Summary

Three cases of the defibrination syndrome in pregnancy are reported: one occurred in association with abruptio placentae at 26 weeks, another in association with caesarean section for placenta praevia at 36 weeks, and the third in association with jaundice at 38 weeks. In all cases the clotting defect was reversed by the use of fibrinogen and all mothers and babies survived. The importance of timely diagnosis and treatment of the defibrination syndrome, even in unusual obstetric situations, is stressed.

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REFERENCES

- Donaldson, I. A. (1964). *J. Obstet. Gynaec. Brit. Cwlth*, **71**, 126.
Ingram, G. I. C., Norris, P. R., and Tanner, E. I. (1960). *Ibid.*, **67**, 367.
McNicol, G. P. (1962). *Scot. med. J.*, **7**, 266.
Nilsen, A. (1963). *Acta obstet. gynec. scand.*, **42**, Suppl. No. 2, p. 1.
Phillips, L. L. (1964). Abstracts Xth Congress of the International Society of Haematology, Stockholm, G. 88.
Sharp, A. A., Howie, B., Biggs, R., and Methuen, D. T. (1958). *Lancet*, **2**, 1309.
Sherry, S., Fletcher, A. P., and Alkjaersig, N. (1959). *Physiol. Rev.*, **39**, 343.

Complications and Death in Chicken-pox

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Chicken-pox is usually a mild disease in which complications are uncommon and death is rare. We wish to record two fatal cases in relation to the same small village outbreak involving between 20 and 30 children; the first of these patients (Case 1) died from encephalitis, and the second (Case 2) as a result of haemorrhagic complications. About the same time, but unrelated to the village outbreak, we observed two further patients (Cases 3 and 4) with haemorrhagic manifestations in relation to chicken-pox, each of whom made a good recovery.

Case 1

A boy aged 8 years fell ill on Christmas Day 1962, and next day developed a rash. During the ensuing few days he began to vomit, complained of "tiredness in the head," became delirious, and in the evening of 28 December was admitted to hospital. After admission he was extremely restless and consciousness was lost. Signs of meningeal involvement were absent; deep reflexes were slightly exaggerated, and there was clonus of the right ankle; the pupils were dilated but equal, and optic fundi were normal. There was a generalized rash which had the characteristic distribution and features of chicken-pox. Examination of other systems revealed no abnormality. Cerebrospinal fluid contained 11 lymphocytes per c.mm.; protein was 30 mg./100 ml. and sugar 58 mg./100 ml. A diagnosis of chicken-pox encephalitis was made.

The boy was sedated with paraldehyde, which controlled the extreme restlessness, but, although his colour remained good, respiration was rapid and stertorous. He continued in this uneasy state for several hours, but during the night his condition deteriorated further; his temperature rose to 105° F. (40.6° C.), and the pulse weakened. Steroid therapy was begun, but he died about nine hours after admission to hospital, and less than four days from the onset of symptoms.

Virological study was not carried out, but material from the rash in siblings was reported as showing "multinucleated giant cells as typically seen in varicella, herpes, and zoster."

The main necropsy findings, apart from the rash, were in the brain and liver. Gross enlargement and swelling of the brain, which weighed 1,600 g., was very striking. The surface vessels

showed intense congestion, but there was no evidence of meningitis. Microscopical examination of numerous blocks from cortex, medulla, and mid-brain confirmed gross oedema, and revealed marked active hyperaemia and perivascular haemorrhages. The basal ganglia and mid-brain grey matter showed early degenerative changes in some neurones and some satellitosis along with mononuclear infiltration, but this was not pronounced, and perivascular cuffing was not observed. These changes are frequently seen in virus encephalitis, and the degree of change is often surprisingly small. Demyelination was not demonstrated by either the Marchi or the Weigert-Pal method. The liver was enlarged, pale, and greasy; microscopical examination showed gross fatty change and areas of focal necrosis with mononuclear infiltration, and an acidophil intranuclear inclusion body was demonstrated. In the areas of focal necrosis small aggregates of fibrin strands were observed. The lesions in the liver appeared to be older than might have been expected from the duration of symptoms.

