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Tolerance and Effects of High Doses of Ascorbic Acid

Dosis facit venenum

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Summary: The few literature references suggesting adverse effects of high doses of ascorbic acid are outnumbered by a large number of clinical studies in which no adverse effects have been observed. Up to 5 g ascorbic acid daily may be administered safely even over a long term. Favourable effects of even higher doses in man may justify therapeutic trials in the range of 15 g daily which in our trials have proven safe during treatment of up to 2 years. Nevertheless, trials in the high dosage range mentioned should always be closely supervised by a physician, being aware that exceptional behaviour can occur at any time, as exception proves the rule.

In the beginning of the 16th century, Theophrastus Bombastus von Hohenheim, called Paracelsus, originator of the new medical science, taught his medical students at the University of Basle that in every substance two qualities are contained, one essential for human well-being called "Essentia", the other producing illness called "Venenum", meaning poison. The alchemists of those days tried to separate both qualities to gain purely therapeutic drugs with no side effects. Paracelsus knew already that only the dosage determines whether a substance is a poison or not. This implies that there is no substance which may be called simply a poison, as manifestation of a poisonous effect depends on several conditions, the most important being the dose. Or we may state that every substance may be a poison, provided a high enough dose is administered. This dose differs widely from substance to substance, varies individually and depends on several other factors such as general health, genetic factors, adaptation, etc.

It is essential to know the tolerance and lexicological limits when administering a substance for therapy. One aspect is safety, the other is reaching full efficacy. The difference between the therapeutic and toxic doses, the therapeutic ratio, is therefore of major imortance in judging safety of an established therapy. A narrow therapeutic ratio is always unfavourable and may prevent the attainment of full therapeutic

activity by causing side effects too early. But many drugs have to be administered near to the very limits of toxicity and sometimes even beyond these limits, e. g. streptomycin, salicylates and many anthelmintics.

The therapeutic risk one takes depends of course always on the severity of the disease.

Knowledge of the toxic dosage limits is especially important for development of a new drug or in a new indication, to deal completely with the suggested therapeutic activity of that substance.

In the case of vitamins, especially of vitamin C, the therapeutic ratio is very favourable. This is undisputed in relation to nutritional intake. For example, to cure scurvy, the classical highly dangerous but in industrialized countries nowadays apparently rare vitamin C-deficiency disease, only a few milligrams of ascorbic acid are necessary for cure, far from any toxic dose. But pharmacodynamically or pharmacologically active doses, especially in possible new fields of application, are far higher, thus posing the question of toxicity anew.

The toxicity differs from species to species and depends greatly on the mode of application. To measure toxicity, a standard reference dose is determined in animal experiments, the lethal dose LD_{50}. Table I summarizes the LD_{50} values for acute toxicity and Table II shows the values for sub-chronic toxicity.

Sodium salt is even less toxic (Table III), and the least toxic for mice is Ascorbyl palmitate (Table IV).

Mice tolerate 2 g sodium ascorbate per kg bodyweight i. v. without symptoms. For comparison also the lethal doses of dehydroascorbic acid may be demonstrated (Table V).

Table VI shows the single maximum doses that have been well tolerated. The aqueous solutions of ascorbic acid were neutralized with NaOH a short time before parenteral application.

To determine chronic toxicity is much more difficult. Some chronic toxicity experiments are summarized in Table VII. Ascorbic acid was administered daily for 7 weeks. In none of these experiments were histopathological changes seen. Histologically kidneys, liver, heart, lungs, adrenals, spleen and intestine were normal. In the dog 250 mg/kg bodyweight of ascorbic acid showed no effect on carbohydrate and protein metabolism. There was no ascorbic acid in the feces. 10 g ascorbic acid per kg bodyweight and day is suggested to be the maximum non-toxic dosage in rats and guinea-pigs [44].

The threshold for toxicity of ascorbic acid is supposed to be depressed in diseased states, especially in severe vitamin C deficiency. With respect to possibly unrevealed deficiency states in the elderly or in the diseased subject, we have studied the effects of high doses of ascorbic acid in severely ascorbic acid-depleted guinea-pigs. Growing guinea-pigs were depleted until a standstill of growth was reached by the beginning of the 3rd week of depletion. Control animals continued to grow normally. Depleted animals were divided into two groups. One group remained on their ascorbic acid-free diet, half of the other group receiving 200 times, and the other half 400 times

Tab. I: Vitamin C, acute toxicity, LD 50. All doses in mg/kg body weight

Species	Mode of administration			
	orally	s.c.	i.v.	i.p.
Mouse	8,021	5,000	1,058	2,000
Rat	> 5,000	5,000	1,000	
Guinea-pig	> 5,000	> 1,000	500	2,000
Rabbit	> 2,000	> 1,000	> 1,000	> 1,000
Cat	> 1,000	> 500	> 500	
Dog	> 5,000	> 200	> 200	

Tab. II: Vitamin C, sub-chronic toxicity (LD 50). All doses in mg/kg body weight

Species	Mode of administration				duration days
	orally	s.c.	i.v.	i.p.	
Mouse	8,021				10
Mouse			1,058		10
Rat	> 6,500				6
Rat		> 600			28
Guinea-pig	> 8,900				6
Guinea-pig		500			7
Guinea-pig				100	16
Rabbit			500		7
Rabbit				100	16
Cat			> 500		9
Dog					7
Dog	100		> 2,000		3

