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IMPAIRED RENAL EXCRETION OF HYPOXANTHINE (Hx) AND XANTHINE (X) IN PRIMARY GOUT. J Puig, F Mateos, M Jiménez, T Ramos, MC Capitán, and A Gil. 'La Paz' Hospital, Departments of Internal Medicine and Clinical Biochemistry, Universidad Autónoma, Madrid, Spain.

Most patients with primary gout show normal uric acid (UA) production rates and a relative underexcretion of UA. To examine if the renal dysfunction for UA excretion in primary gout also affects the excretion of UA precursors, we compared the plasma concentrations and 24 hour urinary excretion of Hx and X in 10 normal subjects, 15 patients with primary gout and UA underexcretion and 10 patients with diverse enzyme deficiencies known to overproduce UA. All subjects showed a creatinine clearance above 80 ml/min/1.73 m^2. Results (mean±SEM) were as follows

	PLASMA			URINE		
	UA	Hx	X	UA	Hx	X
	(μM)			(μmol/24 h/1.73 m^2)		
Controls (n=10)	286±12	1.4±0.1	0.7±0.1	2576±655	53±3	32±3
Primary gout (n=15)	476±30*	3.7±0.4*	1.3±0.1*	2505±1488	25±3*	13±1*
UA overproduction (n=10)	553±71*	4.0±0.9*	1.5±0.3*	9449±1607+	308±95*+	141±33*+

*P < 0.01 vs controls; +P < 0.01 vs primary gout

Urinary UA excretion was correlated with Hx and X excretion (r=0.857; P<0.01 and r=0.927; P<0.01, respectively). A significant direct relationship was found between the renal clearances of UA, Hx and X. These results indicate that patients with gout who underexcrete UA are also underexcretors for Hx and X. The renal impairment for UA excretion in primary gout appears to be more extensive than previously recognized.

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THE ALLOPURINOL HYPERSENSITIVITY SYNDROME: ITS RELATION TO PLASMA OXIPURINOL LEVELS. E Casas, J Puig, F Mateos, M Jiménez, A Michán, and T Ramos. 'La Paz' Hospital, Departments of Internal Medicine and Clinical Biochemistry, Universidad Autónoma, Madrid, Spain.

Adverse reactions to allopurinol frequently involve the skin, liver, kidneys, gastrointestinal system and bone marrow. Pharmacologic studies have suggested that the serum concentration of oxipurinol appear to correlate with the development of life-threatening allopurinol toxicity. A male patient (89-years-old) with asymptomatic hyperuricemia (8.1 mg/dl) was treated with allopurinol (300 mg/24 h). No concommitant medications were administered. Six weeks later he presented fever (39°C), eosinophilia (1.92x10^9/L), exfoliative dermatitis, hepatocellular injury and renal failure (serum creatinine, 4.6 mg/dl). A plasma sample drawn 8 hours after the patient's last dose of allopurinol showed an oxipurinol concentration by HPLC of 50 μM. This drug was discontinued and prednisone was instituted. His symptoms and epidermal necrolysis cleared and liver and renal abnormalities subsided over 2 weeks (serum creatinine, 2.0 mg/dl). Plasma oxipurinol levels in 4 patients with uric acid overproduction (3 with HPRT deficiency and 1 with PRPPs overactivity) who were receiving allopurinol (5-10 mg/Kg/24 h) ranged from 48 to 175 μM. No adverse reactions were documented in these patients. This case illustrates that serious hypersensitivity reactions to allopurinol may occur despite plasma oxipurinol concentrations within what it is considered a normal therapeutic level (< 100 μM).

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SHOULD DIETARY RESTRICTIONS ALWAYS BE PRESCRIBED IN THE TREATMENT OF GOUT ? A González, J Puig, F Mateos, M Jiménez, E Casas, and MC Capitán. 'La Paz' Hospital, Departments of Internal Medicine and Clinical Biochemistry, Universidad Autónoma, Madrid, Spain.

Primary gout is commonly associated with other metabolic disorders such as obesity, arterial hypertension, hyperlipidemia and diabetes mellitus that usually require a dietary regimen. However, long-term compliance to dietary restrictions may be rejected by subjects with a chronic disease and a peculiar tendency for purine-rich food. Among 175 patients with primary gout, 133 (76%) had associated metabolic disorders: 75 were obese (43%), 63 had arterial hypertension (36%), 67 showed hypercholesterolemia or hypertriglyceridemia (38%) and 10 had diabetes mellitus (6%). Besides gout, 42 patients (24%) had no other metabolic derangements requiring dietary intervention. In these patients a purine-restricted diet (< 75 mg/24 h of purines) for 5 days diminished the serum urate concentration from a base-line value of (mean±SEM) 8.9±0.2 to 7.2±0.2 mg/dl (P<0.001) and uric acid excretion from 792±53 to 478±29 mg/24 h (P < 0.001). The administration of allopurinol (300 mg/24 h) for 5 days, while patients were on a self-selected diet, reduced serum urate to 5.4±0.1 mg/dl (P<0.001) and uric acid excretion to 374±22 mg/24 h (P<0.001). These data indicate that allopurinol normalises uric acid metabolism in patients with primary gout who had no associated metabolic disorders, despite the intake of a self-selected diet.

