance. Her temperature had fallen to 99° F., but her pulse rate still averaged 140 per minute, and her respirations were still rapid. The sulphathiazole treatment had been continued for the first twenty-four hours after the commencement of penicillin therapy, but it was now stopped. On May 9 she seemed remarkably well; suction was required less frequently, and her temperature was normal. Her pulse rate and respirations averaged 120 and 40 per minute respectively. The penicillin treatment was continued at the same dosage until 500,000 units had been given. It was discontinued at 5.30 p.m. on May 11. There had been a progressive improvement in her general condition during this time. The tracheotomy tube also was removed on that day after having been in situ for four days. She was discharged home from hospital on May 16. Throat and tracheotomy swabs at various times yielded on culture Streptococcus viridans, Staphylococcus aureus, Staphylococcus albus and Bacillus subtilis.

This girl's brother was also a patient in the Hospital suffering from mild croup from May 9 to May 12, 1944.

CASE VI. C.T., aged one year and seven months, was admitted to hospital on May 5, 1944 with a history of difficult breathing, and of choking on attempting to cough, of thirty-six hours' duration. On examination he presented the usual picture of an extremely toxic child, with inspiratory stridor and chest recession. His temperature was 100° F. and his pulse rate 136 per minute. His colour was good. He was put in a steam tent, and treatment with sulphathiazole was begun, 2.0 grammes being given at once, followed by 1,0 grammes every four hours. His condition did not improve and eighteen hours after admission to hospital his respiratory difficulty increased, his colour deteriorated, and tracheotomy was performed. This relieved his breathing; but the tube repeatedly became blocked, and after a further twenty-four hours, probing and suction with a gum-elastic catheter, followed by the substitution of a larger

tracheotomy tube, were necessary. For the next three days his temperature ranged from 102.8° F. to 104.8° F., and his pulse rate from 160 to 180 per minute, and frequent suction was required. On May 10, at 10 a.m., the sulphathiazole treatment was stopped and the administration of penicillin was commenced. He was given 10,000 units intramuscularly every two hours. That night his temperature was 102.4° F. and his pulse rate 160 per minute. Frequent suction was still required. The next day his maximum temperature was 99.8° F., and his pulse rate by 10 p.m. had dropped to 120 per minute. He looked much better, his respirations were easier, and suction was employed effectively without obstruction. His condition was so greatly improved by May 12,1944, that it was possible to remove the tube. His maximum temperature on that day was 99.2° F., but his pulse rate still averaged 120 per minute. The penicillin treatment was continued until 5 p.m. on May 14, when the fiftieth injection was given - a total of 500,000 units. He was afebrile from May 13 and very bright. No untoward effects from the injections were noted, and the child was discharged from hospital, well, on May 22.

CASE VII. P.P., aged three years, was admitted to hospital at 9 p.m. on May 20, 1944, with a history of a "cold" of two days' duration, and of difficulty in breathing for seven hours. On examination, she had a reddened throat with laryngeal stridor and pronounced chest retraction on inspiration. Her temperature was 100° F., her pulse rate was above 160 per minute, and her respirations numbered 44 per minute. She was put in a steam tent, and sulphadiazine was prescribed, 2.0 grammes at once, followed by 0.5 grammes every six hours; but her condition rapidly became worse, and tracheotomy was performed at midnight. The usual thick mucopus was found in the inflamed trachea. The next day (May 21) she was intensely toxaemic. Her temperature was 103° F., her pulse rate was 160 per minute, and her respirations numbered 50 per minute. The tracheotomy tube frequently required clearing by suction. The sulphadiazine therapy was discontinued, and treatment with penicillin, 10,000 units intramuscularly every two hours, was commenced at

12 mid-day. Her temperature that night was 104.6°F., and her pulse rate above 160 per minute; but the next day (May 22), twenty-four hours after the commencement of pencillin treatment, her general condition was greatly improved, and by evening her temperature was normal. Suction now yielded much less secretion from the trachea. After forty-eight hours of the two-hourly administration of pencillin, the interval between injections was lengthened to three hours for a further thirty hours. Treatment was then stopped, a total of 360,000 units having been given. The child remained well, the tube was removed on May 26, and the patient was discharged from hospital on July 1.