Tab. III: Na-Ascorbate, acute and subacute toxicity. All doses in mg/kg body weight, oral

Species	LD %	24 h after 1st dose	24 h after 5th dose	10 days after 5th dose
Mouse	10	9,880	9,000	9,000
	50	15,500	11,300	11,300
	90	24,300	14,100	14,000
Rat	10	18,000	9,490	9,490
	50	22,600	14,500	14,500
	90	28,300	22,300	22,300

Tab. IV: Ascorbyl palmitate, acute toxicity. All doses in mg/kg body weight, oral

Species	DL %	24 h	10 days
Mouse	10	> 20,000	> 20,000
	50	> 20,000	> 20,000
	90	> 20,000	> 20,000
Rat	10	> 10,000	> 10,000
	50	> 10,000	> 10,000
	90	> 10,000	> 10,000

Tab. V: Dehydroascorbic acid, acute toxicity. All doses in mg/kg body weight, oral

Species	DL %	24 h	10 days
Mouse	10	7,200	6,400
	50	11,000	10,000
	90	16,800	15,700
Rat	10	> 8,000	5,080
	50	> 8,000	8,000
	90	> 8,000	> 8,000

Tab. VI: Well tolerated single doses of ascorbic acid.
Neutralized with NaOH when applied parenterally mg/kg body weight

Species	oral	s.c.	i.v.	i.p.
Axolotl	–	5,000	–	5,000
Frog	–	5,000	–	5,000
Cat	1,000	500	500	–
Dog	500	200	200	–
Guinea-pig	5,000	1,000	500	–
Mouse	5,000	5,000	1,000	2,000
Rabbit	2,000	1,000	1,000	1,000
Rat	5,000	2,500	1,000	–

Tab. VII: Chronic toxicity, 7 weeks. Daily doses in mg/kg body weight

Species	orally	s.c.	i.v.
Dog	100	–	–
Guinea-pig	500	500	–
Rabbit	–	–	500

No histo-pathological changes, no stone formation (gall-, urinary bladder, kidney).

Table. VIII: Claimed adverse effects of high doses of ascorbic acid in man

Adverse effect	Dose/day	Days of administration	Number of subjects	Lit. ref.
Embryotoxicity	6 g i.v.	3	16	Samborskaya [55]
Sickling crisis	high dose	–	1	Goldstein [22]
Decreased fertility	2–5 g	90–180	2	Briggs [14]
Renal stone formation	2 g	14	1	Briggs [15]
Rebound-effect	10–15 g	14	1	Schrauzer [59]
Deep vein thrombosis	3 g	1	1	Horrobin [38]
Vitamin B_{12} destruction	1 g	–	4	Herbert [31]
Priapism	0.5 g	70	3	Port [49]
High-altitude resistance ↓	3 g	6	3	Schrauzer [58]
Proximal esophagitis	0.5 g	1	1	Walta [69]
Pyrexia, rigors pain	10 g i.v. + 10 g p.o.	1.5	1	Campbell [18]
Hodgkin's disease exacerb.	20 g i.v.	10	1	idem
Dyspnea	20 g i.v.	5	1	idem
Heart beat rate ↑ with isoprenaline n.s.	5 g	1	20	Hajdu [24]

Tab. IXa: Effects and side-effects of high doses of ascorbic acid in man

Indication	Dose/day	Days	Effects	Side-effects	Study	Cases	Lit. ref.
Hepatitis	10 g i.v.	5	bilirubin ↓ recovery	none	c	11	Baur [10]
Poliomyelitis	30 g	7–10	return of deep refl.	slight gastro-enteritis	o	5	Greer [23]
Hepatitis	10 g	8	improvement	none	c	93	Baetgen [6]
Hepatitis	10 g	8	improvement	none	c	62	ibidem
Urinary acidification	6–8 g/m^2	4	pHX = 0.49	none	c	12	Travis [66]
Glaucoma	0.4–1 g/kg b.w.	1	normotension	none	c	5	Virno [68]
Glaucoma	0.5–0.7 g/kg b.w.	10	idem	diarrhoea, mild gastric disorder disappearing after 3–4 d	c	25	Virno [67]
Saturation test	5–100 g	1	saturation	–	c	83	Herjanic [32]
Glaucoma	0.5 g/kg i.v.b.w.	1	idem	none, normal blood pressure and heart rate	c	43	Reddy [51]

c = controlled; o = open; b.w. = body-weight

RDA-amounts of ascorbic acid from the 25th day of experiment onwards. The further depleted animals continued to lose weight from about 350 g to 320 g. On the 28th day of the experiment the severely depleted group was further divided into two, one half receiving 200 times, and the other 400 times the RDA-amounts of ascorbic acid (Fig. 1). No adverse effects could be demonstrated [28].

In the course of time, with respect to side effects of high doses of ascorbic acid in man, several papers have been published suggesting or claiming adverse effects. The following table gives an overview (Table VIII). Contrary to these reports, many papers have been published stating no or negligible side-effects of even higher doses of ascorbic acid [40, 70]. A summary is given in Table IX a-c.

The data summarized in the last tables do not claim to cover all papers published so far relating to effects and side-effects of high ascorbic acid intake, but they may be looked at as being representative qualitatively and quantitatively.

Under the influence of high-dosage ascorbic acid therapy, some pathophysiologically important changes in the chemistry of urine have been reported.

