

**RANITIDINE**



*“The Buffalo Trail”, oil on canvas, 1867-68. Albert Bierstadt*

*“I saw immense herds of bisons, grazing in undisturbed possession and obscuring with the density of their numbers the verdant plain: to the right and left as far as the eye was permitted to rove, the crowd seemed hardly to diminish, and it would be no exaggeration to say that at least ten thousand here burst on our sight in the instant...”*

*Observations on the Bison; Expedition of Stephen H. Long  
on the Platte and Missouri Rivers, 1871.*

*The North American Bison were the sole remaining group of a number of bison species that roamed the great plains of North America during the last Ice Age. They not only survived the radically changed conditions, they thrived in the new warmer environment.*

*By the year 1800 they numbered, by some estimates, around 30 million. These magnificent beasts were the dominant species of the Great Plains. By the year 1900 there were only a few hundred. After two million years - in the blink of a geological eye - the bison stood at the edge of the abyss of extinction.*

*It was the same sorry story repeated over and over; as humanity came into contact with large animal species those species would almost invariably be wiped out. It is simple to see the near extinction of the North American bison as a tragic consequence of the European American drive for their "manifest destiny" to exploit the bison and to replace it with their own more productive species of cattle and sheep, and to see the noble North American Indian who had lived in natural harmony with the bison for untold centuries. To any Euroamerican of the mid Nineteenth century, it seemed that the Indian tribes of the great Plains had lived the life of nomadic hunters for untold ages. But this was not the case; the whole tragic story of the bison was far more complex than that. In fact the bison were more correctly "collateral" damage in a clash between a modern European culture and a far more primitive one, barely out of the stone age. It is a story even more damning than simple exploitation.*

*Many North American Indian tribes by the 18th century lived by hunting bison on horseback, yet this was only a very recent phenomenon. In fact the horse had been unknown to the Indians before the time of Cortez, and indeed most Indian societies had been agricultural villages. So what had happened? As Europeans from the Old World came into contact with Indian societies they brought infectious disease along with them, disease to which the Indian populations had no immunity whatsoever. Measles and smallpox took a fearful toll, almost totally exterminating many villages. In part to escape the hellish afflictions of the new settlers, many tribes took to the plains and became nomads, hunting the bison for survival. But they now hunted far more efficiently than had their recent ancestors, by the agency of the horse for which they traded for with the settlers. The demise of the bison had in fact commenced not directly with European settlers, but by their agency through a novel and enforced way of Indian life. The history of the Indian hunter nomad existence in fact lasted only about one and half centuries - it came suddenly and then went just as suddenly and it had come.*

*But the new order did not go well. Europeans living in the eastern cities had a great appetite for buffalo hides and all the products that could be obtained from these. In return by the 1830s they began to trade in whiskey and other hard liquors. The Indian tribes had had no previous contact with European microbes - nor had they with strong alcohol. The effects of whiskey began to take a terrible toll on their already uncertain and precarious new nomadic societies. The nomads now suffered from the Malthusian disaster of relying almost exclusively on a single resource for survival - the bison. They began to trade for guns, which in turn accelerated the destruction of the vast bison herds. Then by the 1870s the pace of destruction took the proverbial quantum leap. In the frantic race to reach the west coast, steamboats were being replaced by the great Union Pacific railroads that paralleled the Arkansas and Missouri rivers. With the new railroads came unprecedented numbers of Europeans, many bringing with them their cattle and sheep to settle on Indian lands. The big ranches were replacing the grazing lands of the bison, destroying their habitat. The nomads were increasingly forced westward. By the time of the Civil War the nomad tribes had become desperate. As a*

*matter of survival war became their only recourse. The Europeans smug in their sense of superiority began to see the nomad Indians as a positive hindrance to their “manifest destiny”. In reaction to Indian raids on ranches and other European settlements their response would be massive and terrible. When the Civil war ended the army turned its attention to the Indians. But as general George Custer discovered at the battle of Little Big Horn, in 1876, it would be no easy task to subdue the nomad tribes.*

*A strategy began to be developed to destroy the nomads’ means of existence - the destruction of their principle resource, the bison. The first inklings of this policy were seen during the Civil war when General William Tecumseh Sherman declared, that the extermination of the bison would force the plains nomads into government reservations - it would be purely a matter of survival. Sherman’s thoughts would be echoed by Columbus Delano, the Secretary of the Interior (1870 - 1875). In 1873 he wrote, “...wherever it is found that any tribe or band of Indians persistently refuse to go upon a reservation and determine to continue their nomadic habits...then the policy contemplates the treatment of such tribe or band with all needed severity....thereby teaching them that it is better to follow the advice of the government...the rapid disappearance of game from their hunting-grounds must operate largely in favour of our efforts to confine the Indians to smaller areas, and compel them to abandon their nomadic customs....I would not seriously regret the total disappearance of the buffalo from our western prairies in its effect on the Indians...”.*

