TABLE I.—*Relative Needs of Male and Female Rats for Vitamin A*

Tests	All Groups			Groups given Vitamin A of Animal Origin			Groups given Vitamin A (β-carotene) of Vegetable Origin		
	No. of Groups in which died:			No. of Groups in which died:			No. of Groups in which died:		
	More Males	More Females	χ^2	More Males	More Females	χ^2	More Males	More Females	χ^2
Fruits and vegetables from Ceylon compared with a sample of cod-liver oil (Z) as standard	78·0	46·0	8·26	29·5	16·5	3·67	48·5	29·5	4·63
Routine tests carried out under war conditions, mostly vegetable products compared with inter. standard	27·5	7·5	11·43	9·0	3·0	3·0	18·5	4·5	9·14
Research tests carried out under war conditions, mostly vegetable products compared with inter. standard	57·0	7·0	39·19	12·0	1·0	8·31	45·0	6·0	29·82
The last 200 groups in tests carried out before the war, mostly animal products compared with inter. standard	137·5	62·5	28·13	91·5	41·5	18·80	47·0	20·0	10·88
For all tests	300·0	123·0	74·06	142·0	62·0	31·37	159·0	60·0	44·75

The significance of the values of χ^2 found above may be judged from the following figures quoted from the χ^2 table. The probability that the difference between males and females in their need for vitamin A is due to chance is 0.10 when $\chi^2=2.706$; 0.05 when $\chi^2=3.841$; 0.02 when $\chi^2=5.412$; 0.01 when $\chi^2=6.635$; 0.001 when $\chi^2=10.027$.

A probability of 0.10 (or more) of the result being due to chance is generally considered a pretty good one, and no significance would be attached to a result giving this probability. A probability of 0.01 to 0.05 of the result being due to chance is not good, and the result would be accepted as fairly dependable. A probability of 0.001 of the result being due to chance is almost *nil*, and the result would be accepted as almost certainty. Most of our separate values are highly significant, and the values of the totals leave no room at all for doubt of the fact that young male rats are more sensitive to a shortage of vitamin A than young female rats. The further analysis of the results shows also the same difference between male and female behaviour whether the vitamin A is of animal or of vegetable origin. Hence young male and female rats seem to have equal ability to convert carotene into vitamin A.

TABLE II.—*Deaths under 1 Year per 1,000 Live Births*

Period	Deaths		Ratio M/F	Period	Deaths		Ratio M/F
	Males	Females			Males	Females	
1891	164	133	1·23	1915	123	96	1·28
2	162	132	1·23	6	102	80	1·28
3	173	143	1·21	7	108	85	1·27
4	150	124	1·21	8	108	86	1·26
5	176	144	1·22	9	100	78	1·28
6	161	134	1·20	1920	90	69	1·30
7	170	141	1·21	1	93	72	1·25
8	175	145	1·21	2	87	66	1·32
9	177	148	1·20	3	78	60	1·30
1900	169	139	1·22	4	85	65	1·31
1	166	136	1·22	5	84	66	1·27
2	147	118	1·25	6	79	61	1·30
3	145	118	1·23	7	79	60	1·32
4	159	131	1·21	8	74	56	1·32
5	141	115	1·23	9	83	65	1·28
6	145	120	1·21	1930	68	51	1·33
7	130	104	1·25	1	75	57	1·32
8	133	107	1·24	2	73	56	1·30
9	120	97	1·24	3	72	55	1·31
1910	116	94	1·23	4	65	51	1·28
1	142	117	1·21	5	64	50	1·28
2	106	84	1·26	6	66	50	1·32
3	120	96	1·25	7	65	50	1·30
4	116	93	1·25	8	60	46	1·30

It is tempting to speculate on the possibility that a low intake of vitamin A by human babies may have a greater influence on male infants than on female infants in their mortality from, say, 0 to 1 year of age. The numbers of deaths under 1 year of age per 1,000 live births of male and female infants published by the Registrar-General are shown in Table II together with the ratio male/female deaths for each year from 1891 to 1938. The numbers of deaths per 1,000 live births have fallen dramatically in that time for both males and females, and this fall must have been due to the influence of a very great many factors. One point, however, is of particular interest: the ratio of male/female deaths, already high in the 1890's, rose steadily from about 1900 to 1920, since when it has remained nearly constant. Assuming that all forms of extra care lavished on infants in the last fifty years have been given to male and female infants equally, is it possible (*a*) that the extra cod-liver oil given since prenatal and child clinics have been operating has been sufficient to bring about some improvement only, which, according to the rats, would be greater in the females than in the males; and (*b*) that by giving abundance of vitamin A, which would mean more cod-liver oil for boys than girls, the ratio of male/female deaths would be reduced to unity?