The predominating organism in cultures of swabs from the tracheotomy tube on May 20 was Streptococcus viridans; on May 21 it had changed to Staphylococcus aureus.

CASE VIII. R.G., aged 5 years, was admitted to a country hospital at 1 a.m. on August 19,1944, with the diagnosis of acute laryngitis. He was placed in a steam tent, but the respiratory obstruction increased and a high tracheotomy was performed at 11.30 a.m. that morning. This gave immediate relief, and the child held his own satisfactorily for the next two days.

During this time the child was given sulphpyridine 1 gramme on admission, followed by 0.25 grammes four-hourly. On August 21. his general condition started to deteriorate, with frequent obstruction of the tracheotomy tube. Accordingly, on the following day (August 22) he was flown to Adelaide and admitted to the Children's Hospital at 7 p.m.

On admission, his temperature was 101.6° F., pulse 160, respirations 48. The child was breathing rapidly and irregularly through the tracheotomy tube. His colour was good. There was very slight rib retraction, his tongue was covered with white debris, and the tonsils were large and red but with no exudate. On auscultation, the breath sounds could be heard normally over the left lung, but there was no audible air entry into the right lung at all. He was immediately put under a steam tent. Half an hour after admission, he suddenly collapsed, becoming very blue and sweating profusely. Respiration momentarily ceased. He was given 1 c.c. coramine subcutaneously,

oxygen through the tracheotomy tube, and artificial respiration. Breathing recommenced, but his colour was very poor. On auscultation there was now very little air entry into either lung. The inner tracheotomy tube was removed and found to be blocked, but air entry into the lungs was still poor. A few drops of sterile physiological saline were introduced through the tracheotomy tube, and a soft rubber catheter inserted into it and passed well down the trachea. A strong electric suction apparatus was attached and copious secretion of thick pus, with very hard lumps of clear inspissated material, almost like bizarre glass beads, ½-1 centimetre in length, was sucked out. Air entry to both lungs was immediately re-established with rapid improvement in colour and condition. Breathing became regular, even and quiet. The inner tracheotomy tube was replaced and the child appeared comfortable. He was given continuous steam inhalations, and oxygen when necessary. A moist tampon was kept over the orifice of the tube, and suction was employed frequently. Penicillin was commenced one hour after admission with a dosage of 10,000 units two-hourly, intramuscularly.

On the second day the temperature was still elevated to 100° F. Respirations were rapid (60 - 70 per minute) but unimpeded. His general condition had improved a little, and there was no cyanosis. It was still necessary, however, to suck out the mucopus from the trachea at frequent intervals. On August 24, after approximately 200,000 units of penicillin, his temperature was settling (99°) F.), and the respiration was much less distressed. His colour was excellent and he was sleeping well. Suction was required much less frequently.

A swab was taken soon after admission through the tracheotomy tube and Staphylococcus aureus was obtained in pure culture. The child's condition steadily improved, and on August 26, the tracheotomy tube was removed, nine days after its insertion. There was no distress and the child was able to breathe through his mouth. Penicillin was discontinued on the same morning after a total dosage of 800,000 units. He remained apyrexial after the first few days, began talking on August 31, and the wound had

healed over except for a small area of skin on the day of discharge (September 8), seventeen days after admission.

DISCUSSION.

