May 1.—Urinary 17-ketosteroid assay (Fraser and Smith, 1941): result—zero figure in 24-hour sample of urine, using Callow and others' (1939) modification of the method of Dingemans, Borchardt, and Laqueur (normal value for women, 1.7 to 12.6 mg. in 24 hours). After attending for a blood count on April 2, Mrs. W. was unable

to report here again. She received no specific treatment and slowly weakened. She died on Oct. 6, 1943, of cachexia and heart failure.

Necropsy (Oct. 6, 1943).—Dryness and desquamation of the skin, oedema of legs; moderate amount of clear fluid in pleural and pericardial sacs; very small thyroid (6.5 g.); thymus not seen; small heart (150 g.); fibrosis at apex of left lung (right 380 g., left 240 g.); thin intestinal wall; small liver (650 g.); spleen, 65 g.; cancerous ulcer in pyloric antrum of stomach 1 in. across and puckering the peritoneum; no metastases or neoplastic glands; adrenals atrophic—combined weight 5 g., cortices very thin, medullae not obvious; kidneys 85 and 100 g., capsules strip smoothly, fine cortical cysts, cortices slightly narrow; tiny uterus (25 g.) and ovaries (3 g. the pair). The base of the brain was hardened *in situ* by formalin in the skull overnight. The pituitary, when removed still attached to the brain, appeared as a collapsed empty shell.

Histology.—Thyroid: Increase of fibrosis. Adrenals: Partial atrophy. Uterus: Atrophy of endometrium and myometrium. Ovaries: Atrophy. Left lung apex: Fibrosis; anthracosis. Liver: Fat ++; variable size of cells and nuclei. Kidneys: Exudate in glomerular spaces; some tubular debris. Spleen: Follicular fibrosis. Pyloric ulcer: Adenocarcinoma. The pituitary was not sectioned; the base of the brain, with attached hypophysis, was given to the Royal College of Surgeons.

Summary

A case of Simmonds's disease is described in a woman aged 59, due to necrosis of the anterior pituitary dating from a confinement 27 years before.

Attention to the obstetrical history makes the presumptive diagnosis simple in this condition.

Among other clinical pathological tests the results of the insulin sensitivity test and the urine 17-ketosteroid assay added weight to the diagnosis.

Necropsy revealed a general splanchnomicria as expected, but also an "early" pyloric carcinoma which was not expected. Was this a coincidence, or was it another result of the pituitary lesion?

I am grateful to Drs. F. M. Rose and F. B. Smith for their co-operation and permission to publish, and to Mr. G. E. Delory, M.Sc., for help with the biochemical tests. I wish also to thank Lieut.-Col. H. L. Sheehan for much interesting advice and correspondence.

REFERENCES

- Callow, N. H., Callow, R. K., Emmens, C. W., and Stroud, S. W. (1939). *J. Endocrinol.*, **1**, 76.
Fraser, Russell, and Smith, Patricia H. (1941). *Quart. J. Med.*, n.s., **10**, 297.
Sheehan, H. L. (1938). *J. Obstet. Gynec. Brit. Emp.*, **45**, 456.
— (1939). *Quart. J. Med.*, n.s., **8**, 277.
— (1940). *Lancet*, **2**, 321.
— and Murdoch, R. (1938). *Ibid.*, **2**, 132.
— (1939). *Ibid.*, **1**, 818.

J. D. Durand (*J. R.A.M.C.*, 1945, **84**, 280) maintains that, though there are other causes of subconjunctival petechiae, it is safe to treat as positive all cases of pyrexia or mental disturbance exhibiting these signs on the first day of the disease during an outbreak of cerebrospinal fever, and begin chemotherapy immediately. The absence of subconjunctival petechiae is a good prognostic sign.