REFERENCES

Coward, K. H., Key, K. M., Dyer, F. J., and Morgan, B. G. E. (1931). *Biochem. J.*, **25**, 551.

Fisher, R. A., and Yates, F. (1938). *Statistical Tables for Biological, Agricultural and Medical Research*, Oliver and Boyd, London.

PUERPERAL CEREBRAL THROMBOPHLEBITIS TREATED BY HEPARIN

BY

F. ROSS STANSFIELD, M.D., F.R.C.S., M.R.C.O.G.

Gynaecologist, East Suffolk and Ipswich Hospital

Thrombophlebitis of the cerebral veins and sinuses has been recognized for many years as a rare and fatal complication of the puerperium. Von Hösslin (1904, 1905) reported a large series of cases in which the nervous system was involved during pregnancy and the puerperal state: these included five fatal cases of cerebral thrombophlebitis. Subsequently, no doubt, other examples of the condition have been recorded as cases of "late eclampsia," but interest seems to have waned until the publications of Symonds (1940), Martin (1941), and Martin and Sheehan (1941). In particular, Symonds points out that it is possible to diagnose the condition during the life of the patient, and says that, in his opinion, the prognosis is not so gloomy as a perusal of the literature would suggest.

Aetiology

The thrombosis has been termed "primary" in Gowers's sense, in that obviously it does not arise out of a local infective condition, but is rather the result of an increased coagulability of the blood. Fresh light has been shed on the problem by the experimental work of Batson (1940), who demonstrated that it was possible for emboli to pass from the pelvic veins via the vertebral venous plexuses to the cerebral veins. The factor favouring this condition was a rise in the pressure in the inferior vena cava.

Armed with this information, one may readily imagine small thrombi in the pelvic veins that would give no clinical evidence of their presence being detached during the effort to use a bed-pan. Normally these emboli would find their way to the lungs and give rise to the signs of pulmonary infarction, but a moderate degree of increased pressure in the inferior vena cava would divert the particles to the by-pass formed by the vertebral venous plexuses, and the clots would finally lodge in the cerebral veins.

Symptoms.—The time of onset of the initial symptoms varies widely; in one case it was as early as the fourth day of the puerperium, and in another as long as 137 days after delivery. Headache, paraesthesiae, and weakness of a limb are the early evidences of the cerebral complication and are soon followed by definite paralysis; in most cases epileptiform convulsions and coma close the scene.

Signs.—Neurological examination of one of these cases usually reveals a monoplegia or a hemiplegia; less commonly an aphasia or a homonymous hemianopia is detected. The intracranial pressure is not uncommonly raised, as evidenced by vomiting, papilloedema, and the increased pressure noted on lumbar puncture. The temperature is markedly raised, but the pulse rate, though quickened, does not rise in proportion. Examination of the cerebrospinal fluid may disclose no abnormality, but commonly there is an increased protein content, with traces of blood.

Differential Diagnosis

(*a*) *Cerebral Haemorrhage, Thrombosis, or Embolism.*—The history of the case and the absence of cardiovascular changes usually admit of a decision being made.

(*b*) *Cerebral Tumour.*—Here reliance must be placed on the history and on the finding of an increased protein content of the cerebrospinal fluid in the absence of blood.

(*c*) *Meningitis.*—This is readily excluded by the examination of the cerebrospinal fluid.

(*d*) *Uraemia and Diabetic Coma.*—These are readily excluded by the examination of the blood and urine.