Case 2

A boy aged 3½ years developed a rash on 2 January 1963, and the following day his parents noticed areas of bruising on both thighs. There was no history of pre-existing bleeding disorders in the patient or in other members of his family. He was admitted to hospital, and was found to have a generalized vesicular rash typical of chicken-pox. The lesions were sparse, and some of the vesicles on the trunk had haemorrhage into them. In addition to the rash there were areas of redness and lividity on the thighs. By 5 January these discoloured areas had increased in size, and the thighs were swollen. At this stage the haematological findings were as follows: haemoglobin 6.6 g./100 ml.; white blood count, 6,600/c.mm. (polymorphs 50%, lymphocytes 37%, atypical monocytes 13%); platelets 35,000/c.mm.; Hess test negative. His condition deteriorated rapidly, and he appeared pale and shocked; the systolic blood-pressure was 90 mm. The thighs were by this time considerably swollen and painful, and there was a large effusion, presumably haemarthrosis, into the left hip-joint. The haemoglobin had fallen to 3.9 g./100 ml.; the prothrombin time was over five minutes, and no fibrinogen could be detected in the blood. Transfusion had been started with packed cells, and when the fibrinogen lack was discovered he was given 2 g. of fibrinogen by slow infusion, the transfusion then being continued with whole blood. On the morning of 7 January he died.

Virological study was negative for smallpox, and material from the lesions showed multinucleated giant cells as typically seen in chicken-pox.

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Permission was granted for limited necropsy only. Again, apart from the cutaneous lesions and the haemorrhagic manifestations, the only gross feature was the presence of several small firm circumscribed haemorrhagic nodules beneath the visceral pleura on the anterior surface of the left lung. Histologically these lesions showed focal areas of necrosis and deposition of fibrin surrounded by mononuclear cells. Intranuclear inclusion bodies were demonstrated, and several of the lung capillaries contained small fibrin clots. Although the liver was pale in colour, microscopical examination did not reveal any abnormality. Heart, spleen, kidneys, and suprarenals were also normal.

Case 3

A boy aged 9 years developed chicken-pox on 9 December 1962, and five days later was admitted to hospital because of severe epistaxis. He was known to suffer from epilepsy, and was on long-term treatment with phenobarbitone. On admission to hospital he was pale but not shocked (blood-pressure 118/64 mm. Hg). There were traces of blood around the mouth and on the tongue, and a post-nasal drip of blood appeared to be from the left nostril. There were bilateral subconjunctival haemorrhages, and bruises were present on the arms, elbows, and knees, with purpuric spots on the lower limbs and more sparsely on the trunk. Most of the chicken-pox lesions had crusted, but a few vesicles containing sanguineous fluid remained.

Haematological findings on admission were: haemoglobin 82% ; white blood count 8,700/c.mm. ; prothrombin time 14 secs. (control 12 secs.). Liver-function tests normal ; plasma fibrinogen content normal.

Within two days of admission the platelet count fell to 20,000/c.mm. and fresh bruising appeared over the trunk. Ten days later the platelets had risen to 40,000, and 30 days after the lowest count they numbered 125,000/c.mm.

On 8 January 1963 (when platelets were 58,000/c.mm.) the child developed acute tonsillitis due to β -haemolytic streptococcal infection, but this did not result in a fall in the platelet count, nor was there any recrudescence of haemorrhagic manifestations. The patient made a good recovery.