One aspect derives from the acidic nature of the vitamin, the other from its endogenous pathway of degradation.

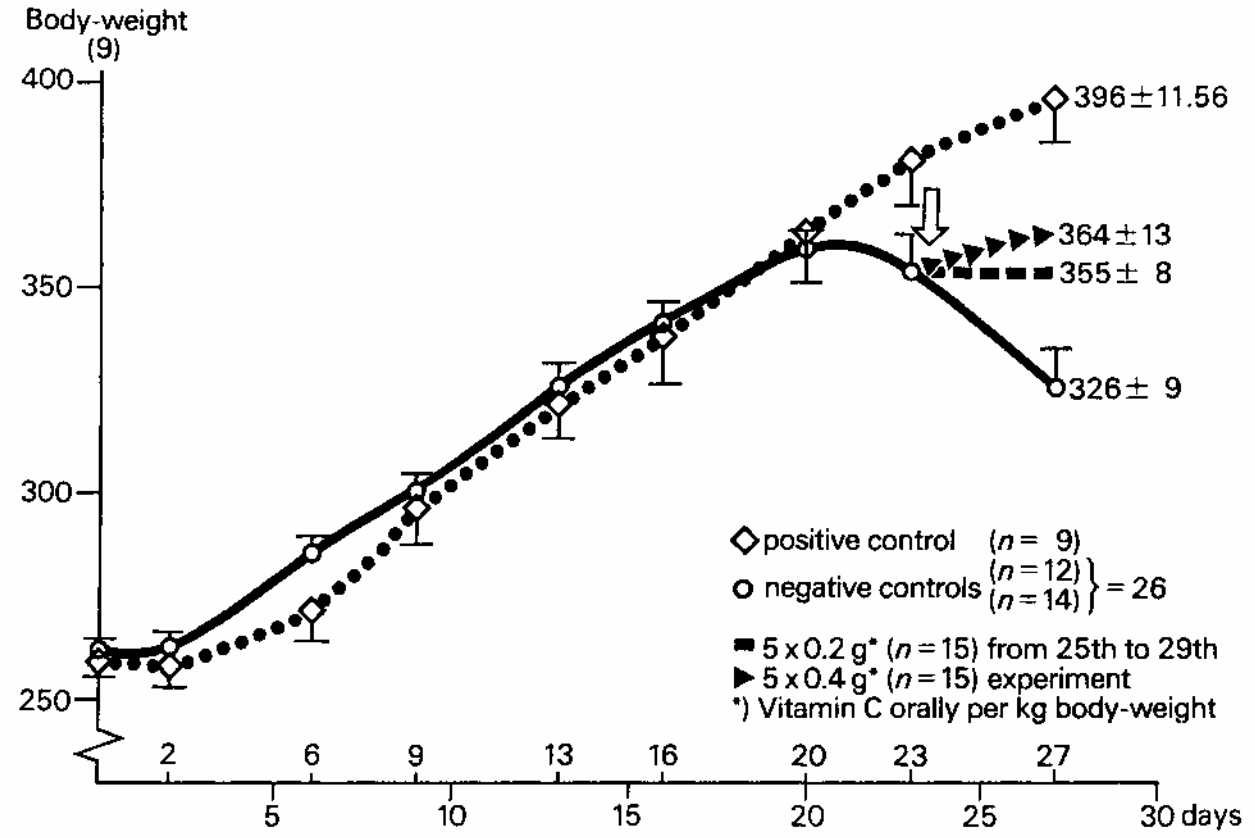

Fig. 1: Development of body weight. Ascorbic acid-deficient animals received ascorbic acid shortly after the begin of bodyweight decline indicated by an arrow.

Tab. IXb: Effects and side-effects of high doses of ascorbic acid in man

Indication	Dose/day	Days	Effects	Side-effects	Study	Cases	Lit. ref.
Common cold	3–30 g	–	severity ↓ frequency	no kidney stones, no miscarriage, but diarrhoe	o	1000	HOFFER [35]
Lenticular opacities	4 g	120	clear lenses	no hyperoxaluria, no nephrolithiasis	o	1	POSER [50]
Common cold	3 g	2000	–	no infertility	o	4	HOFFER [34]
Common cold	2 g	90	symptoms ↓ ⩽30% frequency ↓ ⩽10%			308	ANDERSON [3]
Common cold	4 g	1	symptoms ↓ ⩽30% frequency ↓ ⩽10%	none; no rebound effect	db	275	
Common cold	8 g	1	symptoms ↓ ⩽40% frequency ↓ ⩽20%			305	

o = open; db = double-blind

Tab. IXc: Effect and side-effects of high doses of ascorbic acid in man

Indication	Dose/day	Days	Effects	Side-effects	Study	Cases	Lit. ref.
Osteogenesis imperfecta	50 mg/kg b.w.	300–1300	fractures ↓ incidence	none	c	13	KURZ [41]
Spinal cord injury	4 g	330	acidic urine	none, normal serum B_{12}	o	10	AFROZ [2]
Leg ulcers in thalassaemia	3 g	56	recovery	1 mild «heartburn», 2 diuresis	db	8	AFIFI [19]
Stress	6 g	2	improvement of mental performance	none	db	30	MONTANDON [47]
Migraine	6 g	15	control of headaches	none	db	1	BALI [7]
Bone mineralisation	1 g	–	–	none	c	40	EKVALL (20)
Posttransf. hepatitis	100 mg/kg b.w.	5	hepatitis ↓ incidence	not mentioned	c	141	BANIČ [9]

c = controlled; o = open; db = double-blind; b.w. = body-weight

Ascorbic acid has often been proposed as a urinary acidifying agent, and dangerous effects due to over-acidification of urine by high doses of ascorbic acic have been claimed, especially due to alterations in the dissolubility characteristics of strongly acid urine. This is particularly important when drugs with low pK_a values are taken, in addition.