All these cases were examples of an acute upper respiratory inflammation sufficiently severe to require tracheotomy, and as such they are to be classified as "acute laryngo-tracheo-bronchitis". The response to therapy, however, was generally more favourable than is usually expected. Among the seven patients who recovered, one responded to sulphanilamide, one to sulphadiazine, one to sulphathiazole and four to penicillin. In Case II, in which sulphanilamide may have been one factor in the cure, another may have been the child's "husky" constitution, and his slightly greater age (seven years). In Cases II and III, it seems reasonable to assume that the results might have been very different without sulphadiazine and sulphathiazole respectively; and in the four penicillin cases, the response was sufficiently dramatic to leave no doubt in various observers' minds that more than a coincidence was involved. The patients were probably the most seriously ill children of the series, and yet, after the penicillin treatment was commenced they gave the least cause for worry. There appeared to be no tendency to relapse when treatment was stopped.

The microscopic examination of the trachea in the one fatal case in this small series revealed the necrotic change described by Arden and Duhig; but in the laryngeal region an intense inflammatory cell infiltration of the submucosa was found, which was apparently conspicuously absent in those workers' two autopsy cases. It is obviously unwise to dogmatize on such little material, and to suggest that this constitutes support for the contention that there is more than one pathological entity behind the clinical picture of "acute laryngo-tracheo-bronchitis". In any case, however, one is reluctant to regard the first seven cases described above as clinical and pathological entities, to be classified separately from the other 53 children suffering from

"croup" admitted to hospital over the same period. Indeed, the occurrence of these seven cases during an epidemic of non-diphtheritic "croup", with, in two instances, other cases of mild "croup" in the same families, suggested irresistibly to us that we were dealing with one disease that was varying in its severity rather than in its aetiolgy.

The aetiology cannot be regarded as a solved problem; but the inflammatory cell infiltration in the larynx in the one fatal case in this series, and the response to treatment by bacteriostatics, suggests that bacterial invasion is at least an important factor in the clinical picture.

Staphylococcus aureus was found in tracheal swabs predominantly in two cases, and in two other cases associated with a mixed flora. Streptococcus viridans was found at different times, associated with other organisms, in three cases. In Case IV, tracheal swabs yielded no growth on culture, and in cases III and IV swab culture results were not considered reliable. Although I have no statistics to support me, I am under the strong impression that an epidemic of "croup" such as I have described, amongst children is not unlikely at a time of increased incidence of upper respiratory infections amongst the adult population of a community.

It would not be surprising if, as in coryza, the syndrome of acute laryngo-tracheo-bronchitis is initiated by a viral invasion, and contributed to by a secondary bacterial invasion, as Arden suggests. But the bacterial element nevertheless would appear to remain an important one in the whole picture. The presence usually of a mixed flora does not preclude this hypothesis for the respiratory tract of infancy is even more subject to inflammation from invasion by a variety of organisms than is that of the adult. Also, the bacteriological methods of culturing a swab taken from the inflamed surface may well be inadequate. In the well-recognised entity, for instance, of acute inflammatory obstruction of the glottis due to infection with Haemophilus influenzae, unless the blood is cultured, the causative organism will probably be missed. (5) (6) (7). Whilst

the pediatrician who has seen such a case of gross swelling of the epiglottis and ary-epiglottic folds (causing an expiratory snore rather than an inspiratory stridor), is not likely to confuse it with acute laryngo-tracheo-bronchitis, I mention it to illustrate the pitfalls in isolating a causative organism in inflammations of this region.

I have been struck by the rapidity with which alarming obstructive symptoms can supervene on an apparently mild case of croup, and I would now be very reluctant to treat any such case in its own home away from the trained supervision and facilities available in a hospital. It is considered that when this series of cases was first reported in 1944 (8) a definite advance in the treatment of this serious disease of childhood was made.

SUMMARY.

(1) Seven severe cases of acute laryngo-tracheo-bronchitis in which tracheotomy was required, in a series of sixty cases of non-diptheritic "croup" at the Adelaide Children's Hospital during the first six months of 1944, have been described.

(2) One other case of the same disease which also responded to penicillin is described.

(3) The post-mortem findings in the one fatal case are described.

(4) A low tracheotomy and a mechanical method of applying powerful suction down the tracheotomy tube is considered very necessary.

