Safety of High-level Vitamin C Ingestion

JERRY M. RIVERS*

Cornell University
Ithaca, New York 14853

Vitamin C is widely consumed as a dietary supplement, ingested either as a single nutrient or in combination with other vitamins and minerals. Stewart et al.\textsuperscript{1} reported that 35.1\% of the adult U.S. population ingested a vitamin C supplement, with a median intake of 333\% of the Recommended Dietary Allowance (RDA) and 28 times the RDA at the 95th percentile. Further, gram amounts of ascorbic acid are suggested for treatment and/or prevention of a wide array of health aberrations.\textsuperscript{2-4} Concern about the safety of these practices has been addressed in recent reviews.\textsuperscript{5-7}

**ABSORPTION, METABOLISM, AND EXCRETION**

Ascorbic acid is absorbed in the intestine by an energy-requiring, Na\textsuperscript{+} -dependent, carrier-mediated transport system.\textsuperscript{8-10} In vivo intestinal perfusion of vitamin C at concentrations ranging from physiologic (0.85 mM) to pharmacologic (11.36 mM) levels demonstrated saturation kinetics of absorption with a $K_m$ of 5.44 mM.\textsuperscript{11} Kubler and Gehler,\textsuperscript{12} in a pharmacokinetic study on the absorption of 1.5, 3, 6, and 12 g doses of ascorbic acid, demonstrated an inverse relationship between the size of the dose and the percentage of the dose absorbed. Fifty percent of the 1.5 g dose was absorbed, in contrast to only 16\% of the 12 g dose. From these data an average absorption of 71\% was extrapolated for physiological doses up to 180 mg. Kallner et al.\textsuperscript{13} estimated the absorption of 90 and 180 mg daily dietary intakes of ascorbic acid by using [l-$\textsuperscript{14}$C]ascorbic acid as a marker and measuring radioactivity in the urine over a period of 10 days. Absorption ranged from 78-88\% of the dose. Daily urinary excretion of ascorbic acid following loading with high doses was studied by Schmidt et al.\textsuperscript{14} Ingestion of a single 5 g daily dose resulted in the excretion of approximately 1600-1900 mg, whereas 10 g a day given in 2 doses of 5 g each led to the excretion of 2300-2700 mg, again demonstrating the limited absorption of ascorbic acid at high dose levels. From these results the absorptive capacity in the intestine appears to be reached with oral intakes of about 3 g per day.

Information on tissue concentration of ascorbic acid in humans ingesting large quantities of the vitamin is not available. Tissue levels of ascorbic acid have been compared in guinea pigs fed massive quantities (86 g/kg diet) and control levels (2 g/kg diet) of ascorbic acid for 275 days.\textsuperscript{15} The massive intake resulted in a slight

\* Present address: Graduate Division of Nutrition, University of Texas, Austin, Texas 78712.
elevation of ascorbic acid in all ten tissues analyzed, but this was significant only in the testis. Since the tissues were not perfused before analysis, the high concentration of ascorbate in the extracellular fluid may explain the small increase. These results support the suggestion that tissue levels of ascorbic acid cannot be increased appreciably by ingesting large doses of the vitamin. Studies on tissue transport of ascorbic acid in experimental animals, organs, and isolated cells have demonstrated an active, saturable transport system into the central nervous system, lung cells, adrenal cortical cells, placenta and eye retina. The consistent finding of a total body pool size of about 20 mg/kg body weight in human subjects, even when intake of the vitamin is in excess of that required to achieve this pool size confirms that the body pool size is limited by factors other than dietary intake.

In humans ascorbic acid and its metabolites are eliminated in the urine. The quantity of ascorbate filtered by the glomeruli is a function of glomerular filtration rate and plasma ascorbate concentration. Reabsorption of filtered ascorbate in the renal tubules is an active, saturable process with an average maximal reabsorptive capacity of 2.16 mg/min. A kinetic study of ascorbic acid in humans demonstrated a marked increase in renal turnover of unmetabolized ascorbic acid at plasma concentrations of 0.8 to 0.9 mg/dl. At these plasma levels the reabsorption mechanism was saturated. Absorbed ascorbic acid in excess of that required to maintain plasma levels at about 1 mg/dl is, therefore, efficiently eliminated by the kidney.

