showed no evidence of circulatory collapse or infection and serum electrolytes and blood sugar values were only minimally deranged. The case is unusual because of the recognition and documentation of the syndrome and its subsequent spontaneous reversibility.

Cerebral oedema complicating diabetic coma has only recently received significant attention (Fitzgerald *et al.*, 1961; Young and Bradley, 1967; Hayes and Woods, 1968). These authors reported six patients with the characteristic clinical picture; all were young (aged 9 to 28), with moderately severe ketoacidosis (blood sugar 500 to 800 mg./100 ml.), and after an initial short period of improvement (4 to 16 hours) mental deterioration and death occurred secondary to histologically proved cerebral oedema. It is of particular interest that the presence of cerebral oedema at necropsy had been noted in several earlier publications dealing with ketotic diabetics who died for "unexplained reasons" (Dillon *et al.*, 1936; Di Benedetto *et al.*, 1965; Hayes and Woods, 1968). Nevertheless, the clinical syndrome was neither recognized nor correlated with the pathological findings. Though Young and Bradley (1967) suggested that the occurrence of cerebral oedema in hyperglycaemic hyperosmolar coma was unlikely, Maccario *et al.* (1965) reported the development of this syndrome in such a patient who survived. In this context cerebral oedema has also been documented histologically in patients dying with hyperosmolar non-ketotic coma (Larcon *et al.*, 1963; Bergoz and Hausser, 1964) and recognized in hypoglycaemic coma (Marks and Rose, 1965).

The pathogenesis of cerebral oedema in patients with diabetic ketoacidosis is still uncertain. Dehydration, haemoconcentration, acidosis, and decreased cerebral blood flow lead to cerebral anoxia and suppression of aerobic metabolism (Meyer *et al.*, 1965). Brain cells may become abnormally permeable to sodium ions, and water would follow owing to osmotic pressure gradients (Young and Bradley, 1967; Hayes and Woods, 1968); the result would be intracellular overhydration. Recent studies have suggested that increased activity of the polyol pathway in response to hyperglycaemia results in accumulation of osmotically active fructose and sorbitol in the brain (Clements *et al.*, 1968). The time of occurrence of this complication also suggests many similarities to the disequilibrium syndrome, which may develop during dialysis. Though we have carefully assessed the rate at which our patient's osmolality, acidosis, and hyperglycaemia were corrected, as well as the quantities of sodium, bicarbonate, and water administered, we can find no features to distinguish his therapy from that of our patients who did not develop this syndrome.

Therapy usually recommended for cerebral oedema is urea or mannitol together with glucocorticoids (Matson, 1965). This regimen, however, has been tried with little success in a few instances of cerebral oedema complicating diabetic ketoacidosis (Young and Bradley, 1967). Because of the high mortality from the condition we feel that this mode of therapy needs further evaluation. If there was no improvement in a patient with cerebral oedema after a short period of observation, or if the patient was comatose at the time of diagnosis, we would recommend the use of these drugs. In our patient improvement was rapid and progressive after the diagnosis was made; for this reason, as well as the fact that anti-oedema agents have not always proved beneficial, therapy was withheld.

If this syndrome is to be recognized careful and frequent monitoring of the neurological status of patients treated for diabetic ketoacidosis is necessary. Posner *et al.* (1965) have drawn attention to the interrelationships of blood and cerebrospinal fluid acid-base balance in diabetic ketoacidosis uncomplicated by this syndrome. Simultaneous measurements of blood and cerebrospinal fluid glucose, osmolality, *p*H, and electrolytes will undoubtedly facilitate our understanding and treatment of cerebral oedema.

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Preliminary Communications

Free Amino-acid Concentrations in Fetal Fluids

British Medical Journal, 1970, 3, 747–750

Summary: The pattern of free amino-acid concentrations in maternal venous plasma, fetal umbilical arterial plasma, fetal urine, and amniotic fluid at 15 to 20 weeks' gestation has been determined. Free amino-acid concentrations were greater in fetal plasma than in maternal plasma, amniotic fluid, or fetal urine.