(5) Penicillin administered intramuscularly after tracheotomy in this series altered the formerly grave prognosis of "acute laryngo-tracheo-bronchitis".

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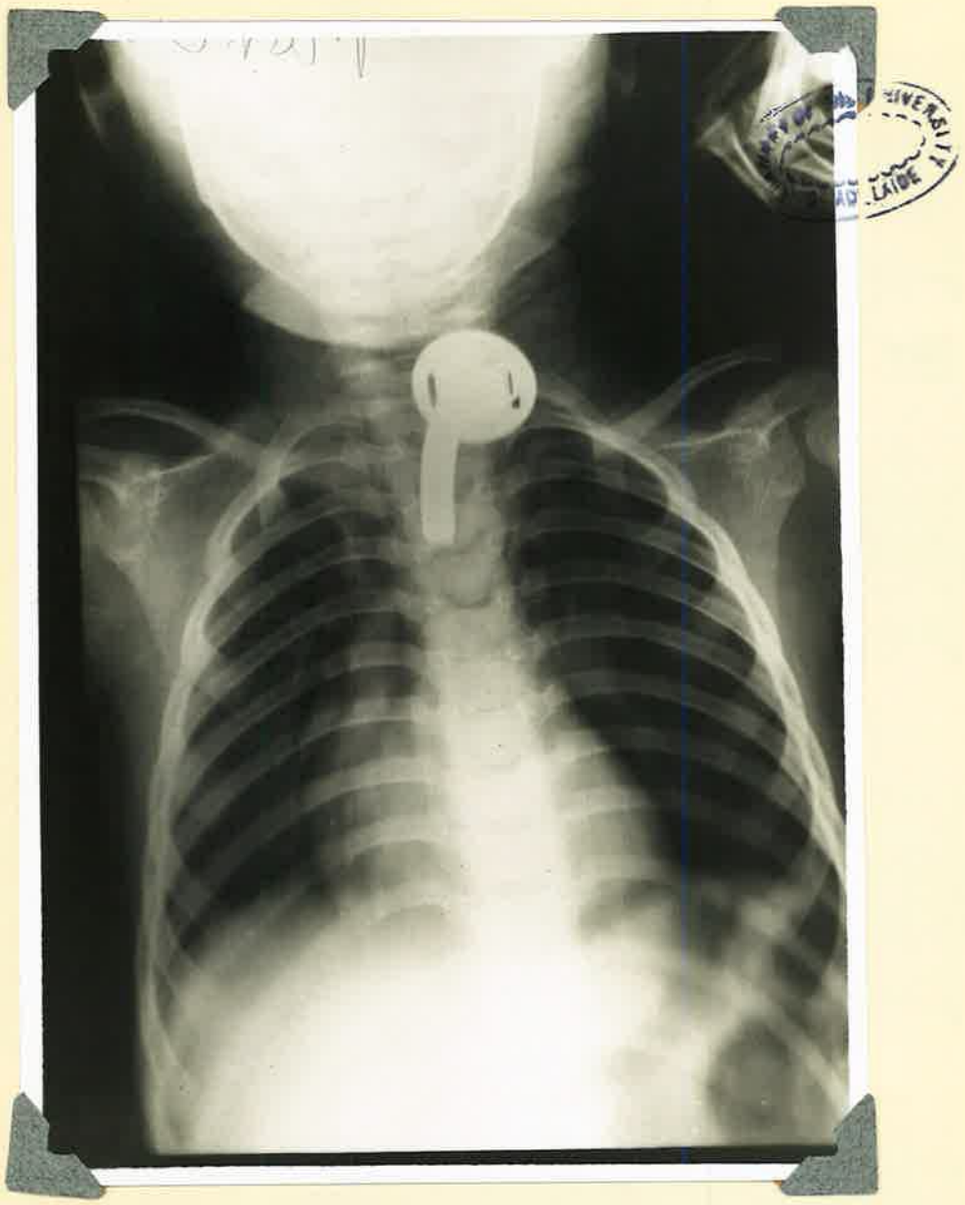

FIGURE II.

