MENSTRUAL EDEMA WITH INTRACRANIAL HYPERTENSION (PSEUDOTUMOR CEREBRI)

Report of a Case

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Within the past few years considerable interest has arisen in the occurrence of edema associated with the menstrual period. Such edema varies from a complaint of "puffiness" which may arouse mild passing interest of the clinician, to gross visible edema of as much as 14 pounds, perhaps, associated with severe papilledema and markedly increased cerebrospinal fluid pressure.

In 1928 Eufinger and Spiegler[1] observed some gain in weight at the menstrual time in 47 per cent of their subjects. Okey and Stewart[2] found 1 to 3 pounds increase in weight at the menstrual time in 5 of 20 women subjects, and Sweeney[3] reported a gain of 3 pounds or more in weight, usually premenstrually, in a third of 42 healthy young women studied. In 1933 Thomas[4] reported 2 cases of massive menstrual edema. In his first case there was a gain of as much as 12 pounds in weight, associated with headache, blurred vision and vomiting, and a previous history of arterial hypertension and albuminuria during pregnancy. In his second case no significant antecedent illness was noted and kidney function tests were normal. The menstrual periods were associated with an increase of as much as 14 pounds in weight, severe headache, "marked choking of the discs" and "markedly increased" spinal fluid pressure. In the case reported by Atkinson and Ivy[5] in 1936, there was marked edema of the feet and legs associated with the menstrual periods. In their case there was no evidence of abnormal serum protein levels nor of impaired renal function. Judging from the frequency with which a similar, although usually milder, picture is seen in clinical practice, this phenomenon must not be rare.

Premenstrual edema in reported cases has been associated with such symptoms as a sense of "puffiness", nervousness, emotional instability, numbness and tingling of the extremities, dizziness, unsteady gait, blurred vision, diplopia, dulled mental reactions, headache, and vomiting. All symptoms usually are aggravated a week to ten days preceding the onset of the menstrual flow.

In the title of this report, the term "pseudotumor cerebri" has been used for the purpose of calling attention to the fact that cases of this kind may be mistaken for cerebral neoplasms. The term "pseudotumor cerebri" is a broad classification, and in general, refers to cases presenting clinical symptoms and signs of intracranial tumor which, after complete study, are shown to have none. Such terms as "serous

meningitis" (Quincke, 1897[6], Davidoff and Dyke, 1936[7]), "serous effusions" (Warrington, 1914[8]), "otitic hydrocephalus" (Symonds, 1931[9]), and "toxic hydrocephalus" (McAlpine, 1937[10]) have been used to relate to conditions, some of which may be similar. The type of cases usually included under the term pseudotumor cerebri which are somewhat similar to the case reported here, are those of cerebral edema such as reported by Sahs and Hyndman[11]. Their cases are more nearly like some previously called "toxic or otitic" hydrocephalus. Three of their five cases occurred in children. All had fever, and one had an antecedent mastoiditis. In these latter respects they differ from such cerebral edema as is clearly associated with the menstrual cycle. Such cases as those of Sahs are similar to the ones reported by Gardner[12] in which increased venous pressure within the skull followed sinus thrombosis. The mechanism involved in such cases appears to be different from that present in the case reported here.

REPORT OF A CASE

The patient was referred to me by Dr. J. W. Schoolnic of East Liverpool, Ohio, and came for study on February 16, 1940. She was a 24 year old married, white, woman. Her chief complaints consisted of headache which had been present for five years and was increasing in severity; and within the preceding three weeks, diplopia.

The headaches were severe, generalized, "pounding" headaches associated with a sense of nervousness, faintness and mild giddiness, but no true vertigo. It was established, to our complete satisfaction, that they preceded a thyroidectomy (to be described below) by at least two years. Headaches occurred once or twice a month, as a rule, and varied in duration from one day to as long as three weeks. They usually appeared between ten days preceding and ten days subsequent to the first day of menstrual flow.

Beginning in December, 1939, she noted a sense of pressure in the head and a "gushing" noise in the right side of the head which seemed to be synchronous with the pulse. For three weeks before admission she had noted shadows shifting across the visual field. The diplopia was mild and had been continuous except for two days during a three-week period.