The ratios of amino-acid concentrations in fetal umbilical arterial plasma and urine indicate that the fetal kidney can effectively conserve amino-acids, possibly reaching an adult level of competence in this respect.

There was little correlation between amino-acid concentrations in the fluids analysed with the exception of that between amniotic fluid and fetal urine.

Introduction

Patterns of urinary free amino-acid excretion have been established for adult man, the newborn infant, and a number of different animal species (Evered, 1956, 1967; O'Brien and Butterfield, 1963). Such patterns are characteristic but can be altered by pathological states. Thus urinary patterns may be disturbed by renal tubular defect or when plasma concentrations of individual or groups of amino-acids exceed the renal tubular threshold (Dent, 1954).

The purpose of this paper is to describe the pattern of plasma and urinary amino-acid concentrations in the fetus during early pregnancy, to relate these to maternal amino-acid concentrations, and to assess their influence on the composition of amniotic fluid.

Materials and Methods

Samples were obtained at hysterotomy pregnancy terminations between 15 and 20 weeks' gestation. The eight mothers

TABLE I.—*Amino-acid Concentrations (μmoles/litre)*

Amino-acid	Maternal Vein Plasma				Umbilical Artery Plasma				Fetal Urine				Amniotic Fluid			
	n	Range	Mean	S.D.	n	Range	Mean	S.D.	n	Range	Mean	S.D.	n	Range	Mean	S.D.
Taurine	7	41–77	53	13	8	150–488	280	103	8	212–397	274	74	8	81–259	123	58
Urea	6	1103–4620	2521	1277	7	1514–4410	2794	1023	7	3219–8731	6374	1857	7	1400–3850	2521	819
Aspartic acid	7	8–60	22	17	8	33–192	73	52	7	2–8	4	3	7	4–36	11	12
Hydroxyproline	7	N.D.	–	–	7	tr–54	–	–	7	49–87	67	15	7	27–52	41	8
Threonine	6	105–245	161	50	7	230–429	329	73	7	47–205	130	50	8	155–276	209	40
Serine	6	80–123	106	17	7	100–307	186	65	7	53–147	93	32	7	18–24	22	2
Asparagine	5	22–51	33	12	4	35–55	46	9	7	12–46	26	12	6	24–47	38	10
Glutamic acid	7	57–282	115	79	7	81–703	260	211	7	2–22	10	8	7	82–256	149	65
Glutamine	6	294–543	426	92	6	566–1103	724	200	7	78–324	182	100	7	42–380	186	118
Proline	7	74–120	107	16	7	173–382	242	72	8	81–202	148	50	7	131–222	181	31
Glycine	7	142–191	166	18	8	176–403	249	68	8	236–359	286	42	8	122–246	163	40
Alanine	7	151–272	218	38	8	286–785	424	169	8	48–166	100	40	8	248–419	327	53
Citrulline	7	15–27	20	5	8	15–34	23	6	8	6–18	11	5	8	tr–22	12	7
α-Amino-*n*-butyric acid	7	7–16	13	4	8	17–24	22	3	7	2–8	3	2	8	7–11	9	1
Valine	7	140–174	155	12	8	230–365	292	47	8	6–36	19	10	8	79–200	148	37
Cystine	7	tr–27	–	–	8	tr–55	–	–	8	26–92	50	21	8	60–155	80	33
Methionine	7	16–20	18	2	8	23–48	32	9	6	tr–5	–	–	8	14–27	19	4
Cystathionine	7	tr	–	–	6	3–6	5	1	6	3–9	6	3	7	2–4	3	1
Isoleucine	7	41–59	45	6	8	49–142	85	31	8	2–6	5	2	8	18–46	34	9
Leucine	7	72–99	91	9	8	107–268	164	58	8	7–31	16	9	8	36–107	77	23
Tyrosine	7	24–45	32	8	8	59–120	84	21	8	8–41	21	12	8	39–62	50	10
Phenylalanine	7	28–46	37	6	8	63–134	88	26	7	6–27	15	9	8	44–78	59	12
β-Alanine	7	N.D.	–	–	7	N.D.	–	–	7	tr–11	–	–	7	tr–10	–	–
Tryptophan	7	tr–35	–	–	7	tr–55	–	–	7	tr–15	–	–	8	4–15	9	4
Ethanolamine	7	tr	–	–	7	13–192	79	61	7	30–124	80	34	7	13–64	31	17
Ornithine	7	32–60	43	9	8	96–192	133	34	8	23–108	55	34	8	18–65	42	18
Lysine	7	111–159	133	16	8	362–553	468	57	8	177–574	357	142	8	133–325	219	69
Histidine	7	68–96	82	10	8	79–128	106	16	8	50–121	75	25	8	57–120	92	20
1-Methyl histidine	7	N.D.	–	–	7	N.D.	–	–	7	tr–4	–	–	7	tr–4	–	–
3-Methyl histidine	7	N.D.	–	–	7	N.D.	–	–	7	tr–11	–	–	7	tr–6	–	–
Arginine	7	36–73	51	13	8	84–132	115	15	7	9–67	23	20	8	31–110	59	24