*Coming from the American secretary of the Interior this pronouncement predicted the end of not only the nomadic way of life for many Indian tribes, but also the death warrant of the bison. Euroamerican hunters were encouraged to “cut out the middle man” and hunt Bison for themselves to sell to the eastern cities. The proverbial “free for all” had begun. Large numbers of Europeans armed with powerful repeating Civil War rifles began to slaughter bison in unprecedented numbers. On the backs of these “business men” also came the hunters - those of the ilk of “Buffalo Bill” who killed purely in the name of “sport”. By the 1870s the bison were being slaughtered on an industrial scale, over two million a year by some estimates. By the 1880s the great herds were gone, and bison stood on the brink of extinction. By 1900 there were less than a thousand.*

*It was around the turn of the century that the full enormity of the slaughter had begun to be appreciated and voices began to speak out at the cruelty and savagery of such wanton destruction. The first proto-groups of “Societies for the Prevention of Cruelty to Animals” were formed largely led by women. Laws were passed to protect the bison as a collective guilt emerged. Today the bison survives but as a sorry genetically impoverished vestige compared to the magnificent beasts that once ran free in their millions on the vast Western Plains of North America, but modern efforts now continue to rehabilitate and reestablish the bison.*

*In the 21st century we now see with a clear hindsight the lessons to be learnt from the tragic story of the bison. The Indian nomads, had an unsustainable way of life, albeit one they were largely forced into. The bison might yet have survived in greater genetically diverse numbers however if it weren’t for the greed of Euroamerican settlers who saw in the destruction of the bison a means by which to gain instant wealth as well as a means to*

*destroy an “inferior” culture that threatened the preordained progress of “civilization”. To them it was simply a matter of survival of a “fitter” race.*

*The Princeton Professor of History, Andrew Isenberg has perhaps best summed the lessons learnt from the sad story of the North American bison...*

*“If the fate of the nomads offers a lesson to other societies that share those predicaments, it is to understand both the futility of riches and the fragility of nature....Over one hundred years ago, the frontier historian Frederick Jackson Turner understood the domestication of the Western environment as a transformation from wilderness to civilization. Western and environmental historians now rely on terms other than Turner’s, terms that carry more analytical subtlety, ecological sophistication, and cultural and moral complexity: encounter rather than frontier, environment rather than wilderness, domestication rather than civilization. The differences are not merely semantic. Nor are the new terms merely regressive counterpoints to Turner’s celebratory, progressive understanding of the transformation of the West. Rather, encounter, environment, and domestication denote interrelationships among human societies and the natural environment. These interrelationships were not unilinear, as in Turner’s conception of the progressive transformation of the wilderness to civilization, but reciprocal”.*

*In the world of “Big Pharma” the drug ranitidine was once the unchallenged dominant species. It roamed the plains of the medical pharmacopeia as the biggest selling drug on the planet. But evolution and “progress” continue and in the blink of a pharmacological instant it was gone! - Replaced overnight by the proton pump inhibitors. It is not entirely extinct, but like the once great bison that roamed the Plains of the North American West, it still clings on to a much impoverished and tenuous existence.*

## RANITIDINE

### Introduction

**Ranitidine** (trade name in Australia, **Zantac**) is a **histamine H<sub>2</sub>-receptor antagonist** that inhibits stomach acid production.

The prototype histamine H<sub>2</sub>-receptor antagonist was cimetidine.

Ranitidine was found to have fewer adverse drug reactions, longer lasting action, and 10 times the activity of cimetidine. It also has 10 % of the affinity that cimetidine has to CYP450, and so it causes fewer side effects.

Subsequent H<sub>2</sub> blockers such as famotidine and nizatidine have no significant CYP450 interactions.

The histamine H<sub>2</sub>-receptor antagonists were then largely superseded by the even more effective **proton-pump inhibitors**, such as omeprazole (which in turn supplanted ranitidine as the world's the biggest selling drug).

In the ED a principle advantage of ranitidine is that it can be administered **IV**.

*It is now principally used in:*

1. Pregnant woman with significant gastro-esophageal reflux, (preferred to PPIs in pregnancy)

*And occasionally used:*

2. If there is a contraindication to a proton pump inhibitor, (rare).
3. In severe anaphylaxis reactions, where it may be used as an *adjunctive* treatment.
4. In scombroid poisoning (along with **promethazine**).