(*e*) *Fat Embolism.*—This is a rare complication of labour, and when present is usually associated with marked trauma. Fat particles may be detected in the urine, but, admittedly, a differentiation from cerebral thrombophlebitis is practically impossible in life.

(*f*) "*Late Eclampsia.*"—This term is a misnomer. Eclampsia developing as late as the fourth day of the puerperium is unknown.

Prognosis

I have succeeded in tracing in the literature 14 definite cases of cerebral thrombophlebitis during the puerperium, of which 8 were fatal; and below are recorded 2 further examples of this complication, one of the patients dying from it. This gives a fatality rate of 56%. Probably that figure is too high, as it is possible to make a confident diagnosis of the condition only in the severer cases. No doubt the increased interest in this particular catastrophe will result in milder cases being detected and larger series of cases being reported, with a consequent revision of our, at present, gloomy prognosis. Theoretically the modern treatment with heparin should provide the answer to our problem.

Treatment

Prophylaxis.—In view of the probable aetiology of cerebral thrombophlebitis during the puerperium every step should be taken to prevent thrombosis in the pelvis and lower extremities by means of prophylactic intravenous injections of heparin as recommended by Crafoord and Jorpes (1941). The circulation in these areas can be promoted by exercises, massage, and the use of a foot-board in conjunction with elevation of the head of the bed. No tight binder should encircle the abdomen, as this would tend to obstruct the inferior vena cava, and straining at stool should be prevented.

Curative Therapy.—Once the disaster has occurred, treatment is directed along three main lines: (1) Control the thrombosis by the use of heparin, which may be given by a continuous intravenous drip in normal saline or 5% glucose solution. Jorpes has shown that, where the large volume of fluid administered by the above method is contraindicated, equally good results may be obtained by four-hourly intravenous injections of concentrated solutions of heparin—i.e., in the form of a 5% solution of heparin standardized to contain 70 Toronto units per mg. and given in 1-c.cm. doses. (2) Reduce the intracranial pressure by lumbar puncture, and give intravenous injections of 50% glucose or 10 c.cm. of 20% magnesium sulphate solution intramuscularly. (3) Control the fits by chloroform anaesthesia initially, and subsequently by rectal avertin or injections of sodium phenobarbitone.

Case Reports

CASE I

A primigravida aged 25 underwent a lower segment Caesarean section under light percaine spinal anaesthesia on August 10, 1940. The puerperium was normal until 4 a.m. on the eighth day, when she complained of numbness in her right forearm. At 8.30 a.m. epileptiform convulsions set in. The fits were controlled by chloroform anaesthesia, whilst a lumbar puncture was carried out. The cerebrospinal fluid was under a pressure of 340 mm. H_2O, and contained 225 mg. of protein per 100 c.cm. and 5,400 red cells per c.mm. Urinalysis showed a trace of albumin, which had been absent previously, and the blood urea was 30.5 mg. per 100 c.cm. Her blood pressure was 140/80. Signs of a right hemiplegia became more obvious during the day. After the anaesthetic had worn off sodium phenobarbitone and nembutal were administered to control the further convulsions, and intravenous injections of 100 c.cm. of 50% glucose solution and intramuscular injections of 10 c.cm. of 20% magnesium sulphate solution were given alternately, in conjunction with repeated lumbar punctures, to control the rising intracranial pressure.

A tentative diagnosis of superior longitudinal sinus thrombosis was made. The same evening the honorary physician, Dr. Ronald Jones, saw the patient. He confirmed the treatment already given, and did not disagree with our view of the case. Despite all our efforts the fits continued until 3.45 a.m. the next day, after which time the patient remained in coma until her death at 10.30 p.m.

A post-mortem examination revealed a thrombosis of the superior longitudinal sinus, extending into the right lateral sinus, and an associated thrombosis of the veins of the left frontal lobe, which was in a softened state. No other abnormality was detected, and no thrombosis could be found in the pelvic veins.

CASE II

A primigravida aged 25 was admitted on October 15, 1940, on account of delay in labour due to the presence of a large foetus and to a minor degree of contraction of the pelvic outlet. Under spinal anaesthesia an episiotomy was performed and a mid-forceps extraction of a living child effected. A catheter specimen of urine taken just after delivery revealed the presence of pus cells, and on culture a scanty growth of *Staph. aureus* was obtained.