HAEMOLYTIC DISEASE AND CONGENITAL SYPHILIS IN SIBLINGS

THE ROLE OF THE Rh FACTOR

BY

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It has been alleged that congenital syphilis may give rise to a clinical picture identical with erythroblastosis (Holt and McIntosh, 1933). A history of neonatal jaundice, foetal dropsy, or intra-uterine death in successive pregnancies has been regarded in the past as confirming the diagnosis of syphilis. On this supposition, even in the absence of serological and histological evidence of the disease, women with such unfortunate obstetric histories have been subjected to prolonged courses of antisyphilitic treatment. Syphilis and erythroblastosis foetalis (or haemolytic disease of the newborn, as it is now called—Parsons, 1943) resemble each other in that each may cause the repetition of obstetric disasters; but the obstetric histories differ characteristically in the two conditions, the earlier children usually being spared in haemolytic disease but dying in syphilis. Levine *et al.* (1941) discovered that the chief cause of haemolytic disease lies in iso-immunization of the mother to the blood-group factor Rh, present in the foetal cells and absent from her own. Tests for the Rh factor are thus of value in differential diagnosis, and provide a criterion by which the importance of syphilis, umbilical sepsis, or other alleged cause of erythroblastemia may be assessed. Since the discovery of the possible results of blood-group incompatibility between mother and foetus the formerly alleged causes of erythroblastosis can no longer be accepted until it has been clearly proved that there is no evidence of, or basis for, iso-immunization. There does not appear to be any published example of erythroblastosis in a newborn syphilitic infant in which a concurrent Rh incompatibility between the mother and child has been excluded. Henderson and Macgregor (1943) reported a case of hydrops foetalis (haemolytic disease Type I) in the child of a syphilitic primigravida with anti-Rh agglutinin in her serum and with unequivocal histological evidence of erythroblastosis in the foetal tissues. This case supports the new concept that the foetal condition was attributable to the Rh incompatibility rather than to the syphilis.

I have recently observed a family in which haemolytic disease and congenital syphilis have appeared in siblings. This family illustrates well the value of tests for the Rh factor in confirming the diagnosis of haemolytic disease in the presence of maternal syphilis.

Case Notes

Mrs. C., aged 34. Group A, Rh-negative (rr). Husband overseas. Obstetric history: (1) 1935: female, premature, alive, Group A, Rh-positive. (2) 1939: male, full-time, died of icterus gravis neonatorum (haemolytic disease Type II). (3) 1941: six-months miscarriage. (4) Female, full-time, alive, Group O Rh-negative.

In 1939 the patient gave birth to a full-time male child who became jaundiced some hours after birth and died two days later. This infant was put to the breast, and on account of jaundice and petechiae in the skin he was given an intramuscular injection of 18 c.cm. of maternal blood. During this pregnancy the diagnosis of maternal syphilis had been made, and the mother continued to receive antisyphilitic treatment more or less regularly from that time until early in the fourth pregnancy. Post-mortem examination of the second infant revealed widespread erythroblastosis of the organs with abundant extramedullary haemopoiesis, the appearances being characteristic of haemolytic disease Type II. Histological evidence of syphilis was entirely lacking in all the organs and tissues.

In 1942, in the course of a study on haemolytic disease of the newborn, this patient's blood was first examined for the Rh factor and found to be Rh-negative. It was then disclosed that she had had a miscarriage about 20 months previously, and, in spite of the lapse of time since her last pregnancy, powerful anti-Rh agglutinins were present in her serum (titre 1/128).

In 1944, during the fourth pregnancy, the maternal serum was tested repeatedly from the fourth month onwards, from which time the patient remained under observation in hospital on account of her cardiac condition. The Wassermann reaction was positive, and the serum contained anti-Rh agglutinin type anti-Rh, (i.e., rho and rho,) throughout the remainder of the pregnancy (titre 1/128).

In view of the previous occurrence of haemolytic disease in this family preparations were made to give the fourth baby a transfusion of Rh-negative blood immediately after birth if its cells were shown to be Rh-positive or agglutinable by the irregular antibody in the maternal serum. The fourth child, a female weighing 8 lb. 10 oz., was born spontaneously at term; tests on the cord blood within an hour of birth showed that this baby was Rh-negative and that its cells were not agglutinated by the mother's serum. The cord blood gave a positive Wassermann reaction, its haemoglobin content was 140%, and there was no erythroblastemia. As the maternal and foetal bloods were compatible as regards the Rh factor, blood transfusion was not given and signs of haemolytic disease never developed.