Case 4

A girl aged 2 years developed chicken-pox on 27 December 1962. The illness was apparently unremarkable until the sixth day, when vomiting occurred ; next day she was drowsy, her colour was poor, and she was admitted to hospital. A rash of moderate density and consistent with varicella of seven days' duration was present on admission, and there were petechial spots on the buttocks, lower abdomen, and inner aspects of thighs. The child was drowsy, but abnormal neurological signs were absent, and cerebrospinal fluid was normal. On the day after admission the platelet count was 75,000/c.mm. ; two days later it had risen to 200,000. The petechial rash faded in a few days, and the child made a straightforward recovery.

Discussion

Comprehensive reviews of para-infectious encephalitis have been published by Underwood (1935) and Miller *et al.* (1956). From these it appears that the fatality rate in chicken-pox encephalitis is around 10%, about one-sixth of the recoveries having sequelae. Males are affected more often than females, and the mortality is greater in males ; fatality is greatest between the ages of 6 and 10 years ; 75% of cases occur in the first week of the disease.

The cause is uncertain. The main possibilities include the direct action of chicken-pox virus, the activation by chicken-pox of another virus latent in the patient, or an allergic response of the central nervous system to the virus. The histological appearances of perivascular demyelination in some cases and the beneficial effect of steroids support the allergic theory. Moreover, virus has never been isolated from the brain, and nerve-cell damage is usually slight. Our own case can add little to the controversy because of the rapid progress to a fatal

issue. The histology of the liver was no different from that seen when a known virus attack on this organ has occurred, and, in view of the pathologist's comment, it is possible that some of the effects may have resulted before the chicken-pox became symptomatic. Certainly, it is thought that the incubation period is initiated by a viraemic phase.

The association of haemorrhagic manifestations with virus infections has long been recognized, but haemorrhagic varicella is quite rare. The earliest description is that of Bérard and de Lavit in 1816 and we have found published accounts of some 40 cases since then, excluding those on steroids or with pre-existing chronic disease (Andrew, 1890 ; Hamann, 1892 ; de Lannöise, 1896 ; Lockwood, 1897 ; Grancher and Comby, 1904 ; Rundle, 1906 ; Porter, 1907 ; Alexander, 1909 ; Elliott, 1910 ; Knowles, 1911 ; Storrie, 1914 ; Campbell, 1915 ; Whitaker, 1915 ; Shanks, 1922 ; Wanklyn, 1922 ; Gordon and Rolleston, 1927 ; Knauer, 1927 ; Apert and Goldberg, 1930 ; Slim, 1930 ; Tancredi, 1933 ; Cohen, 1936 ; Mir, 1938 ; Stoesser and Lockwood, 1938 ; Ford and Marin, 1944 ; Cohen and Bansmer, 1947 ; Marsden and Coughlan, 1952 ; Ghosh *et al.*, 1955 ; Welch, 1956 ; Krugman *et al.*, 1957 ; Charkes, 1961 ; Rotem, 1961). Among these cases 10 fatalities are recorded. While haematological details were not always complete, it seems clear that there is no consistent clinical or haematological picture. Nevertheless, several points emerge—namely, (a) the condition is rare ; (b) the more severe cases usually show the features of purpura fulminans, and, in those surviving, the lesions often progress to gangrene ; (c) in most of the fatal cases the haemorrhagic phenomena occurred within four days of the appearance of the ordinary rash ; (d) thrombocytopenia varies in degree, platelets were normal in three cases (Knauer, 1927 ; Tancredi, 1933) ; (e) bleeding-time, clotting-time, and capillary fragility may all be abnormal, but show no consistent pattern: in our own case and in a case described by Knauer (1927) the reduction of fibrinogen may well have been secondary to haematoma formation.

Development of anomalous rash in chicken-pox may be influenced by pre-existing abnormality of the skin (De Salles-Gomes *et al.*, 1963), long-term steroids (Haggerty and Eley, 1956 ; Johnson and Nelson, 1960), debility (Whitaker, 1915), or co-existing disease (Haggerty and Eley, 1956 ; Johnson and Nelson, 1960). It may be that the various forms of haemorrhagic varicella arise as a result of diverse factors and triggering mechanisms such as allergy, toxicity (especially on capillaries and/or bone marrow), or interaction between chicken-pox virus and some already abnormal moiety of the body.