Antero-posterior chest X-ray of a child, aged 1 year 6 months, with a tracheotomy tube inserted via a low incision.

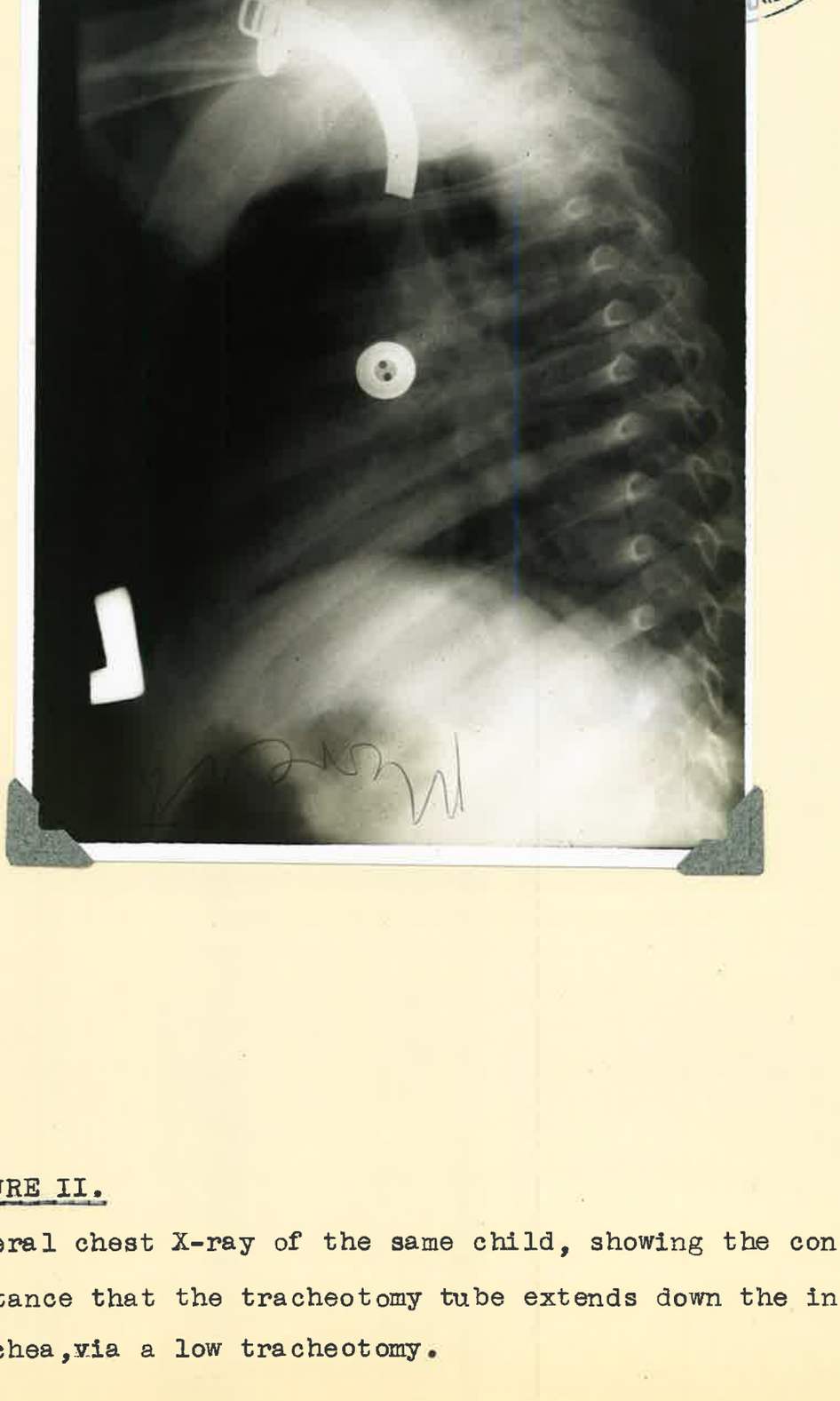

FIGURE II.