In 1936 she had had a right sided purulent otitis media, for which myringotomy was done. Contact with the physician who attended her at that time has established that there was no evidence of lateral sinus thrombosis.

On November 11, 1937, thyroidectomy was performed elsewhere for symptoms very similar to those present on admission to the clinic. Her symptoms were not relieved. Shortly after this operation puffiness of the eyelids developed, along with paresthesiae of the hands, a reduction in energy, dryness of the skin and brittleness of the nails. It has always been possible to control these symptoms by taking desiccated thyroid, which she has used irregularly since that time. Basal metabolic rate determinations were not done before thyroidectomy. In April, 1938, the basal metabolic rate was minus 29 per cent. She had taken desiccated thyroid (Lilly) in doses of 1½ grains per day following that finding. This dose was sufficient to cause a disappearance of the dryness of the skin and nails and was followed by loss of weight, but in spite of this the headaches and related symptoms continued to become more severe. On January 26, 1940, when the headache had been severe, the basal metabolic rate was minus 1 per cent. On that date thyroid medication was stopped. On February 11, the basal metabolic rate was minus 16 per cent.

The patient had had the childhood diseases without complications, and three years previously an only pregnancy ended in abortion. History of the special systems

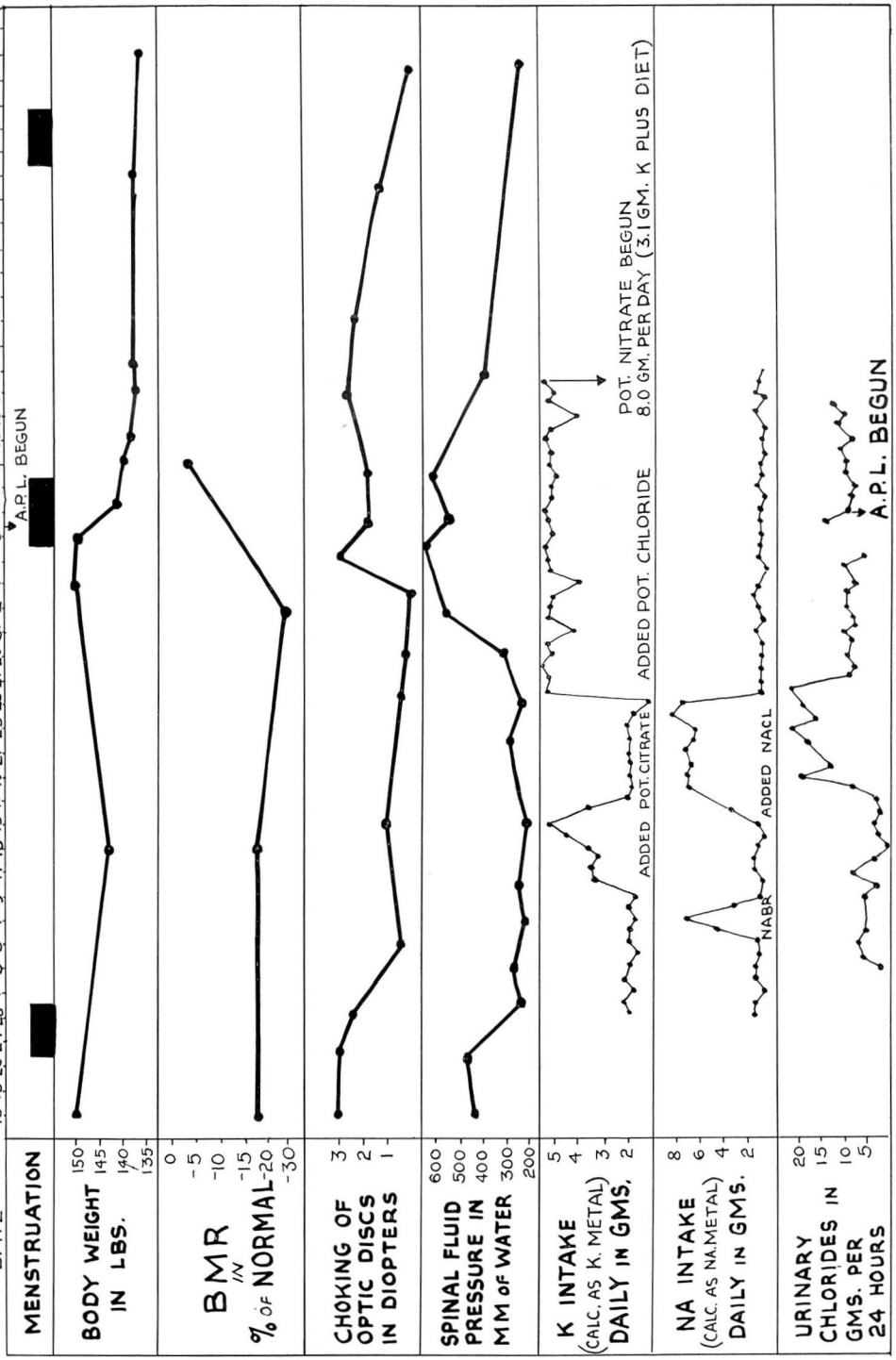

FIGURE 1: Showing variation in certain factors in the course of menstrual edema and lack of response to administration of certain electrolytes.

revealed nothing of importance. The menarche occurred at the age of 10½ years, and the menses had always been regular within a few days, occurring about every twenty-eight days and lasting from five to seven days.

No history suggestive of allergic reactions could be established. A slight elevation of temperature existed for two or three days following encephalography, but apart from the history of otitis media, no fever was known to have been present and there was none while she was under our observation. There was no history suggestive of encephalitis.

Physical examination revealed a rather short, stout, slightly pale young woman who was agitated and emotional and wept frequently. Her face looked mildly edematous. Her height was 63½ inches, and weight clothed 150 pounds. Her temperature was 99.2° F., pulse rate 84, and blood pressure 130 mm. systolic and 94 mm. diastolic.