N.D. = Not detected. tr = Trace.

studied were physically fit, and had no personal or family history of metabolic disorder. Anaesthesia was induced by intravenous thiopentone and maintained with nitrous oxide and 30% oxygen.

Amniotic fluid was aspirated through a large-bore needle from the intact amniotic sac after the uterus had been opened. The sac was then opened and umbilical arterial blood was withdrawn by syringe through a large-bore needle and transferred to a dry lithium-heparin tube. The fetal skin was dried with tissue, and urine (0·1—0·8 ml.) expressed from the bladder per urethra was collected in a clean dry test-tube. Maternal blood was obtained from the antecubital vein at the time of delivery and transferred to dry lithium-heparin tubes. Within 20 minutes of collection blood, urine, and amniotic fluid samples were centrifuged and the plasma or supernatant fluids were separated. Plasma and amniotic fluid were deproteinized by ultrafiltration, the ultrafiltrates and urine being adjusted to *p*H 2 with HCl and stored at −30°C. Free amino-acid concentrations in the samples were measured within seven days by ion-exchange chromatography (Cockburn *et al.*, 1970).

RESULTS

The means, ranges, and standard deviations for free amino-acid concentrations measured in each of the four groups of samples are given in Table I. The relative concentrations of amino-acids in umbilical arterial plasma and maternal venous plasma, umbilical arterial plasma and fetal urine, maternal venous plasma and amniotic fluid, umbilical arterial plasma and amniotic fluid, and fetal urine and amniotic fluid are shown in Table II. All of the amino-acids found in maternal and fetal plasma were present in fetal urine and amniotic fluid, but small quantities of β-alanine and 1-methyl and 3-methyl histidines were detected only in the urine and amniotic fluid.

The concentrations of amino-acids in umbilical arterial plasma were uniformly greater than those in maternal venous plasma and generally greater than those in fetal urine and amniotic fluid; concentrations in amniotic fluid tended to be greater than in maternal venous plasma and fetal urine.

Values for the ratios of urinary free amino-acids to umbilical arterial plasma free amino-acids are shown in the Chart.

Urea concentrations in maternal venous plasma, umbilical arterial plasma, and amniotic fluid were practically identical, but fetal urine contained significantly higher concentrations of urea.

Correlation coefficients were calculated between the amino-acid concentrations in the various fluids sampled after a few extreme values, where likelihood of occurrence was less than a 5% probability, had been excluded. The results are given in Table III.