Summary

Chicken-pox is generally a trivial ailment, but we report here death in two patients—in one instance as a result of encephalitis and in the other as a result of haemorrhagic complications. The cases of two other patients with haemorrhagic chicken-pox who recovered are described. The literature on haemorrhagic chicken-pox is reviewed.

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REFERENCES

- Alexander, D. A. (1909). *Brit. med. J.*, 1, 276.
- Andrew, J. (1890). *Trans. clin. Soc. Lond.*, 23, 79.
- Apert and Goldberg (1930). *Bull. Soc. Pédiat. Paris*, 28, 106.
- Bérard, F. J., and de Lavit, M. (1818). *Essai sur les anomalies de la varicelle et de la varicelle*. Chez Sevalle, Montpellier.
- Campbell, D. G. (1915). *Canad. med. Ass. J.*, 5, 610.
- Charkes, N. D. (1961). *Ann. intern. Med.*, 54, 745.
- Cohen, H. J. (1936). *Arch. Pediat.*, 53, 773.
- Cohen, J. J., and Bansmer, C. (1947). *New Engl. J. Med.*, 237, 222.
- De Salles-Gomes, L. F., Machado, C. G., and Augusto, J. J. (1963). *Post-grad. med. J.*, 39, 91.
- Elliott, R. W. (1910). *Cleveland med. J.*, 1, 37.

- Ford, R. A., and Marin, R. B. (1944). *J. med. Soc. N.J.*, **41**, 440.
 Ghosh, M., Kumar, A., and Paul, N. G. (1955). *J. Indian med. Ass.*, **25**, 180.
 Gordon, E., and Rolleston, J. D. (1927). *Arch. Pediat.*, **44**, 337.
 Grancher, J., and Comby, J. (1904). *Traité des Maladies d'Enfance*, **1**, 383.
 Haggerty, R. J., and Eley, R. C. (1956). *Pediatrics*, **18**, 160.
 Hamann, C. A. (1892). *Med. News (Phlad.)*, **61**, 363.
 Johnson, R. W. P., and Nelson, A. M. (1960). *Brit. med. J.*, **1**, 1183.
 Knauer, H. (1927). *Jb. Kinderheilk.*, **118**, 1.
 Knowles, F. C. (1911). *N.Y. med. J.*, **93**, 876.
 Krugman, S., Goodrich, C. H., and Ward, R. (1957). *New Engl. J. Med.*, **257**, 843.
 de Lannöise, M. (1896). *Thèse de Paris*.
 Lockwood, W. F. (1897). *Arch. Pediat.*, **14**, 680.
 Marsden, J. P., and Coughlan, W. J. (1952). *Brit. med. J.*, **1**, 1066.
 Miller, H. G., Stanton, J. B., and Gibbons, J. L. (1956). *Quart. J. Med.*, **25**, 427.
 Mir, J. (1938). *Bol. Soc. cuba Pediat.*, **10**, 457.
 Porter, C. R. (1907). *Lancet*, **1**, 1359.
 Rotem, C. E. (1961). *Brit. med. J.*, **1**, 944.
 Rundle, C. (1906). *Lancet*, **1**, 1692.
 Shanks, W. F. (1922). *Brit. med. J.*, **2**, 1077.
 Slim, S. J. (1930). "La Varicelle Hémorragique." M.D. Thesis, Univ. Genève.
 Stoesser, A. V., and Lockwood, W. W. (1938). *J. Pediat.*, **12**, 641.
 Storrie, H. C. (1914). *Brit. J. Child. Dis.*, **11**, 62.
 Tancredi, A. (1933). *Pediat. prat., Modena*, **10**, 221.
 Underwood, E. A. (1935). *Brit. J. Child. Dis.*, **32**, 83.
 Wanklyn, W. McC. (1922). *Brit. med. J.*, **2**, 977.
 Welch, R. G. (1956). *Arch. Dis. Childh.*, **31**, 38.
 Whitaker, A. G. (1915). *Brit. med. J.*, **1**, 15.