The metabolic turnover of ascorbic acid is also a saturable process. Kallner et al. reported saturation when metabolic turnover reached 40 to 50 mg per day. This quantity of metabolites was associated with a total daily turnover (metabolized plus nonmetabolized) of about 60 mg ascorbic acid. The 40 to 50 mg per day metabolic turnover corresponded to a plasma concentration of 0.8 to 0.9 mg/dl. Metabolic turnover was not increased at higher levels of total turnover, which indicates that large doses of ascorbic acid will not further increase the quantity of metabolites formed.

Physiological mechanisms of ascorbic acid absorption, tissue uptake, metabolism, and elimination by the kidney support the theory that an overload of ascorbic acid is unlikely to occur in man. Reference to these physiological mechanisms will be made in discussing individual topics related to the safety of vitamin C.

**OXALATE**

Oxalate is a major metabolite of ascorbic acid in man. Ascorbic acid accounts for 35-50% of the 30 to 40 mg of oxalate excreted daily; the remainder arises primarily from glycine degradation (about 40%) and from food (5-10%). Theoretically, large doses of ascorbic acid should not result in increased oxalate formation since the metabolic turnover of the vitamin is limited.

Studies on the effect of large doses of ascorbic acid on urinary oxalate have produced contradictory results. Part of the confusion on the relationship between high intakes of ascorbic acid and urinary oxalate excretion may be explained by assay procedures that result in either erroneously high or low oxalate estimations. Evaluation of the literature is difficult because different methodologies are used, and in some cases information on sample collection, storage, extraction, and assay procedures is incomplete.

Early studies revealed no appreciable increase in urinary oxalate when up to 4 g of ascorbic acid was ingested daily, but a daily intake of 9 g increased oxalate excretion
by about 50-60 mg.\textsuperscript{30} Similar results were reported with oral intakes of 2 or 3 g ascorbic acid for time periods of up to 6 months\textsuperscript{31-34} and with 9 g intakes for 3 days.\textsuperscript{52} Urinary oxalate excretion was increased only 4 to 11 mg per day in subjects ingesting 1 g ascorbic acid daily.\textsuperscript{35,36} However, others\textsuperscript{37,38} have reported that high doses of ascorbic acid markedly increase urinary oxalate excretion.

Recently, urinary oxalate excretion after 5 and 10 g daily intakes of ascorbic acid was measured by a new method\textsuperscript{39} which is more specific than methods used previously. In this study,\textsuperscript{14} 5 g ascorbic acid given daily in five doses of 1 gram each increased the average urinary oxalate excretion by 14.8 mg above baseline values. With intakes of 10 g daily (5 doses of 2 g each) for 5 days urinary oxalate increased from about 50 mg to 87 mg. The 15 to 37 mg per day average increase in oxalate excretion resulting from these large doses of ascorbic acid is similar to the change in urinary content of oxalate that results from consuming normal diets.\textsuperscript{27}

An interesting observation, which has been reported in several studies,\textsuperscript{14,34,40} is the occasional individual who excretes considerably more oxalate than the other subjects ingesting the same dose of ascorbic acid. The reason for this is unknown but it suggests that some apparently healthy persons have an abnormality in either oxalate absorption or ascorbate metabolism to oxalate. However, it seems safe to conclude that ingestion of large quantities of the vitamin does not constitute a risk factor for calcium oxalate stone formation in most healthy persons.

The role of large ascorbic acid intakes in persons who have a tendency to form stones is less clear. Intakes of 1 g ascorbic acid per day resulted in an average increase of only 5 to 11 mg of oxalate per day in stone-forming subjects, an increase no greater than that observed in the healthy subjects.\textsuperscript{35,36} In contrast, Chalmers et al.\textsuperscript{41} reported that stone formers excrete significantly more oxalate than do normals following 2 g oral daily intakes of ascorbic acid. Another finding was depressed ascorbic acid excretion in the stone formers. Following intravenous infusion of 500 mg of ascorbate, oxalate excretion did not differ between normals and stone formers, although ascorbate excretion was again lower in stone formers. The authors postulated that in stone formers most of the oxalate is derived from malabsorbed ascorbate in the gastrointestinal tract. The decreased excretion of ascorbate by stone formers compared with controls after both oral and intravenous ascorbic acid administration was interpreted as suggesting depleted ascorbate stores in the stone formers. The methodology utilized in this study for specific determination of oxalate in urine samples yields reliable results.\textsuperscript{28} This study raises interesting questions about the ascorbate status of stone formers and the source of the increased urinary oxalate observed here and in a few apparently healthy persons as previously discussed.