The skin was rather dry. The pupils were equal, regular and reacted normally. There was 3 diopters of papilledema bilaterally, and perimetric fields showed bilateral enlargement of the blind spot. Extra-ocular muscle movements were normal. The oral hygiene was good. There was no lymphadenopathy. The thyroidectomy scar was in good condition and thyroid tissue was palpable on both sides of the neck. No abnormality of the heart, chest, abdomen or pelvis was noted. Neurological examination showed a suggestion of right facial weakness. Deep reflexes were hyperactive, but equal in the arms and legs; superficial reflexes were normal and no abnormal reflexes were found.

On February 19, 1940 the spinal fluid pressure was found to be 450 mm. of water. At that time Dr. A. T. Bunts made a ventriculogram which showed the ventricles to be normal in size and contour. Because the ventriculogram showed no cause for the increased intracranial pressure, it was decided that an encephalogram should be made. Immediately following the first procedure all obtainable cerebrospinal fluid was removed from the lumbar subarachnoid space, there being 75 cc. present. This was replaced by 85 cc. of air. Roentgenograms showed, in addition to normal ventricles, normal filling of the basal cisterns and cortical subarachnoid pathways. During the course of study, lumbar puncture was performed seventeen times. The cerebrospinal fluid was always under increased pressure, but it varied greatly, as is shown on the accompanying chart (Fig. 1).

Certain blood examinations are shown in Table 1. Blood chemistry studies were done on fasting blood unless otherwise stated.

Other laboratory data were as follows: Urinalysis, repeated at intervals on nine occasions, showed no abnormalities. The specific gravity was found to be as high as 1.029 and 1.032 on various occasions. The pH ranged from 5.5 to 7.5.

The blood volume was normal on March 11, 1940. On that day her spinal fluid pressure was also virtually normal. This test was not repeated when the spinal fluid pressure was high. The Wassermann and Kahn tests of the blood and spinal fluid were negative. The high levels of blood sodium are worthy of comment. In our laboratories, levels of blood sodium on normal individuals range commonly as high as 360 mg., but levels as high as those found in this case are not ordinarily seen.

Estrogen assays were done on March 3 and 7 on 24-hour specimens of urine; the first contained between 10 and 20, and the second less than 10 rat units, according to the method of Gustavson and D'Amour[13].

Urinary androgens were estimated by the capon method of McCullagh and McLin[14], and were 14 international units on March 2.