Following a daily intake of 10 g ascorbic acid for 10 days, a mild metabolic acidosis and moderate urinary acidification was reported [54]. In a crossover trial, 12 normal males received 4 and 6 g ascorbic acid daily. The 4 g per day (4 doses) treatment resulted in a mean urine pH significantly different from that in both control periods. The 6 g per day (4 doses) treatment was not different from the control period. The largest mean pH decrease was 0.34 when compared with the control periods. No gastrointestinal upset, cramping, diarrhea or other side-effects occurred [48].

In two separate trials we have investigated the influence of 4 g ascorbic acid per day on pH and redox potential of 24-h urine and their diurnal variations in healthy volunteers.

In the first trial, 12 healthy volunteers ingested 4 g ascorbic acid daily for a period of 2 weeks. 24-h urine was sampled on the last day of a week in which no vitamins had been taken. Then the ingestion of ascorbic acid was started and 24-h urine was collected every second day. The pH-value and redox potential were measured by an electrical pH-meter. The results are given in Tables X and XI.

The mean values show that there is no significant influence of the ingestion of 4 g ascorbic acid on urinary pH or on the redox potential. Haifa year later, a second trial was conducted in the same 12 volunteers again with 4 g ascorbic acid daily for 3 weeks. In this trial, each specimen of urine was checked for its pH and redox potential immediately after being passed. In this trial, the urine specimens were also checked during one week prior to vitamin intake. For technical reasons immediate urinary pH and redox potential could only be measured during working days, each day except Saturday and Sunday. In all trials there were no restrictions in food intake. The results are given in Table XII.

These data again show no significant differences between the control and treatment periods. In the period preceding the high ascorbic acid intake, the lowest measured urinary pH was 5.15, and during the period of daily intake of 4 g ascorbic acid the lowest pH was 5.03. In normal men urinary pH is 5.7, which corresponds very well with the mean value of 5.66 which we have found. In no significant contrast to that the mean pH value of 345 specimens was 5.55 during the experimental period. Normal human urine shows a diurnal rhythm of the pH. Urine is least acid on awakening and most acid about midnight. According to LICHTWITZ urinary pH is a reflection of stomach and pancreatic function [45].

Urine becomes less acid during gastric hydrochloric acid secretion and more acid when pancreatic juice is excreted. This diurnal variation in urinary pH has been recognized for many years, whilst diurnal variation of urinary redox potential has been poorly investigated. Changes in urinary pH are of great interest with respect to

urological diseases as well as to changes in solubility of metabolites and drugs occurring in human urine.

In general the pH of human urine should be kept in the acidic range. Alkaline urine always suggests a urinary tract infection and favours it. Oral ascorbic acid intake normalizes pathological urinary pH [46] and may be used for the prevention of recurrent urinary tract infection [37]. Figure 2 shows the diurnal rhythm of urinary pH in man with and without a daily intake of 4 g ascorbic acid for 3 weeks. It is shown that the diurnal rhythm of urinary pH is preserved during the period of ascorbic acid intake. Figure 3 shows the diurnal rhythm of urinary redox potential, which also shows a preserved diurnal rhythm. All our data (Table XIII) show that even with very high daily dosage of ascorbic acid normally achievable acidic urinary pH is not exceeded.

Tab. X: Urinary pH, influence of 4 g ascorbic acid (AA) 12 males, daily intake, 2 weeks, 24-h urine

AA (g)	$\bar{X}$	N	SD	SEM
0	5.66	12	0.34	0.10
4	5.75	68	0.35	0.04

Tab. XI: Urinary redox potentional (mV) with and without 4 g ascorbic acid (AA) intake daily, 12 males, 2 weeks, 24-h urine

AA (g)	$\bar{X}$	N	SD	SEM
0	24	10	22	7
4	23	68	21	3

Tab. XII: Urinary pH (a) and redox potential (b), with and without 4 g ascorbic acid (AA) intake daily, 12 males, 3 weeks

AA (g)		$\bar{X}$	N	SD	SEM
a)	0	5.66	139	0.60	0.06
	4	5.55	345	0.54	0.03
b)	0	28.50	137	37	3
	4	32.50	345	32	2