Results of the study by Chalmers et al.\textsuperscript{41} indicate that recurrent stone formers should avoid high-dose ascorbate intake. Patients with renal impairment and patients on chronic hemodialysis\textsuperscript{42} should also be advised not to ingest large quantities of the vitamin.

**URIC ACID EXCRETION**

Uric acid and ascorbic acid are both reabsorbed in the proximal tubule. If the two compounds share a common transport system, then some have reasoned that the increased tubular load of ascorbic acid following large intakes could decrease uric acid reabsorption due to competitive inhibition. Underlying this reasoning is the
assumption that tubular reabsorption of ascorbic acid can be increased by increasing the tubular load. This assumption appears invalid since the tubular reabsorption of ascorbic acid is a saturable process. However, several studies have investigated the influence of high ascorbic acid intakes on the excretion of uric acid.

Stein et al. gave single graded doses of ascorbic acid (0.5, 2.0, and 4.0 g) to three, four, and nine patients respectively. They reported a 70-90% increase in the fractional clearance of uric acid with the 4.0 g dose, but no increase was observed with the 0.5 g and 2.0 g doses. Serum uric acid was not changed. In another test, three patients were given 8.0 g of ascorbic acid daily in four divided doses of 2 g for 3 to 7 days. Fractional clearance of uric acid increased to 174% ± 24% of control values and serum uric acid declined by 1.2 to 3.1 mg/dl. The validity of this study cannot be determined. The patient population consisted of five with gout, three with asymptomatic hyperuricemia and six with normouricemia. Initial laboratory values for these patients showed a three- to fourfold range in serum and urine uric acid and a twofold range in creatinine clearance. A description of the patients actually used in the experiments is not given.

Results of the study by Stein et al. have not been confirmed by others. Berger et al. reported results of renal clearance studies on five nongouty and six gouty men. The subjects had comparable renal function. A priming dose of ascorbic acid was given intravenously, followed by a sustaining infusion at rates varying from 2.5 to 10 mg/min. The resulting plasma ascorbic acid values varied from 2.9 to 12.4 mg/dl. In eight studies with plasma ascorbic acid ranging between 3.5 and 5.6 mg/dl, the mean Curate : GFR did not differ significantly from the control value. In 10 other studies with plasma ascorbic acid greater than 6 mg/dl, the mean Curate : GFR increased significantly although only to a moderate degree, from a control of 0.081 ± 0.20 to 0.116 ± 0.026. The relatively small increase in urate excretion at extremely high, nonphysiological plasma ascorbate levels led the authors to suggest that either urate has a preferential affinity for the transport mechanism or an additional secretory transport system not shared with ascorbic acid.

Studies on healthy subjects have also shown that large intakes of ascorbic acid do not influence uric acid excretion. Mitch et al. conducted studies on normal subjects, four men and two women. The ingestion of 4 or 12 g ascorbic acid daily, taken in four divided doses of 1 or 3 g, had no effect on serum uric acid concentration, urine uric acid, or uric acid clearance. Similar results were reported by Schmidt et al. Four healthy male subjects ingested 10 g ascorbic acid daily in five divided doses of 2 g for five days. Ascorbic acid loading had no effect on excretion of uric acid.

The evidence does not support claims for an ascorbic-acid-induced uricosuria. Even in patients with gout or hyperuricosuria, it appears doubtful that large doses of ascorbic acid would lead to increased uric acid excretion.