Medical Memoranda

Urinary Tract Infection with *Torulopsis glabrata* Treated by Alkalinization of Urine

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It has been known for many years that *Torulopsis glabrata* can be isolated from the urinary tracts of human beings (Lodder and Kreger-van Rij, 1952). It seems to be fairly common nowadays, since routine cultures in 100 women with infections of the urinary tract demonstrated *T. glabrata* in six cases (Guze and Haley, 1958). *T. glabrata* is an anascopogenous yeast not forming pseudomycelia, which ferments and assimilates glucose but not galactose, sucrose, maltose, and lactose. However, little is known about the clinical and non-taxonomic microbiological characteristics of this yeast. Its pathogenicity has been doubted or considered limited, but more recently fatal infections have been described—for example, Minkowitz *et al.* (1963); Edebo *et al.* (in press).

During the course of a septicæmic infection blood cultures from the patient were inoculated on to blood and haematin agar and also into anaerobic blood culture flasks. Only weak growth of *T. glabrata* resulted; the colonies were so small and the broth so clear that the diagnosis was almost missed. However, close to a disk impregnated with terramycin the growth was more abundant (Edebo *et al.*, in press).

EXPERIMENTAL OBSERVATIONS

It was found possible to obtain larger yeast colonies on blood agar by the addition of a small amount of hydrochloric acid or acetic acid on to the inoculum streak. Where the drops fell, the colonies reached the same size as those grown on Sabouraud agar (pH=5.6).

The influence of pH on the growth *in vitro* of *T. glabrata* was further investigated in Sabouraud dextrose broth with different amounts of citric acid or sodium citrate added. Volumes of 50 ml. of broth with pH values ranging from 3.5 to 8.8 were added to each of a number of 250-ml. Erlenmeyer flasks provided with side tubes fitting a Coleman junior spectrophotometer. The flasks were inoculated to a concentration of 2.5×10^5 cells/ml. with each of four different isolations of *T. glabrata* from the patient described here, and with two isolations from a patient described earlier (Edebo *et al.*, in press). As a comparison one flask each of *Candida albicans* and *Torulopsis dattila* were inoculated to the same concentration of cells. After 16 hours at 37° C. the absorbance at 650 nm. and the pH were measured (Fig. 1).

The growth of *T. glabrata* at pH values above 6.4 was very scanty. However, when inoculated into flasks with moderately high pH (probably as a result of fermentation) the yeast succeeded in lowering the pH of the medium—for example, from 7.5 to 6.3, where full growth was observed. In one flask, where the initial pH was 8.8, the pH was reduced to 7.1 without conspicuous growth.

These experiments indicated that *T. glabrata* would grow well only in acid media—a property common to many non-

FIG. 1.—Different isolations of *Torulopsis glabrata*, *Candida albicans*, and *Torulopsis dattila* inoculated into Sabouraud broth with various pH. The growth and pH was recorded after 16 hours at 37° C. Since no growth of *T. dattila* could be observed then, those flasks were incubated for another 24 hours before reading off.

pathogenic yeasts (Morris, 1958). This feature suggested that unfavourable conditions for growth of the yeast could be obtained in the urinary tract by rendering the urine alkaline. *Candida albicans* grew well in all tubes, lowering the pH from 8.8 to 6.7. Similar results have been obtained with *C. albicans* on Czapek's medium (Johnson *et al.*, 1954).

CASE REPORT

A 78-year-old widow (526/1963) had a brother who had died of pulmonary tuberculosis, and a father and elder sister who had suffered from diabetes mellitus. Her previous medical history