The spinal fluid protein on several occasions varied between 30 and 35 mg. per 100 cc. There were no cells and no globulin. On each of ten occasions the amounts of various electrolytes in the spinal fluid were determined, and no variation in them was found which appeared to be related to the shifts in the patient's weight, papilledema and spinal fluid pressure. The calcium varied from 5.2 to 5.8 mg. per cent; the phosphorus was 1.2 throughout; the chlorides were between 643 and 695 mg. per 100 cc. on all occasions but one. Sodium was between 373 and 398 mg. This showed some tendency to be higher at the times when the cerebrospinal fluid pressure was high, but the shift of both sodium and potassium levels were not of sufficient extent or consistence to be definitely significant. (Table 2).

TABLE 1

BLOOD COUNTS AND CHEMISTRY

Date	*2/16/40*	*2/21/40*	*2/28/40*	*3/4/40*	*3/7/40*	*3/11/40*	*3/26/40*
Red blood cells	4,400,000					5,140,000	
White blood cells	5,300					6,600	
Hemoglobin	84%					91%	
Volume						3,816 (26 cc. cells per Kg.)	
Sugar	85 mg. (1 hr. p.c.)						
Cholesterol					222 mg.		
Calcium	10.3 mg. 4½ hrs. p.c.)				10.3 mg.		9.8 mg.
Phosphorus	3.2 mg. 4½ hrs. p.c.)				4.0 mg.		
Chlorides		462 mg.	561 mg.				
Sodium		384 mg.	382 mg.				
Potassium		17.5 mg.	21.3 mg.				
Proteins				7.9%			
Albumin				5.9%			
Globulin				2.0%			

TABLE 2

Sodium and Potassium Levels of the Cerebrospinal Fluid

Date	*Sodium mg./100 cc.*	*Potassium mg./100 cc.*
February 28	394	11.0
March 6	387	8.5
14	387	10.2
25	398	10.5
29	398	9.1
April 1	391	8.8
5		10.2
17	373	10.0

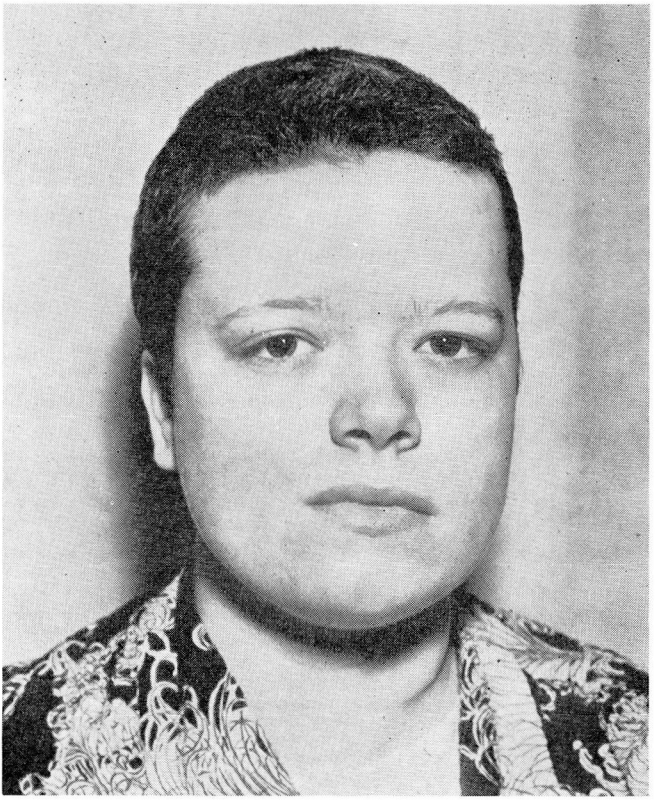

FIGURE 2: April 2, 1940, showing the facial edema present. The hair had been cut in preparation for surgery. Photograph taken during a menstrual period.

The hospital stay lasted until April 18, 1940, a period of 63 days. Throughout most of this time it was necessary frequently to use aspirin, phenacetine and codeine for headache. Occasionally morphine or Pantapon were necessary for pain, and barbiturates frequently were prescribed as hypnotics.

The course of some of the important factors in this case as they changed during her hospital stay are presented graphically in the accompanying chart (Fig. 1).