**IMPAIRED VITAMIN B\(_{12}\) STATUS**

In 1974, Herbert and Jacob reported that increasing levels of ascorbic acid added to homogenized test meals before incubation at 37°C for 30 minutes produced increasing destruction of vitamin B\(_{12}\). This study was repeated in another laboratory, except in this case the diets were assayed either (1) directly, (2) after extraction by the Association of Official Analytical Chemists (AOAC) procedure, or (3) by the procedure published by the British Analytical Methods Committee. Vitamin B\(_{12}\) was
determined by both microbiological assays and radioassays. The results differed sharply from those in the previous report. No loss of vitamin B<sub>12</sub> was observed in the test meals after incubation with 0.5 g of ascorbic acid. Additional studies on the interaction of vitamins B<sub>12</sub> and C<sup>50,51</sup> confirmed this finding. When cyanide in the extraction step was adequate to liberate protein-bound cobalamins and convert them to stable cobalamins, the vitamin B<sub>12</sub> content of serum and food was not decreased, even with ascorbic acid concentrations as high as 1.0 g/dl.<sup>51</sup> Hogenkamp<sup>52</sup> reviewed the stability of cobalamins under varying conditions. Among the naturally occurring cobalamins, only aquocobalamin is readily reduced and subsequently destroyed by ascorbic acid. Aquocobalamin is not one of the major cobalamins in biological materials. Thus, it is highly unlikely that megadoses of ascorbic acid will induce vitamin B<sub>12</sub> deficiency.

Results of studies on human subjects support the conclusion that a large intake of ascorbic acid will not induce vitamin B<sub>12</sub> deficiency. Altronz <i>et al.</i><sup>53</sup> reported no deleterious effect of 4 g per day or more intake of ascorbic acid on serum vitamin B<sub>12</sub> levels in spinal cord injury patients. In another study, long-term ingestion of daily mean doses of 1.65 g of supplemental ascorbic acid by 20 myelomeningocele children did not impair vitamin B<sub>12</sub> status. These children showed neither deficient serum B<sub>12</sub> levels, anemia, nor elevated mean corpuscular volume. Herbert <i>et al.</i><sup>55</sup> obtained low serum vitamin B<sub>12</sub> levels in four of 18 patients with spinal cord injury. These patients had received 2 g of ascorbic acid daily for varying periods of time up to 29 months. Bone marrow examination of the two patients who had serum vitamin B<sub>12</sub> levels below 100 pg/ml revealed a normoblastic pattern of erythropoiesis and a normal deoxyuridine suppression test. Repeat sera from these two subjects were not available after the authors discovered the protective effect of KCN in the assay procedure. They suggest that the low serum levels were probably an artifact of the assay method.

Neither theoretical considerations nor experimental results provide support for concern that large daily intakes of ascorbic acid will induce vitamin B<sub>12</sub> deficiency. The evidence has consistently demonstrated that vitamin B<sub>12</sub> in food and the body is not destroyed by ascorbic acid.

**IRON OVERLOAD**

Ascorbic acid enhances absorption of dietary nonheme iron<sup>56-58</sup> and fortification iron from food.<sup>59</sup> Ascorbic acid supplementation has been used as a means of reducing the prevalence of iron deficiency in populations whose diets are low in sources of heme iron.<sup>59</sup> Enhancement of iron absorption by the vitamin does not occur in a linear fashion. An almost optimal absorption promoting effect is obtained with 25-50 mg ascorbic acid per meal.<sup>60</sup> Therefore, it appears highly unlikely that large doses of the vitamin would lead to excessive iron accumulation in the body.

Cook <i>et al.</i><sup>61</sup> examined the influence of high ascorbic acid supplementation on body iron stores. Healthy subjects took 1.0 g doses of ascorbic acid with each of the two largest meals of the day for 4 to 24 months. Serum ferritin determinations indicated no significant effect of the vitamin C on iron stores. The authors concluded that the regulatory mechanisms that control body iron stores override any pronounced alterations in food iron availability.

Concern that massive doses of ascorbic acid might lead to progressive iron accumulation in healthy, iron-replete individuals appears unwarranted. Persons who are
genetically susceptible to iron overload may be adversely affected by long-term ingestion of large doses of vitamin C.