DISCUSSION

Umbilical arterial plasma amino-acid concentrations at all gestational ages studied are significantly greater than in maternal venous plasma (Prenton and Young, 1969). It is clear from the results shown in Table II that at 15 to 20

TABLE II.—*Comparison between Mean Amino-acid Concentrations in Maternal Venous Plasma (MV), Umbilical Arterial Plasma (UA), Amniotic Fluid (AF) and Fetal Urine (FU).*

Amino-acid	UA:MV	UA:FU	UA:AF	MV:AF	FU:AF
Taurine	+	ND	+	–	+
Aspartic acid	+	+	+	ND	ND
Hydroxyproline		ND	ND		+
Threonine	+	+	+	–	–
Serine	+	+	+	+	+
Asparagine	ND	+	ND	ND	–
Glutamic acid	ND	+	ND	ND	–
Glutamine	+	+	+	+	ND
Proline	+	+	+	–	ND
Glycine	+	ND	ND	ND	+
Alanine	+	+	+	–	–
Citrulline	ND	+	+	+	ND
α-NH_2-*n*-butyric acid	+	+	+	+	–
Valine	+	+	–	ND	–
Cystine	ND	ND	+	–	–
Methionine	+	+	+	ND	–
Cystathionine		ND	+		+
Isoleucine	+	+	+	+	–
Leucine	+	+	+	ND	–
Tyrosine	+	+	+	–	–
Phenylalanine	+	+	+		–
Tryptophan	ND	+	+	ND	ND
Ethanolamine		ND	+		+
Ornithine	+	+	+	ND	ND
Lysine	+	+	+	–	+
Histidine	+	+	ND	ND	ND
1-Methyl-histidine					ND
3-Methyl-histidine					+
Arginine	+	+	+	ND	–
Urea	ND	–	ND	ND	+

+ Indicates that the amino-acid concentration in the first-named specimen is significantly greater ($P<0.05$) than that in the second named, – indicates that it is significantly lower, and ND indicates no significant difference.

TABLE III.—*Significant Correlations (Correlation Coefficients where P < 0·05 between Amino-acid Concentrations in Maternal Venous Plasma (MV), Umbilical Arterial Plasma (UA), Amniotic Fluid (AF), and Fetal Urine (FU)*

Correlation between:	UA : MV	UA : FU	UA : AF	MV : AF	FU : AF
No. correlations examined	22	27	27	24	29
Amino-acids where significant correlations were found	Isoleucine (pos) Leucine (neg) Phenylalanine (neg) Lysine (pos)	Proline (pos) Ornithine (pos)	Serine (neg)	Threonine (pos) Cystine (pos)	Taurine (pos) Valine (pos) Methionine (pos) Cystathionine (pos) Isoleucine (pos) Leucine (pos) Tyrosine (pos) Phenylalanine (pos) Histidine (pos) 3-Me-histidine (pos)

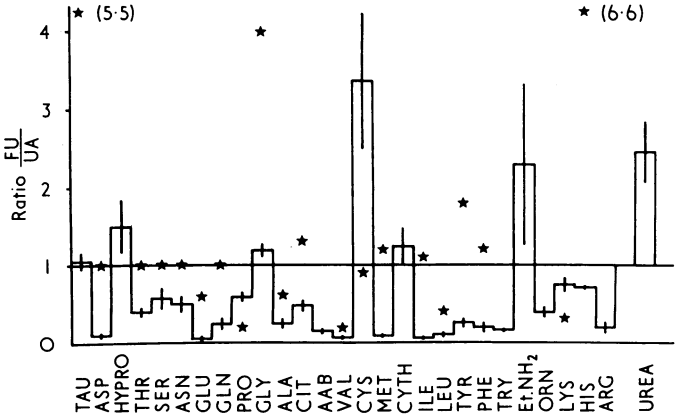

Chart showing ratios for free amino-acid concentrations between fetal urine (FU) and umbilical arterial plasma (UA). Columns represent mean values and the vertical lines ±1 S.E. of mean. The asterisks indicate corresponding adult values (Evered, 1967).

weeks' gestation amino-acid concentrations in fetal urine, amniotic fluid, and maternal plasma are less than those of fetal plasma.