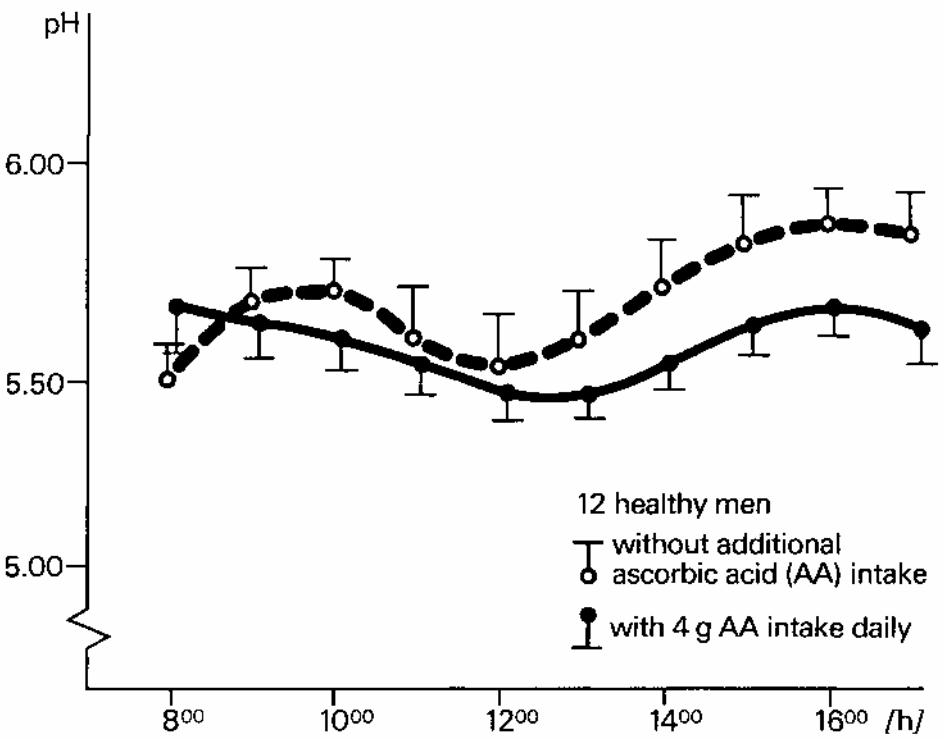

Fig. 2: Diurnal rhythm of urinary pH.

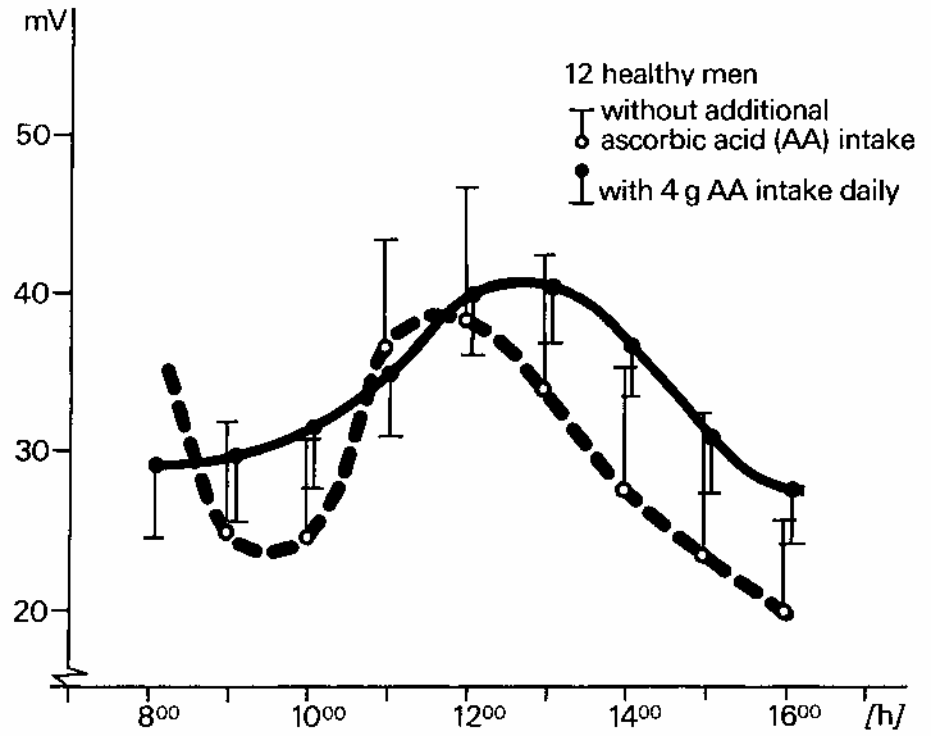

Fig. 3: Diurnal rhythm of urinary redox potential.

The ability of high doses of ascorbic acid to stabilize urinary pH in the acidic range is favourable and only in exceptional cases unfavourable, for example, when it is therapeutically desirable to obtain alkaline urine. In this connection, the question of the contribution of ascorbic acid intake to oxalic acid formation would appear to be of greater significance. Part of the ingested ascorbic acid is transformed in the body into oxalic acid and eliminated in the urine. As the formation of insoluble calcium oxalate in the form of new oxalate stones or oxalate mixed stones in the urinary tract can lead to serious pathophysiological consequences, there have been repeated warnings against the intake of high doses of ascorbic acid. Information on the connection between ascorbic acid intake and oxalate elimination, or between oxalate elimination and kidney stone formation, is thus of great importance in estimating the tolerance of high doses of ascorbic acid with regard to this aspect. Investigations using labelled ascorbic acid have shown that, with ascorbic acid intake in the RDA range, roughly 44% is metabolized to oxalate which is then eliminated in the urine [29]. The total amount of oxalate normally eliminated by this route is around 30 mg (range 13 to 49 mg) daily. Approximately 40% results from the breakdown of ascorbic acid, while the rest comes from dietary sources or from general cell metabolism; chiefly from glycine via glyoxylic acid. The following schedule provides an overview (Fig. 4).

On the basis of the contribution of ascorbic acid to the urinary oxalate pool, several experiments have been carried out in animal and man [8, 17, 42, 56, 62, 65, 71]. Results of the studies in man are summarized in Table XIV.