### History

**Cimetidine** was the first in the class of histamine H<sub>2</sub>-receptor antagonists, and was developed by **Sir James Black** and launched in the United Kingdom under the trade name of **Tagamet** in November 1976

**Ranitidine** was first prepared as AH19065 by John Bradshaw in 1977

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Ranitidine was introduced in 1981 and quickly become one of “Big Pharma’s” most successful drugs. By 1987 it had become the world’s biggest selling prescription drug.

Since then it has largely been superseded by the even more effective proton-pump inhibitors, such as omeprazole (which in turn, supplanted ranitidine as the world’s the biggest selling drug).

### Classification

Antihistamines can be classified as follows:

#### 1. **Histamine H<sub>1</sub> receptor antagonists:**

##### First generation sedating antihistamines:

These agents are moderately to heavily sedating and possess some mild anticholinergic effects:

They include:

- Azatadine
- Chlorpheniramine
- Dexchlorpheniramine
- Cyclizine
- Cyproheptadine
- Pheniramine
- Diphenhydramine
- Doxylamine
- Promethazine
- Trimeprazine

##### Second generation non-sedating antihistamines:

These histamine H<sub>1</sub>-receptor antagonists do not cross the blood - brain barrier appreciably when given in normal therapeutic doses.

They do not produce significant sedation and so have become known as the non (or less) sedating antihistamines.

In addition they possess only minimal, if any, anticholinergic activity (dry mouth, blurred vision, constipation and urinary retention).

They include:

- Loratadine
- Desloratadine
- Cetirizine
- Fexofenadine
- Levocetirizine

## 2. **Histamine H2 receptor antagonists:**

These include

- Cimetidine
- **Ranitidine**
- Famotidine
- Nizatidine

### Preparation

Ranitidine hydrochloride as:

Tablets:

- 150 mg, 300 mg.

Liquid:

- 15 mg/mL, 300 mL

Ampoules:

- 25 mg/mL, 2 mL

## Mechanism of Action

Ranitidine competitively blocks **H<sub>2</sub> receptors** on parietal cells, with the gastric mucosa thus reducing gastric acid secretion.

Ranitidine has no significant interaction at histamine H<sub>1</sub>-receptors or muscarinic receptors

## Pharmacodynamics

Oral or intravenous administration of ranitidine inhibits both basal gastric secretions and gastric acid secretion induced by histamine, pentagastrin and other secretagogues.

On a weight basis ranitidine is between 4 and 9 times more potent than cimetidine.

## Pharmacokinetics

### Absorption:

- All the H<sub>2</sub> histamine antagonists are well absorbed orally, including ranitidine, but absorption can be reduced by antacids.

Ranitidine can also be administered **IV**.

It can be given IM, but IV is the preferred route of administration.

### Distribution:

- Serum protein binding of ranitidine in humans is in the range of 10 - 20 %.
- Ranitidine is excreted into breast milk.
- Ranitidine can cross the human placenta.

### Metabolism and excretion:

- The plasma half-lives of all the histamine H<sub>2</sub>-receptor antagonists are short but their *duration of action is longer*, and so they allow for once or twice daily dosing.
- All the histamine H<sub>2</sub>-receptor antagonists are predominantly renally excreted.
- The elimination half-life of ranitidine is approximately 2 hours.

## Indications

These include:

1. Gastric acidity related conditions, where a PPI is contraindicated:
  - Dyspepsia
  - Peptic ulcer disease (PUD)
  - GORD
    - ♥ Including pregnant women with significant gastro-esophageal reflux, (preferred to PPIs in pregnancy)
  - Stress ulcer prophylaxis
2. Occasionally used in conjunction with a PPI, for gastric acidity related conditions, where a PPI is not completely effective.
3. Severe anaphylaxis reactions, where it may be used as an adjunctive treatment.
4. Scombroid poisoning (along with **promethazine**).

### Contraindications/ Precautions

These include:

1. All the histamine H<sub>2</sub>-receptor antagonists are predominantly renally excreted, so dose reduction may be required in significant renal impairment.
2. **It should be noted that relief of symptoms due to the use of histamine H<sub>2</sub> antagonists does not exclude the possibility of a gastric malignancy**
3. Known hypersensitivity to ranitidine (rare)

Cimetidine inhibits liver oxidative enzymes, decreasing the metabolism of drugs such as warfarin, phenytoin, carbamazepine, metoprolol and theophylline. Famotidine, nizatidine and **ranitidine** however do *not* have clinically significant effects on liver metabolism

### Pregnancy

Ranitidine is a category B1 drug with respect to pregnancy.

Category B1 drugs those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage

Ranitidine use during pregnancy has not been associated with an increased risk of congenital malformations.

Ranitidine is known to cross the placenta, and detectable amounts of the medicine have been found in the amniotic fluid and neonatal blood at term, but harmful effects have not been reported.