The amino-acid composition of umbilical arterial plasma must approximate to that of renal arterial plasma. Fetal urine to fetal umbilical artery plasma ratios for amino-acids give some indication of renal plasma amino-acid clearance (Evered, 1956). These endogenous clearances or ratios are given in the Chart and are contrasted with adult human ratios reported by Evered (1956, 1967). The fetal ratios are usually less than 0·5 in the presence of high plasma amino-acid concentrations (and presumably high concentrations in the glomerular filtrate), implying efficient conservation of most amino-acids even at this early stage of fetal development. The ratio for urea is nearly 2·5. Fetal ratios are generally much less than those for the adult. These lower fetal ratios could be due to reduced capillary permeability to amino-acids. This seems unlikely because at 16 weeks of gestation 30% of glomeruli appear histologically mature and allow the passage of radio-opaque dye and other substances of moderately large molecular weight (Vernier, 1964). A more likely explanation is that there is greater reabsorption of water by the adult renal tubules, with the production of a more concentrated urine.

If we assume that the concentrating power of the fetal kidney is half that of the adult, the fetal urine to umbilical artery plasma ratios obtained show that the capacity of the fetal kidney to conserve amino-acids is comparable to that of the adult kidney. Little of most of the essential amino-acids reaches the urine, with the particular exception of lysine. The high lysine ratio is difficult to interpret but is a very constant feature. Ratios for taurine, glycine, and histidine are relatively high, as would be expected; for these compounds are poorly absorbed compared with most other amino-acids (Evered, 1956; Cusworth and Dent, 1960). The high value for free hydroxyproline excretion is interesting as the total urinary excretion of this amino-acid has been taken as an index of growth rate (Younoszai *et al.*, 1969). The high cystine ratio may be spurious, for there is a variable loss of cystine from plasma during sample collection and preparation. Tryptophan is also partially destroyed during the ultrafiltration and elution processes.

The high number of significant positive correlations which exist between amino-acid concentrations in early fetal urine and in amniotic fluid suggests that among the various fluids sampled the closest relationship existed between these two. In addition to the 10 significant correlations there were a further four positive correlations for which P was less than 0·1.

These correlations could be explained on the basis that fetal urine makes a significant contribution to amniotic fluid amino-acid composition or, alternatively, that the chorio-amnion might selectively transfer amino-acid in a pattern comparable to that maintained by the fetal kidney tubule.

All 10 significant correlations between amino-acid concentrations in fetal urine and amniotic fluid were positive, but in contradistinction to this there was a significant negative correlation between urea concentrations in fetal urine and amniotic fluid. This might imply a completely different mechanism for urea transport.

Clearly the amino-acids in amniotic fluid must ultimately come from the mother. There is normally an active, rapid, and selective transfer of maternal plasma free amino-acids across the placental villi to umbilical venous plasma (Dancis, 1960). Direct transfer of amino-acids can occur across the amnion and chorion (Sugawa *et al.*, 1963), and may occur across the fetal surface of the placenta and the umbilical cord. During early pregnancy there is a considerable quantity of Wharton's jelly lying between the chorion and amnion which might contribute amino-acid to amniotic fluid. Fetal skin, salivary glands, lung fluid, and intestinal secretions could all make a contribution. Our data throw no light on these other sources from which the amniotic fluid might draw for its amino-acid content.

The normal early pregnancy amniotic fluid amino-acid values reported provide a basis for further study of amniotic fluid amino-acid content in the mother known to be a carrier of an inborn error of amino-acid metabolism. Inborn errors which result in altered fetal urinary amino-acid excretion might thus be identified in utero.

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Medical Memoranda

Macroglobulinaemia Treated with Prednisone, Azathioprine, and Folic Acid

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Primary macroglobulinaemia is a condition within the spectrum of the malignant immunoproliferative disorders and is generally treated with cytotoxic drugs in an attempt to suppress growth of the abnormal cells. This report describes the case of a patient in whom severe anaemia responded to treatment with prednisone, folic acid, and azathioprine when other cytotoxic drugs had failed and the patient appeared to be in a terminal stage of the illness.

Case Report

A woman aged 39 came to hospital in 1960 with gingivitis, palatal ulcers, and fever and was found to have a neutropenia. Some enlarged lymph nodes were present, but the spleen was not palpable. Bone marrow examination suggested chronic lymphatic leukaemia, and plasma protein electrophoresis showed a band within the gammaglobulin (total gammaglobulin 2·4 g./100 ml.). The patient responded to betamethasone after chlorambucil treatment had been unsuccessful. She remained well for eight years, with normal peripheral blood counts, while taking a small maintenance dose, and then relapsed in 1969 with similar clinical and haematological features though no lymph node enlargement was now found.