In hyperoxaluria, ascorbic acid does not contribute significantly to the total amount of oxalic acid excreted in 24-h urine. According to ATKINS [4, 5], glycine and ascorbic acid give rise to 40% and 5% respectively, of the urinary oxalate, and the latter value represents 40% of the metabolic turnover of ascorbic acid. The data available suggest that in general ascorbic acid intakes up to about 5 g per day will not

Tab. XIII: Effect of ascorbic acid (AA) and urinary pH in man

Dose/Day	Days	N	pH U_O	pH U_{AA}	Side-effects	Study	Lit. ref.
4 g/m^2	⩾4	6	6.03	5.51	none	c	TRAVIS [66]
6 g/m^2	⩾4	7	6.10	5.58	none	c	ibidem
8 g/m^2	⩾4	5	5.94	5.50	none	c	ibidem
4 g	14	68	5.66	5.75	none	c	HANCK [26]
4 g	21	345	5.66	5.55	none	c	ibidem
4 g	5	10	6.18	6.03	none	co	NAHATA [48]
6 g	5	10	6.18	6.06	none	co	ibidem
10 g	10	1	–	5.20	none	c	ROY [54]
4 g	5	20	5.43–6.51	5.06–6.82	none	db	HETEY [33]

Abbrev.: Uo = before AA intake; UAA = during AA intake; N = 24-h specimens
c = controlled, co = cross-over, db = double-blind

significantly influence urinary oxalate excretion. Higher daily intakes may give rise to an increase in urinary oxalate. But it has to be taken into account that part of the excreted ascorbic acid may also be decomposed into oxalic acid in the final urine. Besides that, in very rare cases individuals may show an accelerated turnover to oxalic acid. But how this relates oxaluria to urolithiasis is unclear, since oxaluria may often occur in relation to high oxalate and low calcium intake by chance.

Tab. XIV: Relation of urinary oxalate increase to dietary ascorbic acid intake

AA/day	Days	N	Urinary oxalate	Lit. ref.
4 g	2	11	12 mg	LAMDEN [43]
8 g	2	11	45 mg	ibidem
9 g	2	11	68 mg	ibidem
9 g	–	–	⩽30 mg	TAKENOUCHI [63]
2 g	180	10	0 mg	TAKIGUSHI [64]
4 g	3	7	0 mg	EL-DAKHAKHNY [19]
4 g	7	2	⩽700 mg	BRIGGS [13]
1 g	>30	1	50 mg	ROTH [53]
⩾4 g	⩾360	5	40 mg	SMITH [60]
10 g	5	4	18 mg	SCHMIDT [57]

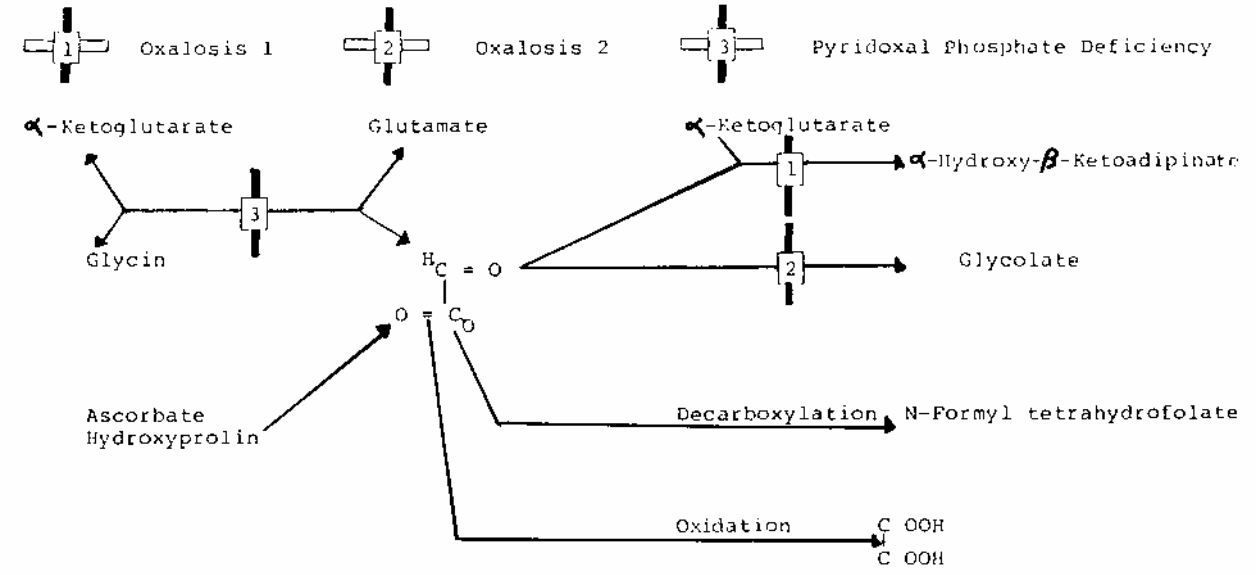

Fig. 4: Metabolic pathways and blocks leading to hyperoxaluria.