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RED BLOOD CELL MORPHOLOGY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): EFFECT OF OXYGEN THERAPY VERSUS ALLOPURINOL. A Michán, J Puig, P Crespo*, F Macías*, A González, and J Ortíz. 'La Paz' Hospital, Department of Internal Medicine, Universidad Autónoma, Madrid, and *Department of Histology, Granada, Spain.

Morphologic abnormalities in red blood cells depend on diverse factors which may include the intracellular content of oxygen. Hypoxemia increases adenine nucleotide turnover and may influence erythrocyte morphology. To test this hypothesis in 7 patients with clinically stable COPD we measured red cell ATP (iATP) levels by HPLC and observed erythrocyte morphology by scanning electron microscopy. Studies were carried out in 3 situations: basal state (mean±SEM; PaO_2, 58±3 mm Hg), after 7 days on oxygen therapy (PaO_2, 79±4 mm Hg; P<0.01) and following a 7 day course on allopurinol (300 mg/24 h; PaO_2, 58±3 mm Hg). iATP concentrations were similar in the 3 experimental conditions. However, significant differences were observed with respect to the distribution of discocytes, stomatocytes and sphero-stomatocytes. Stomatocytes decreased markedly from a mean base-line number of 23.8% of total red cells to 12.0% on oxygen therapy (P<0.001) and to 14.5% on allopurinol (P<0.001). These data indicate that hypoxemia promotes red cell morphologic alterations that do not depend on iATP levels. Short-term allopurinol administration to COPD patients decreases morphologically abnormal cells by reducing the production of stomatocytes to a level similar to that observed with oxygen therapy.

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CHANGES IN TROPHOBLASTIC PURINE METABOLISM WITH AGING OF THE PLACENTA. Karl O. Raivio and Kim Vettenranta, Children's Hospital, University of Helsinki, Helsinki, Finland

With advancing gestation, growth of the placenta stops before the deceleration of fetal growth, and complications related to placental insufficiency become more common. It has been postulated that the fetus "outgrows" its placenta. We have compared the metabolic properties (purine nucleotide synthesis and their catabolism in response to oxygen and glucose deprivation) of trophoblastic cells, cultured from first (I) and third (III) trimester human placentae and shown by immunofluorescence (cytokeratin) and hormone production (chorionic gonadotropin) to retain their specialized trophoblastic character in primary culture.

Purine synthesis de novo (14-C-formate incorporation) in I was two orders of magnitude lower than in fetal fibroblasts, but even lower (1/4) in III. The rate of 14-C-hypoxanthine phosphoribosylation was at least 10-fold higher than de novo synthesis in both I and III, and unresponsive to high extracellular Pi. ATP level or energy charge (EC) were not influenced by glucose or oxygen deprivation for 8 hr, but 2-deoxyglucose caused a fall in prelabeled ATP to 1/5 and in EC to 0.42-0.46 (control 0.66-0.71) in 30 min in both I and III. Inhibition of oxidative phosphorylation by rotenone had similar effects than 2-deoxyglucose in III, but significantly more delayed in I.

We conclude that human trophoblast at term is metabolically less active and less tolerant to energy substrate deprivation than early in gestation.

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ARTEFACTS DUE TO RADIATION-INDUCED CELL DAMAGE IN PULSE-LABELING EXPERIMENTS USING TRITIATED NUCLEIC ACID PRECURSORS. Juha Salonen, Karl O. Raivio, and Lauri Saxén. Department of Pathology and Children's Hospital, University of Helsinki, Helsinki, Finland.

In studies on embryonic induction, unexpected results were obtained when cultured kidney tissue from mouse embryos was pulse-labeled with 3H-thymidine or -adenine and then subcultivated. A 2-h pulse of 20 μCi led in 2-3 days to morphologically detectable cell death in the mesenchyme and to impaired growth. After day 1, the DNA content of untreated control explants increased linearly, whereas no increase occurred in labeled explants until day 4, when a linear growth phase ensued. On day 8 the DNA content was 50-60% of the controls. Onset of linear growth coincided with the disappearance of label from the acid-insoluble fraction of the tissues, suggesting elimination of the initially labeled cells. In tissues treated with high pulses, the adenylate energy charge in the acid-soluble extracts decreased to 0.5.

We postulated that radiation-induced DNA damage activates poly(ADP-ribose)polymerase, which leads to consumption of NAD and a rapid drop in the ATP-level, eventually resulting in cell death. Dose-dependence experiments supported our hypothesis: labeling of the acid-insoluble fraction increased linearly until a pulse of 10 μCi 3-H-adenine, whereafter the curve leveled off. The critical point corresponds to ca. 1-5 DPM/ng DNA. The leveling-off was prevented by 3-aminobenzamine, an inhibitor of poly(ADP-ribose) polymerase.

Our findings suggest that subsequent cell growth may be affected by rather low doses of low-energy radiation.