**SYSTEMIC CONDITIONING**

Concern that scurvy could result upon cessation of high doses of ascorbic acid has resulted from uncontrolled observation on humans. Cochran reported two cases of scurvy in infants who apparently received adequate vitamin C intakes. He proposed that an "ascorbic acid dependency" was prenatally induced since diet histories revealed a high intake of ascorbic acid by their mothers during pregnancy. Another poorly documented observation was the occurrence of scurvy in two men who presumably decreased ascorbic acid intake after prolonged ingestion of large quantities of the vitamin. A more recent report on conditioned oral scurvy due to megavitamin C withdrawal in an adult male suffers from lack of vitamin C analysis of serum and uncontrolled vitamin C intake. A report on guinea pigs suggested systemic conditioning in utero due to high intakes of the vitamin during pregnancy. Weanling guinea pigs from dams fed a high level of ascorbic acid during pregnancy and then fed a vitamin-C-free diet died sooner than did controls. These results are questionable. Normally, weanling guinea pigs fed a vitamin-C-free diet die of scurvy within 18 to 21 days, whereas in this study some of the control animals lived 40 to 50 days. Others found no increase in the mortality of newborn guinea pigs whose mothers had been injected with 400 mg ascorbic acid per kg daily. Another study on guinea pigs is frequently cited as confirming systemic conditioning, when, in fact it demonstrates the exact opposite. In guinea pigs fed massive quantities of ascorbic acid (86 g/kg diet) for 275 days and then fed diets containing either 3 mg/kg for 68 days or 0 mg/kg for 44 days, there was no evidence to suggest that they would develop scurvy sooner than guinea pigs initially fed control levels (2 g/kg diet). In fact, after feeding the diets to induce chronic and acute deficiency, tissue levels of ascorbic acid in the experimental group were consistently higher than in the control group. Others have reported similar results in pups from mothers fed diets high in ascorbic acid during pregnancy and then switched to a diet providing the minimal daily requirement.

The claim that abrupt cessation of large doses of ascorbic acid will lead to scurvy because of conditioning is not supported by the evidence.

**MUTAGENICITY**

The idea that ascorbic acid was mutagenic and, therefore, harmful if ingested in large doses originated from a paper by Stitch et al. published in 1976. Unfortunately, the results of this in vitro study were erroneously applied to in vivo systems. Cultured human fibroblasts and microbial cells treated with a mixture of ascorbic acid and Cu exhibited DNA fragmentation, DNA-repair synthesis, and chromosome aberrations including chromatid breaks and exchanges. No mutagenic action was observed with pure ascorbic acid. Other investigations using Salmonella typhimurium as the test organism, demonstrated that ascorbic acid does not have intrinsic mutagenic activity. If the bacteria were treated with a freshly mixed solution of 5 mM ascorbic
acid and 1 or 5 μM cupric ion or if Cu$^{2+}$ ions were added to the bacterial medium containing ascorbic acid,$^{71}$ mutagenic action was extensive.

The evidence indicates that ascorbic acid breaks DNA when hydroxyl radicals are produced in the presence of oxygen, a reaction that is stimulated by Cu$^{2+}$ ion$^{71}$ and inhibited by catalase.$^{72}$ The mutagenicity of the ascorbic acid Cu$^{2+}$ system in vitro probably results from ascorbate reduction of oxygen to H$_2$O$_2$ and Cu$^{2+}$ to Cu*. Presumably the Cu$^+$ then reacts with H$_2$O$_2$ to produce hydroxyl radicals. Mammalian organisms seem well protected against damage induced by H$_2$O$_2$ and radicals. Glutathione peroxidase catalyzes reactions of glutathione with H$_2$O$_2$ and other peroxides; catalase and superoxide dismutase prevent the destructive action of peroxides and free radicals. Furthermore, copper does not exist as free Cu$^{2+}$ ions in the body, rather it occurs only in bound forms.

The inapplicability of in vitro studies on ascorbate mutagenicity to in vivo systems was clearly demonstrated in studies on sister-chromatid exchanges (SLEs).$^{73,74}$ Ascorbate caused a dose-dependent increase in SCEs in Chinese hamster ovary cells and in human lymphocytes.$^{75}$ In contrast, oral and intraperitoneal administration of ascorbic acid ranging from 0.2 to 10 g/kg body weight caused no induction of SCEs in the bone marrow of Chinese hamsters.$^{74}$

Concern about a potential mutagenic effect of ascorbic acid is surprising in view of the extensive work on the antimutagenic activity of the vitamin. Presently there is no evidence that high intakes of ascorbic acid will be mutagenic in man.

**CONCLUSION**

An attempt has been made in this review to select papers that represent opposing views and to present a critical nonbiased interpretation of the results. This has led to the conclusion that the practice of ingesting large quantities of ascorbic acid will not result in calcium-oxalate stones, increased uric acid excretion, impaired vitamin B$_{12}$ status, iron overload, systemic conditioning, or increased mutagenic activity in healthy individuals.