The frequency of renal calculi is relatively high in Europe and in North America and seems to be increasing. There are "stone belts" in the United States of North America (for example, the Southeast), where for unknown reasons calcium oxalate stones are much more common than elsewhere [11]. The pathogenesis of calculus is unsolved and successful therapy is not always possible. Renal colic as a consequence of calculus formation within the urinary tract is a very painful event. There is always the danger of functional impairment of the affected kidney. Prophylaxis against recurrence is difficult. The following kinds uf urinary calculi can be discriminated which show different frequences.

1. Pure calculi, that means about 95% of the urinary calculi consist of one compo nent: Calcium phosphate, calcium oxalate, uric acid or cystine.
2. Calculi of mixed composition: calcium phosphate-calcium oxalate calculi; uric acid phosphate; or uric acid-oxalate. Magnesium-ammonium phosphate or car bonate is often a component. The frequency of xanthine calculi is lower.

Hyperparathyroidism is an underlying disease in 3% of calcium phosphate-calcium oxalate calculi formers. Uric acid or xanthine calculi are a consequence of disturbed uric acid metabolism. Cystine calculi have a genetic basis. These latter kinds of calculi are not relevant with respect to a possible influence of ascorbic acid on urolithiasis, but only those containing oxalate.

In general, the formation of renal calculi is thought to follow simple physico-chemical rules: when the solubility product of the components is exceeded, renal calculi are formed. The solubility product of the components of renal calculi is very low; thus in many studies only oxalic acid excretion in urine is checked in relation to ascorbic acid intake. But an influence on oxalate excretion does not mean automatically an influence on the formation of calcium oxalate calculi within the urinary tract. Urinary calculi can form in urine with a normal calcium content. An important factor in calculus formation seems to be the formation of an abnormal activated mucoprotein. This abnormal mucoprotein derives from a mucoprotein of molecular weight 7×10^6 Daltons which is considered to be the principal product of the secretory activity of the urinary epithelium. This uromucoid is found in the urine of both normal subjects and patients with calculus disease, whereas the abnormal one is found only in calculus formers. This abnormal anti-infective mucoprotein is thought to initiate calcinosis. It forms calculi in the urine of normal patients as well as in that of patients already suffering from renal calculi. The abnormal mucoprotein binds all calcium and oxalate available, forming calculi, whereas the normal uromucoid solubilizes calcium and oxalate even in hypersaturated solutions. It is suggested that the abnormal mucoproteins, brought about, e.g. by bacterial infection, chelate calcium from solution to form relatively insoluble micelles of colloidal calcium mucoprotein units. This is the initial step in calcigerous stone formation and is followed by crystallization within the meshes of the mucoprotein micelle [12]. Endogenous oxalic acid production cannot be blocked entirely, and even on zero intake of oxalate or ascorbic acid renal calculi already formed will continue to grow. Prophylaxis against infection seems therefore to be a major point in the prophylaxis against renal calculi.

For prophylaxis of renal calculi, ascorbic acid has even been recommended [36]. Judging from experience gained from cancer patients with a daily intake of far higher doses of ascorbic acid (15 g) for several months or even years, ascorbic acid may not play a major role in urolithiasis, even in these extreme doses, since no complaints have been reported.

A further fear was expressed in relation to blood coagulation when on a high dose ascorbic acid regimen.

The influence of ascorbic acid on bleeding is well known in ascorbic acid deficiency. This quality to cure the deficiency disease scurvy even coined the word ascorbic acid, acid against scurvy. The word "scurvy" is derived from a Germanic word meaning cracked, sore and bloody mouth. In scurvy there is an influence on the coagulation system, but the main cause of bleeding is a change in the coagulation-promoting quality of subendothelial collagen and loss of tone in the venules. Russian authors have reported on slightly shortened coagulation times in man on high doses of ascorbic acid, but this is not in agreement with the results of others [16]. We have investigated the influence of a daily intake of 4 g ascorbic acid on different coagulation parameters by means of a thromboelastograph. This amount of ascorbic acid administered for 3 weeks showed no significant influence on coagulation of venous blood. Figure 5 shows the denomination of the parameters measured, r is the reaction time, k is the thrombus-forming time, the tangent a gives the thromboelastogram index, and t is a parameter of fibrinolytic activity. Table XV shows the mean values of 7 different coagulation parameters from 10 subjects. The differences in these parameters in individual subjects (before and after administration of ascorbic acid) were checked for significance by the means of the WILCOXON test for pair differences. No significant differences were found. The values are comparable with those in the literature [25].

A further claim put forward was the influence of high doses of ascorbic acid on warfarin anticoagulation. An appreciably reduced prothrombin time of a warfarin-stabilized patient was attributed to uncontrolled high ascorbic acid intake [52]. But 1 g of ascorbic acid per day for 14 days did not interfere with the effect of warfarin on coagulability in 5 patients receiving long-term anticoagulant therapy [39]. Another