Thyroid medication was withheld until March 28. It should be noted that the symptoms had increased steadily previous to her admission and were severe up to January 26, when the basal metabolic rate was minus 1 per cent. Subsequently, following the menstrual period in February there was a striking fall in spinal fluid pressure, during which time no desiccated thyroid was being given. These facts, together with the consideration that the symptoms preceded thyroidectomy, make it appear most unlikely that the subsequent fall in intracranial pressure was due to thyroid medication. Desiccated thyroid was begun in doses of 2 grains per day on March 28, 1940 and has been continued.

During the hospital stay, an attempt was made to control the intake of certain electrolytes and water. The food was weighed to the fraction of a gram and the electrolyte content was calculated. This was difficult in itself although some degree of success was attained. It was clearly recognized that the level of sodium and chlorides still remained too high to be expected to cause diuresis in itself. The water intake, however, was

FIGURE 3: August 18, 1941. Photograph taken during a menstrual period.

inconstant, the patient behaving for most of the time very unlike a guinea pig and much more like a human female. The urinary output was measured as accurately as possible, but showed no clear correlation to the rise and fall of spinal fluid pressure and body weight. The lowest urinary volumes were 600 to 900 cc. March 2 to 7, whereas amounts of 2000 were found on March 22 and 24; 1900 on April 1; and 2100 and 2000 on April 5 and 6 respectively.

When the potassium intake was first increased, as shown on the chart, it was suspected that this might be capable of maintaining the low levels of spinal fluid pressure which were observed or of depressing them further. We attempted to test this by changing to a low potassium, high sodium intake, but no significant effect was seen. Following this the potassium was again increased to high levels by adding potassium chloride. It was apparent that this too had little effect for the spinal fluid pressures rose during its administration to the very high levels shown. On March 31 after preoperative orders had been written and subtemporal decompression seemed imminent, it was urged that observation be extended beyond one more menstrual period. We then wondered whether the chloride ion might be the important one, or whether the shift was due to other factors associated with the menses. The same dose of potassium chloride was therefore maintained until the menstrual flow began and during the time it was being given there was a striking fall in spinal fluid pressure and in body weight, amounting to ten pounds in eight days. On April 17 the potassium chloride was discontinued and potassium nitrate in doses of 8 grams per day was substituted. The spinal fluid pressure had already fallen from 610 mm. to 300 mm. of water.

On April 9, 1940, A. P. L. (Ayerst) was begun on the basis of improvement reported in Thomas'[4] case mentioned above. If any medication can be said to have influenced the course of this disease, it was A. P. L. It was continued from that time until June, 1941, as shown below. For most of the time it was used in conjunction with a low sodium diet, desiccated thyroid in doses of 2 grains daily; potassium nitrate, 6 to 8 grams per day was continued for many months. When the potassium nitrate was first discontinued in June, 1940, the symptoms recurred, A. P. L. having been reduced at the same time. Later, it was apparent that the symptoms were very well controlled without the use of potassium nitrate, provided adequate doses of A. P. L. were given.

Date	*A.P.L. Daily in international units*	*Potassium nitrate orally in grams per day*	*Progress*
4/9/40	600		
4/17		6.0	
4/23	500	8.0	
5/2			Menses began
5/3			Papilledema, 1 to 2 diopters
5/13	500	8.0	Discs hazy. Spinal fluid pressure 230 mm.
6/3	500	8.0	
6/4		8.0	Menses began
6/6	250	Discontinued	Optic fundi normal
6/15			Headaches recurred and becoming severe. Face puffy.
7/3	500	8.0	Menses. Visible edema
8/1	Discontinued	8.0	Fundi marginal blurring. Menses. No edema. Remained well until menses in September, when edema and headache recurred.
9/26	250 alternate days	Discontinued	Fundi normal
10/–	250 daily begun	Discontinued	Edema and headache 10 days premenstrual.
11/8	250	Discontinued	Menstrual period symptom-free
	250	Discontinued	Menses remained relatively free of edema, headache and no visual blurring recurred.
6/9/41	250 discontinued. Stilbestrol, ½ mg. per day begun		
9/18/41	A.P.L. used for 10 days in July. None since. No potassium nitrate. Stilbestrol orally, ½ mg. 5 days preceding and succeeding menses.		Symptoms minimal. Fundi oculi normal. By this date the patient's weight had fallen gradually to 129 pounds.