The interaction of ascorbic acid with dietary essential mineral elements other than iron is not included in this review. Research on this topic is revealing interesting results, but is insufficient at this time to formulate valid conclusions.

**REFERENCES**

E. Hope (SUNY Stony Brook, Stony Brook, N. Y.): May I ask you for a working definition of large doses? Are we talking about greater than 1 gram or perhaps less than 10 grams?

J. M. Rivers (University of Texas, Austin, Tex.): I think we're talking in the range of 5 g and greater.

E. Hope: Have there been any studies indicating less than 5 g in relation to these?

J. M. Rivers: Oh, yes, many studies have been done: 4-g, 3-g, 2-g, and 1-g dose levels. There is no effect.

E. Hope: Greater than the 5 g to what top limit are we talking about?

J. M. Rivers: In my review of the literature the highest level used in any of these studies was around 12 g per day, except the i.v. infusion studies.

E. Hope: These studies were based on otherwise healthy subjects?

J. M. Rivers: Yes, definitely. I think in some of the studies, for example on oxalate, there were stone formers as well as healthy non-stone formers in the studies; they had gouty men and nongouty men in some of the uric acid studies, but for the most part healthy individuals.

A. Taylor (Tufts University, Boston, Mass.): I'd like to just follow up on the observations in your review by one comment about a paper that was published by Dr. Fleming and coworkers from the Pauling Institute last year, and I think many people who read that paper would have thought that elevated ascorbate might be
procataractogenic. From some of the work that was described by Prof. Varma, and which has been corroborated by J. Blondin and some other people in my lab, it's clear that elevated ascorbate would indeed delay the onset of protein damage caused by ultraviolet radiation in a cataract rather than be procataractogenic.

B. LANE (Columbia University School of Public Health, New York, N.Y.): I don't want to take time to comment on the role of ascorbic acid, for example in enhancing ocular accommodation, that's eye focusing, and I don't want to take time to comment on the role of high amounts of ascorbic acid megadoses in depressing calcium metabolism transport or in affecting chromium uptake or in helping to chelate with too much vanadium in the system.

But I would like to mention a paper I presented last year to the National Eye Institute at their symposium on eye disease epidemiology. We found that supplemental ascorbic acid greater than 1500 mg led to an eightfold increased risk for specific disorders of the vitreous.

Furthermore, when the enzyme superoxide dismutase measured in red blood cells was depressed below normal this led to a 24-fold increase in vitreous disorders.

UNIDENTIFIED SPEAKER: There's been a controversy on the different ascorbates being taken internally, like calcium ascorbate, and sodium ascorbate. Is there a problem in one over the other? For instance, would there be more uric acid calculi formed with calcium ascorbate?

J. M. RIVERS (University of Texas, Austin, Tex.): I can't answer the question. I know there has been concern about the effect of ingesting, for example, high quantities of sodium along with sodium ascorbate and with calcium and calcium ascorbate but to my knowledge I'm not aware of the studies that have been done on various forms, various salts of the vitamin and whether or not you would get differences.

S. D. VARMA (University of Maryland School of Medicine, Baltimore, Md.) A lot of people say that if you take ascorbic acid in large quantities and then stop it, there are withdrawal symptoms. Could you comment on that?

J. M. RIVERS: It seems pretty far-fetched to me that you could get withdrawal symptoms taking large quantities of vitamin C and then going back to a physiological intake level. I'm not aware of any reports in the literature of that occurring. I do think, though, that it's pretty safe to assume that you're not going to increase the metabolism of ascorbate with large quantities.

W. LOHMANN (University of Giessen, Giessen, FRG): All you said is probably true for oral intake, but I think it might not be true if you infuse it intraperitoneally.

J. M. RIVERS: That is correct. I hope that I have not implied that massive quantities of ascorbic acid are safe. I chose specific topics on which we have data to support the lack of an adverse effect only for these conditions. I think the work that we need to do on minerals is tremendous. There may be many adverse effects of taking very massive quantities of the vitamin for long periods of time, but at least for those I discussed on which we have considerable data I think it's safe to conclude that large doses will not produce adverse effects.
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Part VI. Metabolism, Requirements, and Safety

Safety of High-level Vitamin C Ingestion. By JERRY M. RIVERS ...... 445