The bone marrow again showed a pronounced excess of lymphoid cells, some of which had numerous microsomes and a poorly formed endoplasmic reticulum. Erythropoiesis was normoblastic and the serum folate concentration was normal. Plasma protein electrophoresis showed an M band, subsequently found to be a 19S (IgM) globulin, and immunofluorescent studies with an antiglobulin prepared from the patient's own abnormal serum protein suggested that it was derived from large marrow cells, thought to be reticulum or blast cells. The serum immunoglobulin concentrations were abnormal (IgG 760 mg./100 ml., IgA 40 mg./100 ml., and IgM 1,500 mg./100 ml.). Other findings were: Hb 12·4 g./100 ml.; W.B.C. 1,600/mm^3 (neutrophils 1%, lymphocytes 90%, monocytes 9%); reticulocytes <1%; platelets 356,000/mm.^{3}; urinary urobilinogen not detected at 1 in 20 dilution; Bence Jones protein absent; skeletal *x*-ray picture normal; Coombs test negative; cryoglobulin absent; total gammaglobulin 1·9 g./100 ml.

In spite of treatment first with chlorambucil in addition to a small dose of betamethasone and then with a combination of cyclophosphamide and prednisone, the haemoglobin fell steadily over 10 weeks to 1·6 g./100 ml. and the total white cell count to 350/mm.^{3}, without any change in the marrow appearances. Throughout this period there was no reticulocytosis or increase of urobilinogen in the urine. Blood transfusion was accompanied on three occasions by clinical evidence of a severe reaction, including jaundice, and was abandoned. The patient was then treated with azathioprine 150 mg. and prednisone 40 mg. daily. Though the marrow was normoblastic, folic acid was also given in a dosage of 5 mg. twice daily in case there might be an unexpected haemopoietic response. A pronounced reticulocytosis resulted almost immediately and was followed by clinical and further haematological improvement. The marrow seven weeks later showed a decrease in abnormal cells and an increase in granulocytes and normoblasts. Normal peripheral blood counts were obtained after four months, when the chemotherapy was reduced to azathioprine 100 mg. and prednisone 20 mg. daily together with the folic acid and have so far persisted for more than a year. The serum immunoglobulin concentrations have not been significantly altered by the therapy.

Discussion

Macroglobulinaemia, like myeloma, is predominantly a disease of the older age groups. In this patient, who was only 39 at the time of her first hospital attendance, the diagnosis has been based on the demonstration of an abnormal quantity of 19S (IgM) globulin in her plasma together with the results of light microscope, electron microscope, and immunofluorescent studies of the bone marrow. These are consistent with macroglobulinaemia (Maldonado *et al.*, 1966; Marmont and Damasio, 1968). The severity of the anaemia, together with the low concentration of circulating macroglobulin and the unchanged level of total gammaglobulin eight years after the appearance of symptoms, is not the usual pattern in primary macroglobulinaemia (Waldenström, 1965) and for this reason the patient is thought to have the condition in an atypical form.

The main feature that we wish to stress is the response to a combination of azathioprine, prednisone, and folic acid when other methods of therapy had failed. The pronounced reticulocytosis which followed soon after the introduction of this regimen might suggest that the abnormal process was a depression of haemopoiesis, perhaps immunological, which has been corrected by the treatment. The improvement in the marrow appearances, however, indicates clearly that therapy reduced the number of abnormal cells. Our reasons for giving folic acid were not very good, particularly as the serum folate level had been normal. Nevertheless, it is still possible that the folic acid helped the regeneration of erythropoietic tissue.

The way in which these drugs acted in this patient is uncertain. Perhaps this combination of drugs has a mode of therapeutic action differing from that of other cytotoxic agents, and it should be tried, possibly without folic acid, in other such patients who are deteriorating.

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