Lateral chest X-ray of the same child, showing the considerable distance that the tracheotomy tube extends down the intrathoracic trachea, via a low tracheotomy.

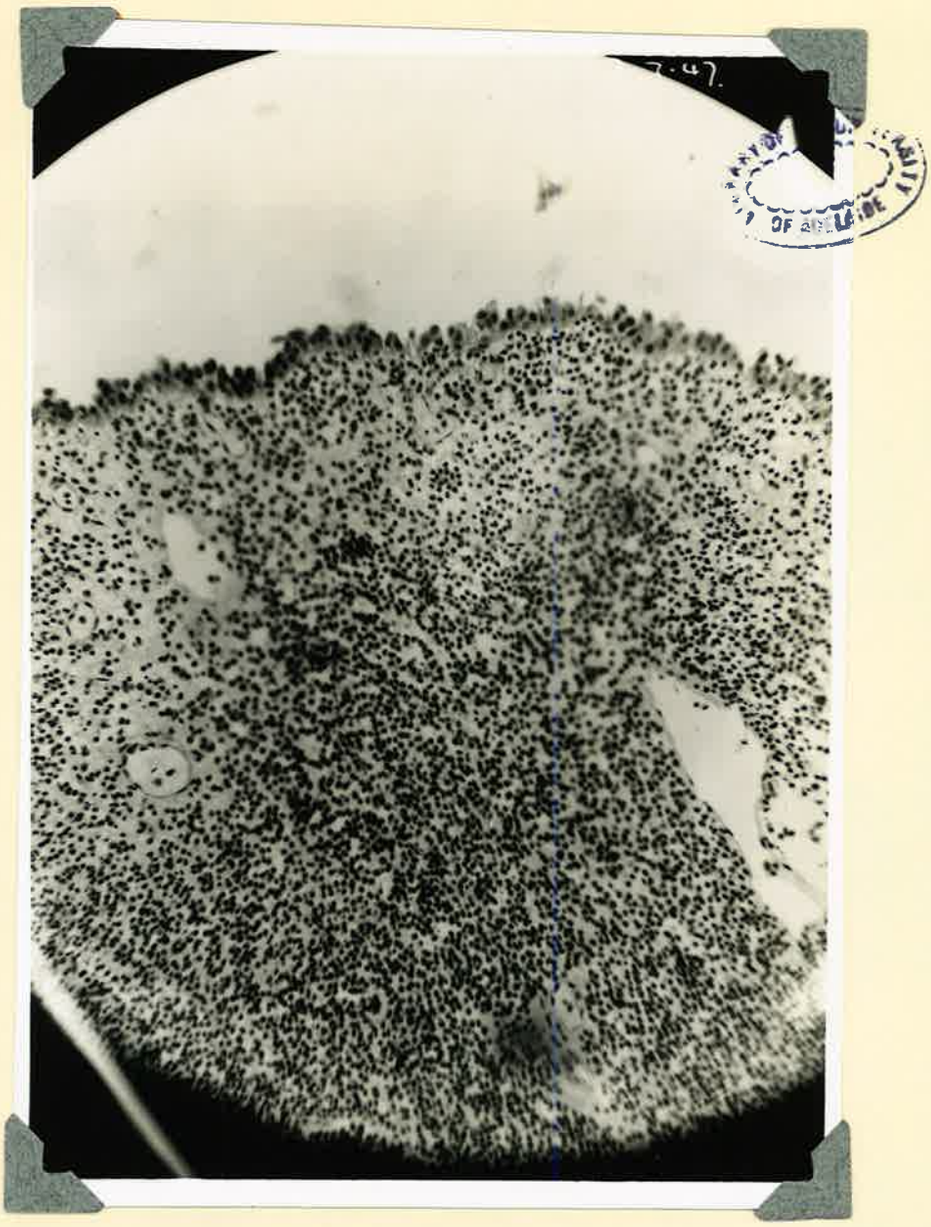

FIGURE III.