Comment

This family provides a valuable commentary on the supposition that congenital syphilis may cause erythroblastosis. In the second child erythroblastosis was present, but naked-eye and histological evidence of syphilis was lacking. The presence of powerful anti-Rh agglutinins is proof that iso-immunization to the Rh factor had occurred and may reasonably be supposed to have been responsible for the foetal haemolytic disease and possibly for the subsequent miscarriage. The outcome of the fourth pregnancy, however, shows conclusively that serological evidence of syphilis in the mother and infant may be present without foetal erythroblastosis, even in a family in which haemolytic disease has previously appeared. Haemolytic disease did not develop in this child, in spite of the powerful anti-Rh agglutinins in the mother's blood, owing to the lack of the Rh-positive antigen in the foetal cells. From the persistently positive Wassermann reaction it may be inferred that syphilis was not eradicated from the mother, and time will show whether the infant develops signs of congenital syphilis other than the positive Wassermann reaction. There is at present no satisfactory evidence to show that congenital syphilis or other infection can bring about, by itself, the clinical and pathological features of erythroblastosis foetalis, and blood-group incompatibility is the only proved cause of this neonatal disorder.

REFERENCES

- Henderson, J. L., and Macgregor, A. R. (1943). *J. Obstet. Gynaec. Brit. Emp.*, 50, 427.
Holt, L. E., and McIntosh, R. (1933). *Holt's Diseases of Infancy and Childhood*, 11th ed., New York.
Levine, P., Katzin, E. M., and Burnham, L. (1941). *J. Amer. med. Ass.*, 116, 825.
Parsons, L. G. (1943). *British Medical Journal*, 1, 53.

GLANDULAR FEVER WITH NEUTROPENIA

BY

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Lieut.-Col. Shirley Smith and Major Trevor Shaw in their valuable article in the *British Medical Journal* of April 28, 1945, on treatment of anginous forms of glandular fever with intravenous arsenic, stress the fact that neutropenia is present in many cases. In the series they quote, only two cases have a marked neutropenia; the others can be considered low normals. The case reported below shows an even higher degree of neutropenia than any referred to in their paper. Like them, owing to exigencies of overseas service, we have not had full access to literature, but neither of us remembers neutropenia of a marked degree associated with glandular fever; nor is it mentioned in any of the standard works on medicine or haematology we have consulted.

Case History

Lieut. A., aged 27. Previous history: malaria, 1943 (type uncertain; ? B.T.). The patient was admitted to a military hospital, C.M.F., with the diagnosis of "loose body in left knee-joint." After a period at a convalescent depot, Major Bickerton operated on March 3, 1945. That evening, while on routine sulphathiazole by mouth, Lieut. A.'s temperature rose and continued to swing from 97° to 104.4°. His only complaint was tightness of the throat. Many blood slides were negative for malaria. Quinine (10 gr. t.d.s. for 3 days) had no effect on the fever. A few crepitations appeared at the right base. Sulphathiazole was discontinued on March 8