For the first nine days of the puerperium the only abnormal feature was an evening temperature ranging from 98.4° to 99.4° F. At 10 a.m. on the ninth day the patient complained of tingling in the right hand, mistiness of vision, and a right frontal headache. Examination showed that a right homonymous hemianopia was present. At 6 p.m. dysarthria was noted, and the first epileptiform fit occurred at 9.33 p.m. Our recent experience with Case I made the diagnosis only too obvious: treatment was at once instituted on similar lines. A lumbar puncture revealed a normal pressure of the cerebrospinal fluid, which contained 5 cells per c.mm. and 65 mg. of protein per 100 c.cm.

Dr. Ronald Jones saw the patient the next morning and agreed with the diagnosis. After discussion heparin therapy was tried, as it seemed to be a rational line of attack and it had previously given good results in cases of thrombophlebitis of the lower extremities in the gynaecological ward. An intravenous drip of 5% glucose saline was started, and was continued at the rate of a pint every four hours. Each pint contained 200 mg. of heparin, equivalent to 16,000 Toronto units. This therapy raised the blood coagulation time to over forty minutes, a considerably longer period than that recommended by McClure and Lam (1940). Heparin therapy was continued on the above lines for four days, by which time the patient had apparently fully recovered.

A thrombophlebitis developed in the left leg on November 12 and in the right leg on the 15th, while there was a return of the cerebral symptoms in a very mild form on the 17th. Further heparin treatment rapidly relieved these troubles. On November 23 septicaemic symptoms appeared and a blood culture revealed the presence of *Staph. aureus*. This infection was treated with sulphathiazole and staphylococcal antitoxin, and after twelve days of pyrexia and rigors the condition resolved. No heparin therapy was given on this occasion for fear of disturbing the normal mechanism of protective thrombosis. A septic anaemia was dealt with by means of blood transfusions, and the patient was discharged, well, on December 24.

Summary and Conclusion

A review of the subject of puerperal cerebral thrombophlebitis is given, and a case successfully treated by heparin is recorded.

The introduction of heparin gives us an effective weapon to treat what has invariably been a fatal complication of the puerperium, and the clinician's reward for an early diagnosis will be the survival of the patient rather than the sterile pleasure of making an accurate diagnosis and confirming it in the post-mortem room.

REFERENCES

Batson, O. V. (1940). *Ann. Surg.*, **112**, 138.
Crafoord, C., and Jorpes, E. (1941). *J. Amer. med. Ass.*, **116**, 2831.
Hösslin, R. von (1904). *Arch. Psychiat.*, **38**, 730.
—— (1905). Ibid., **40**, 445.
McClure, R. D., and Lam, C. R. (1940). *J. Amer. med. Ass.*, **114**, 2085.
Martin, J. P. (1941). *British Medical Journal*, **2**, 537.
—— and Sheehan, H. L. (1941). Ibid., **1**, 349.
Symonds, C. P. (1940). Ibid., **2**, 348.

Medical Memoranda

Puerperal Cerebral Venous Thrombosis

The following case is worthy of record in view of the interest shown in the articles published by Drs. Martin and Sheehan (March 8, 1941, p. 349) and by Dr. Martin (October 18, p. 537).

Case Report

The patient, a primipara aged 21, was admitted as an emergency case on March 2, 1941. She had not been seen antenatally. There was no history of previous pregnancies or illnesses. The expected date of confinement was March 17.

On examination she was confused to some extent; she had had two fits at 10 and 10.20 a.m. on the day of admission. These fits were diagnosed by her doctor as being due to eclampsia. During the previous twenty-four hours she had had headaches, blurred vision, and swelling of the legs. There was no history of epigastric pain or abnormal micturition. The membranes may have ruptured three days previously. Morphine 1/4 grain had been administered before admission. The pulse was 90, the temperature 98° F., and the blood pressure 160/128. The urine boiled solid with albumin. There was no oedema of the legs. The heart and lungs were normal. The uterus was equal in size to that of a thirty-six-weeks pregnancy. The position of the foetus was L.O.A., and the head was not engaged. The foetal heart was heard.