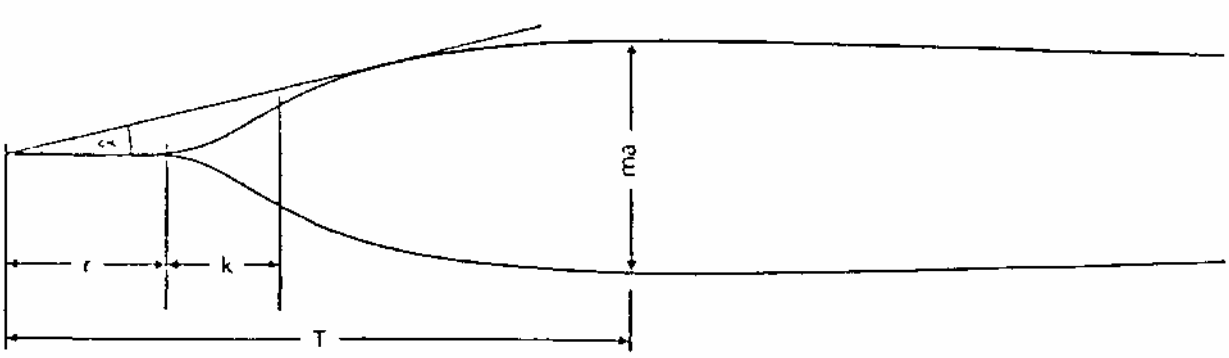

Fig. 5: Standard dimensions of thrombelastogram.

patient was described by SMITH [61], who showed an increased need for warfarin to produce anticoagulation during a period of 16 g ascorbic acid intake. But FEETAM *et al* [21] reported a lack of a clinically important interaction between warfarin and ascorbic acid in 19 patients stabilized on long-term warfarin therapy, when receiving 3, 5 and 10 g ascorbic acid per day during and after a 7-day period, although a fall in total plasma warfarin was observed. The claimed interference of even relatively low doses of ascorbic acid with dietary vitamin B_{12} [31] recently turned out to arise from an analytical difficulty in determining the vitamin B_{12} content of a meal when high doses of ascorbic acid were present. By use of an adequate method no influence of high doses of ascorbic acid on vitamin B_{12} status could be demonstrated [30]. To judge any effect of high doses of ascorbic acid on the vitamin demands of man, we have controlled the vitamin status of healthy volunteers before and after two and three weeks of 4 g oral ascorbic acid intake. Table XVI demonstrates the results. No

Tab XV: Thromboelastogram data before (a) and after (b) daily intake of 4 g vitamin C during 3 weeks

		$\bar{X}$	N	±SD	±SEM	Range
r (min)	a	13,1	11	2,1	0,6	10–16
	b	13,1	11	2,2	0,7	10–18
k (min)	a	8,8	11	2,3	0,7	6–13
	b	8,0	11	1,7	0,5	6,5–12,5
r+k (min)	a	21,9	11	3,5	1,1	16,5–28
	b	21,0	11	2,6	0,8	17,5–26,5
ma (mm)	a	48,8	11	5,0	1,5	42–60
	b	51,2	11	4,1	1,2	43–58
E	a	97,2	11	12,5	6,5	72–150
	b	106,0	11	15,7	4,7	75–138
TEG-index	a	50,7	11	9,2	2,8	37–65
	b	52,9	11	7,8	2,3	41–65
T (min)	a	44,4	11	8,5	2,5	25,5–54
	b	43,1	11	6,7	2,0	30–52

Tab XVI: Vitamin status in plasma (mean + SEM): its relation to dietary ascorbic acid (AA) intake (4 g daily, 11 volunteers, during 2 and 3 weeks).

Vitamins	Controls	2 weeks	3 weeks
A (IE/100 ml)	256 ± 11	256 ± 12	263 ± 13
B_1: α ETK	1.077 ± 0.01	1.106 ± 0.014	1.106 ± 0.017
B_2: α EGR	1.08 ± 0.01	1.01 ± 0.01	1.06 ± 0.01
B_6: α EGOT	1.62 ± 0.06	1.86 ± 0.10	1.79 ± 0.09
E (mg/100 ml)	1.50 ± 0.10	–	1.58 ± 0.11
C (mg/100 ml)	1.03 ± 0.07	1.59 ± 0.07	1.58 ± 0.10
Carotin	32 ± 4	44 ± 6	50 ± 5

statistically significant differences could be demonstrated. The administration of 4 g ascorbic acid daily was tolerated without side-effects by all test subjects [27].

For about two years we have also been studying the effect of high doses of ascorbic acid in cancer patients. 10 to 15 g ascorbic acid are administered daily to some of them for about two years. In these cases, no side-effects have been reported, except a laxative effect in the beginning. This effect as a rule vanished after 3 to 4 days. To judge efficacy, treatment is felt to be still too short, for most of these patients were treated for less than one year. These patients were not treated with cytostatics nor by radiation. Some of them had only palliative operations. These patients treated with 10-15 g ascorbic acid for at least one year and a half showed an extremely remarkable amelioration. One patient with local recurrence of a head and neck tumor, histologically proven, became free from symptoms during treatment with 14 g ascorbic acid daily lasting now 2 years and a half. At the beginning of 1979, another patient was seen suffering from an inoperable carcinoma of the bronchus. He was in a very bad general condition. During therapy with 15 g ascorbic acid per day he gained bodyweight and has now regained his full working capacity. The third patient suffered from a local recurrence of a breast carcinoma. This tumor regressed during combined treatment with interferon and high doses of ascorbic acid. In an attempt to explain and to predict response of carcinoma to high doses of ascorbic acid we have measured cellular immunostimulation. This was increased in all patients taking high doses of ascorbic acid, compared with controls having a normal intake. In the treated group all vitamin parameters were within the normal range, independent of the length of therapy. Only the basic activity of the transketolase was slightly below the lower limits of our normal range, but it was even lower in the untreated patients. Urinary excretion of ascorbic acid varied within 10-15% of the high dose administered, in contrast to the non-treated subjects who excreted about 0.5% of their daily intake.

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