CASE I.

Photomicrograph of the laryngeal mucosa showing intense inflammatory infiltration.

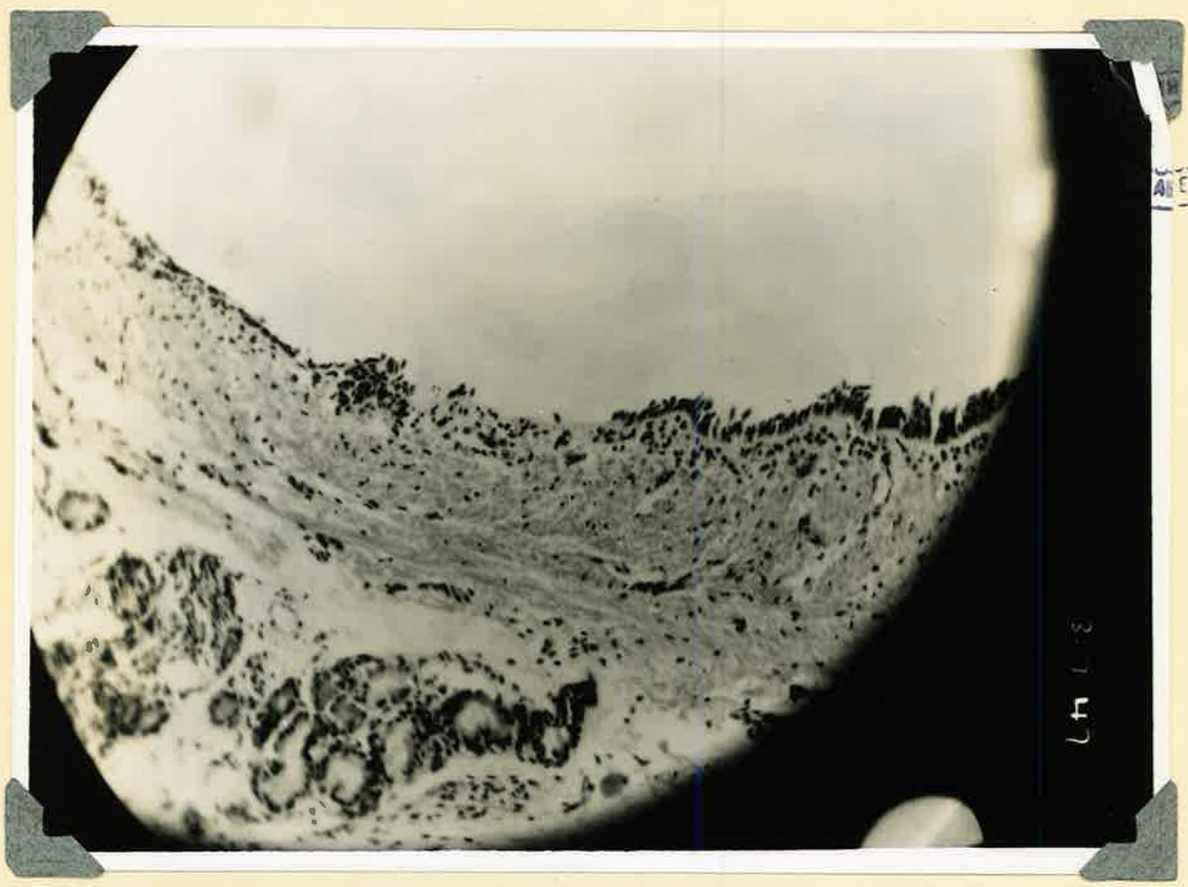

FIGURE IV.

CASE I.

Photomicrograph of the tracheal mucosa, showing considerable loss of the epithelium, and hyaline necrosis of the submucosa.