Treatment for eclampsia was instituted along the lines recommended by Stroganoff (prior to the magnesium sulphate treatment). From March 3 to 7 the patient had no fits, the blood pressure was about 165/115, the intake and output of fluid were satisfactory, the pulse remained about 80 to 90, and the temperature was normal. Esbach's albuminometer reading was 14 on the day of admission and 2½ on March 7.

Induction of labour by medical means was begun on the 7th, and labour started at 6 p.m. on the 8th. It continued normally until 4.50 a.m. on the 9th, when the membranes ruptured. At 5 p.m. the same day the cervix was fully dilated. After two hours forceps were applied under ether anaesthesia and a macerated foetus of 5 lb. was delivered. The third stage of labour was normal. The general condition of the mother following delivery was good.

For the first three days of the puerperium the temperature in the evening was about 100° to 101° F., and the pulse ranged between 100 and 120. The general condition of the patient was fairly satisfactory. The blood pressure was 135/90, and the output of urine was good. The lochia were slightly offensive and of normal quantity and colour. Involution of the uterus was normal. A throat and cervical swab revealed no haemolytic streptococci. The urine contained a large amount of albumin, some pus cells, and a pure growth of non-haemolytic streptococci. At 10.15 a.m. on the fourth day of the puerperium (March 12) the patient suddenly went into coma. This lasted about twenty minutes and was followed by a confused state. There were no preceding convulsions, and on examination nothing abnormal was noted in the nervous system. A lumbar puncture was performed. The fluid was found to be under normal pressure, and laboratory examination revealed no abnormality. The blood pressure was 140/90, and there was some albumin in the urine.

On the 13th the patient was incontinent of urine and faeces and showed paralysis of the right arm and leg, with weakness of the right side of the facial and lateral rectus muscles. There was aphasia. The blood pressure was 136/96, and the Esbach reading was 1. The temperature rose in the evening to 100° to 101° F., and the pulse was about 110 for a week; both settled down by the twelfth day of the puerperium.

During the next week speech returned and the incontinence passed off. There remained a residual paralysis of the right arm and leg. Massage and exercises were then carried out, and the patient's movements returned to some extent. The leg improved more rapidly than the arm, and six weeks after the initial coma the patient was walking about. She has been seen periodically since discharge, and more movements of the limbs could be carried out, but they showed the characteristics of an upper motor lesion of the left side of the brain.

Pathological investigations revealed the following data. March 22, Wassermann and Kahn doubtful; March 27, Wassermann doubtful, Kahn negative; April 17, Wassermann weakly positive, Kahn positive (weak); Oct. 18, Wassermann doubtful. (On Oct. 17 the husband's Wassermann reaction was negative.) The urine on April 16 showed a large amount of albumin, with no pus, red cells, or casts. On March 19 a full blood examination had been carried out, and the only abnormality was a haemoglobin of 64%.

Discussion

The lesion is obviously a vascular one. Among the possible causes is haemorrhage due to hypertension associated with eclampsia. This can be excluded, since the blood pressure was down when the coma occurred; also, cerebral haemorrhages associated with eclampsia generally occur during the eclampsia. The patient showed no cerebral symptoms for eleven days after her eclampsia. In addition, patients who get cerebral haemorrhages during eclampsia usually die at the time. Lastly, it is doubtful whether eclampsia occurs after the first day of the puerperium. An embolus passing through a congenital opening from the right to the left side of the heart is a possibility, but it is very rare and is usually fatal. A rupture of an aneurysm of the circle of Willis is also a possibility, but there was no blood in the cerebrospinal fluid, and such a rupture would not produce a hemiplegia of this type.

It seems fairly certain that thrombosis of a vein occurred somewhere on the frontal lobe, as there were no localizing signs at first. Then followed the extension of the thrombosis to one or more veins over the Rolandic area which produced the hemiplegia. The aetiology of this condition has been discussed by Martin. He suggests that fragments of clot may pass from the pelvic veins, if they are thrombosed, into the vertebral venous system. This possibility cannot be excluded in the