(total 30 g.). On March 13 he complained of a sore throat, and both tonsils were found to be enlarged, with a follicular exudate. Enlarged glands, not tender on palpation, were present in both axillae and the right side of the neck. The spleen became palpable (one fingerbreadth) in the next few days, but was never tender. By March 19 the fever began to abate by lysis. Crepitations were present over both bases. No exudate was now found on the tonsils. Painless enlarged glands, never tender to palpation, were present in groins, axillae, right side of neck, supracondylar regions along the brachial arteries, and just posterior to the right nipple. His only complaints at this time were of slight tenderness over the roots of both canines and tingling of a throbbing nature in the fingers, in the ulnar distribution, which disappeared as the glands subsided, but could be reproduced by pressure over the still slightly enlarged glands above the elbow. On March 22 temperature was normal. Since then the glandular enlargement has disappeared, but the spleen even now (June 5) is still palpable half a fingerbreadth on full inspiration, and up to three weeks before that date the moist sounds persisted in both lower lobes. As the neutropenia first noted on April 2 persisted, the effect of pentide was tried on April 15. Three injections of 10 c.cm. I.M. caused fever, shivering, flushes, nausea, and splenic contraction. Blood slides were negative, and the symptoms were without doubt directly attributable to the injections, as he noticed them after every injection, becoming more marked each time. Injections of adrenaline failed to cause splenic contraction or alteration in the blood picture.

Investigations.—(1) White blood cells (see Table). Hb 80% (Haldane) on April 6. (2) Blood slides $\times 12$ —negative for malaria parasites. (3) Blood culture—negative after 14 days. (4) Paul-Bunnell (Stitt's technique) on March 20—negative; April 13—sheep cells agglutinated to 1/128. (5) Agglutinations to *B. proteus* OX 2 and OX 19—negative. (6) Kahn—negative. (7) Formol-gel—negative.

White Cell Counts

	W.B.C.	Polys.		Lymphs.		Monos.		Eosins.		
		%	No.	%	No.	%	No.	%	No.	
8/3/45	5,700	64	3,648	28	1,603	7	399			
11/3/45	14,800	38	4,484	50	5,900	8	944	1	118	
20/3/45	7,600	33	2,508	66	5,016	1	76			
2/4/45	5,000	17	850	74	3,700	8	400	1	50	
4/4/45	5,550	16	880	78	3,900	5	275	1	55	
6/4/45	5,300	23	1,219	72	3,816	4	212	1	51	Hb 80%
12/4/45	6,200	12	740	72	4,495	5	310	0.5	31	
15/4/45										
Pentide, 3 $\times$ 10 c.cm. I.M.										
17/4/45	7,100	55	3,940	42.5	3,017	3	213			
18/4/45	4,600	33	1,518	56	2,576	10	460	1	46	
19/4/45	4,800	29	1,392	64	3,072	6	288	1	48	
21/4/45	6,600	15	990	73	4,818	8	528	4	264	
10 mins. after 7 minims adrenaline subcutaneously										
26/4/45	8,750	13	1,131	78	6,786	8	696	1	87	
26/4/45	5,850	27	1,566	61	3,538	7	406	5	290	
24/5/45	5,300	25	1,325	69	3,657	3	159	2	106	
6/6/45	8,400	25	2,100	66	5,544	4	336	3	252	

Of interest is the persistent neutropenia since April 2, apart from the immediate effect of 30 c.cm. pentide I.M. The patient was perfectly well and making a normal convalescence all this time, and throat and mouth were normal. Crepitations were so persistent at both bases that atypical pneumonia was suspected, but two skiagrams of the chest were normal. The persistence of splenic enlargement is not unusual in these cases; in this instance it will be of interest to see if the blood count returns to normal at the same time as the spleen.

It is thought sulphathiazole therapy played no part in the production of any of his signs, as he had had only a few doses at the time of operation, which was also the time of onset of his fever. Nevertheless, neutropenia, splenomegaly, and glandular enlargement are known to occur as toxic reactions in sulphonamide therapy, and it is just possible that the drug alters the body's response to the infection of glandular fever. The whole course of the disease, however, and the persistence of the neutropenia are against a drug intoxication.

Comment

Sulphathiazole, given as a routine in clean knee cases as pre-operative preparation, was discontinued 5 days before the onset of throat symptoms. The neutropenia was not permanently affected. The effect obtained by injections of pentide lasted only 36 hours. Moist sounds occurred in the chest—a feature we have noted in other cases of glandular fever. They are similar to those heard in atypical pneumonia, except that they are bilateral. These signs persisted for some weeks. The spleen is still palpable, about half a fingerbreadth below the