TREATMENT AND SUBSEQUENT COURSE

Desiccated thyroid, 2 grains per day, and a low sodium diet and fluids limited to approximately 1200 cc. per day have been continued throughout. A placental extract containing estriol glucuronide (Emmenin) was used orally in doses of 1 dram four times daily for two months following September 26, 1940, and no improvement could be seen to follow it.

On September 30, 1941 the patient was seen again. She had continued the use of stilbestrol as outlined above but had followed no other therapy. Within the past month headaches have increased, and visible edema recurred with the last menstrual period. Her optic discs showed no evidence of pressure and her urea clearance test showed 90 and 83 per cent clearance in each of two hours, the blood urea being 33 mg. per cent.

COMMENT

The mechanism involved in the production of menstrual edema is not clearly understood. Recent studies in hormonal metabolism do afford some insight, however, into the process. The many points of interest cannot be discussed here, but a few of the salient ones may be recalled. The chief consideration is the fact that many of the steroid hormones have the power to cause retention of sodium, chloride, other electrolytes and water in the body. The adrenal cortical hormone desoxycorticosterone has a very powerful effect in this regard and no physician who has watched critically the effect of this hormone on the fall in hematocrit level and the rise in body weight of patients with Addison's disease could fail to be impressed. So great is this power that this hormone, if used in excessive amounts, may cause pulmonary edema and death. Thorn[15] has shown that the same type of action exists for estrone, estradiol, testosterone and progesterone. Such effects for testosterone propionate have also been shown by Kenyon[16], and for testosterone propionate and methyl testosterone by me [17], [18]. The fact that this power is not relegated to the estrogens alone, but to testosterone and progesterone as well, is interesting to consider here in view of the fact that both of these substances have been recommended for the therapy of phenomena similar to menstrual edema. Thorn[19] feels that the hormones of the adrenals and gonads may, under certain conditions, "act as precipitating factors in the production of edema". Whether a change in rate of excretion of these substances is a factor of importance is not certain. Such a mechanism has been suggested by Frank[20]. Further discussion as to the mode of action of pregnancy urine extract in cases of this kind would at present be more philosophical than scientific.

Various forms of treatment have been suggested. In Thomas'[4] case, calcium lactate and calcium gluconate were helpful and pregnancy urine extract produced spectacular improvement. In the case of Atkinson and Ivy[5], desiccated thyroid, ammonium nitrate, potassium chloride, calcium gluconate and viosterol failed. Good results were obtained at first with pregnancy urine extract, but these could not be repeated. Finally, a good result was obtained with an estrogenic placental extract (Emmenin) which contains estriol glucuronide. Thorn[19] recommends absolute restriction of sodium chloride in the diet for seven to ten days preceding the onset of menstruation, plus 10 cc. of a 20 per cent solution of potassium citrate in fruit juice two or three times daily.

Frank[20] reported good results in overcoming premenstrual tension with the use of magnesium sulfate by mouth, and recommended roentgen ray castration. In one case of severe premenstrual tension with neurologic signs, we prescribed roentgen therapy to the ovaries, with good results.

Hormones have been used for their antagonistic effect on estrogens and good results have been reported by Israel[21] following the premenstrual administration of progesterone, and Greenblatt[22] has used testosterone propionate successfully for the same purpose. Whether these later affect premenstrual molimina by virtue of hormonal action not dependent upon electrolyte response is not clear.

More recently Greenhill and Freed [23] ascribed premenstrual distress to retention of water in the tissues, and report excellent results following the qualitative restriction of sodium chloride, plus the oral administration of 1.0 gm. of ammonium chloride three times per day. In some of our cases apparently similar to the one reported above, subtemporal decompression has been necessary to prevent blindness.

Much more experience is needed in the management of menstrual edema before an accurate evaluation of the various types of therapy can be made.

SUMMARY AND CONCLUSIONS

Observations are reported on a case of menstrual edema with increased intracranial pressure (pseudotumor cerebri).

Hypothyroidism was a complicating feature, but the use of desiccated thyroid failed to control the recurrent edema.

Potassium citrate, sodium chloride, potassium chloride, and Emmenin appeared to influence the course of the disease little, if at all. Potassium nitrate in doses of 8 grams daily may have been of some value.

A. P. L. (Ayerst), a pregnancy urine extract, in large doses appears to have had a distinct influence upon the disease.

To the time of writing, the patient remains almost completely symptom-free, but there are evidences of mild exacerbations.

REFERENCES

1. Eufinger, H. and Spiegler, R.: Der Einfluss des mensuellen Zyklus auf den Wasserstoffwechsel, Arch f. Gynäk, 135:223-231, 1928.
2. Okey, R. and Stewart, D.: Diet and blood cholesterol in normal women. J. Biol. Chem. 99:717-727, (February) 1933.
3. Sweeney, J. S.: Menstrual edema; preliminary report, J.A.M.A. 113:234-236, (July 28) 1934.
4. Thomas, W. A.: Generalized edema occurring only at the menstrual period., J.A.M.A. 101:1126-1127, (October 7) 1933.

5. Atkinson, A. J. and Ivy, A. C.: Menstrual edema; report of case controlled by emmenin but not by theelol or theelin, J.A.M.A. 106:515-517, (February 15) 1936.

6. Quincke, H.: Ueber Meningitis serosa und verwandte Zustände, Deutsch. Ztschr. f. Nervenh. 9:149-168, 1897.

7. Davidoff, L. M. and Dyke, C. G.: A presentation of a series of cases of serous meningitis, J. Nerv. & Ment. Dis. 83:700-705, (February) 1936.

8. Warrington, W. B.: Intracranial serous effusions of inflammatory origin, Quart. J. Med. 7:93-117, (January) 1914.

9. Symonds, C. P.: Otitic hydrocephalus, Brain, 54:55-71, (April) 1931.

10. McAlpine, D.: Toxic hydrocephalus, Brain, 60:180-203, (June) 1937.

11. Sahs, A. L. and Hyndman, O. R.: Intracranial hypertension of unknown cause, Arch. Surg., 38:428-442, (March) 1939.

12. Gardner, W. J.: Otitic sinus thrombosis causing intracranial hypertension, Arch. Otolaryng. 30:253-268, (August) 1939.

13. Gustavson, R. G., and D'Amour, F. E.: A biologic assay of "international standard" estrin and of certain commercial preparations, J. Pharmacol. and Exper. Therap. 57: 472-481, (August) 1936.

14. McCullagh, D. R. and McLin, T. R.: Extraction of androgens from urine, Endocrinol. 22:120-121, (January) 1938.

15. Thorn, G. W. and Engel, L. L.: Effect of sex hormones on renal excretion of electrolytes, J. Exper. Med. 68:299-312, (September) 1938.

16. Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C. and Lotwin, G.: A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism, Endocrinol. 26:26-45, (January) 1940.

17. McCullagh, E. P. and McGurl, F. J.: Effects of testosterone propionate on epiphyseal closure, Na and Cl balance and on sperm counts, Endocrinol. 26:377-384, (March) 1940.

18. McCullagh, E. P. and Rossmiller, H. R.: Methyl testosterone. II. Calorigenic activity, J. Clin. Endocrinol. 1:503-506, (January) 1941; III. Effect upon body weight and growth, J. Clin. Endocrinol. 1:507-510, (June) 1941.

19. Thorn, G. W. and Emmerson, K.: The role of gonadal and adrenal cortical hormones in the production of edema, Ann. Int. Med. 14:757-769, (November) 1940.

20. Frank, R. T.: Hormonal causes of premenstrual tension, Arch. Neurol. & Psychiat. 26:1053-1057, (November) 1931.

21. Israel, S. L.: Premenstrual tension, J.A.M.A. 110:1721-1723, (May 21) 1938.

22. Greenblatt, R. B.: Syndrome of Major menstrual molimina with hypermenorrhea alleviated by testosterone propionate, 115:120-121, (July 13) 1940.

23. Greenhill, J. P. and Freed, S. C.: Electrolyte therapy of premenstrual distress, J.A.M.A. 117:504-506, (August 16) 1941.