Lifestyle modifications (including dietary changes) and antacids are considered first line treatments for heartburn and gastro-oesophageal reflux disease during pregnancy.

If symptoms persist, ranitidine is considered safe to use at the recommended doses during pregnancy

### Breastfeeding

Small amounts of ranitidine are excreted into breast milk and accumulation of the medicine in the breast milk may occur.

However, maternal use of ranitidine at the recommended doses is unlikely to pose harmful effects in the breastfed infant.

Therefore, ranitidine is considered safe to use during breastfeeding.

### Adverse Effects

As a group adverse effects are uncommon with the histamine H<sub>2</sub>- receptor antagonists, but all may *occasionally* cause reactions which are significant.

These reactions can include:

1. Severe liver toxicity
2. Blood dyscrasias
4. Skin hypersensitivity reactions.
5. Excessively rapid IV administration may cause bradycardia.

In therapeutic doses the older agent, cimetidine could cause gynaecomastia and occasionally confusional states, particularly in elderly people and in patients with renal failure.

The other H<sub>2</sub>-receptor antagonists are safer options in these regards.

### Dosing

#### Oral:

Exact dosing and duration of dosing depend on the condition being treated as well as the severity of symptoms.

*In general terms:*

- *Oral*, initially 300 mg daily as a single evening dose (or 2 divided doses) for 4 - 8 weeks.
- *Maintenance*, oral 150 - 300 mg daily as a single evening dose.

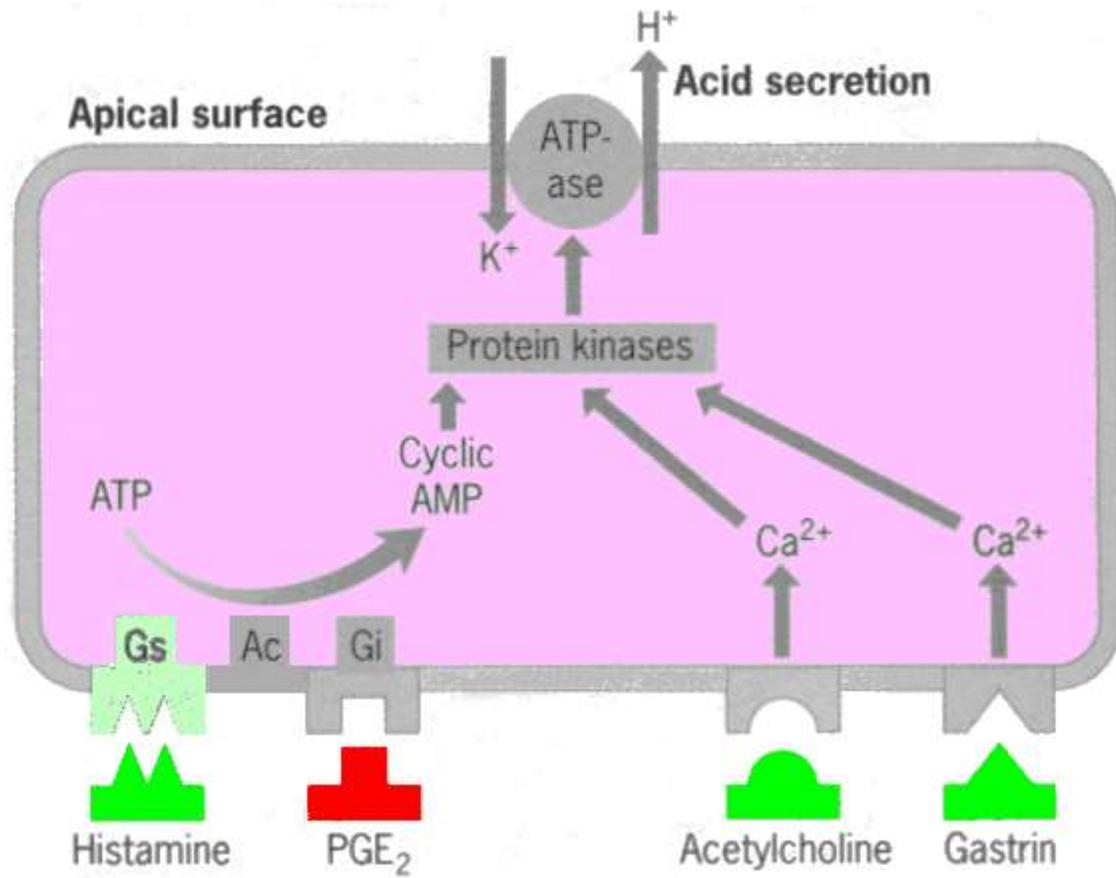
IV:

- *IV* 50 mg every 6 - 8 hours. <sup>4</sup>

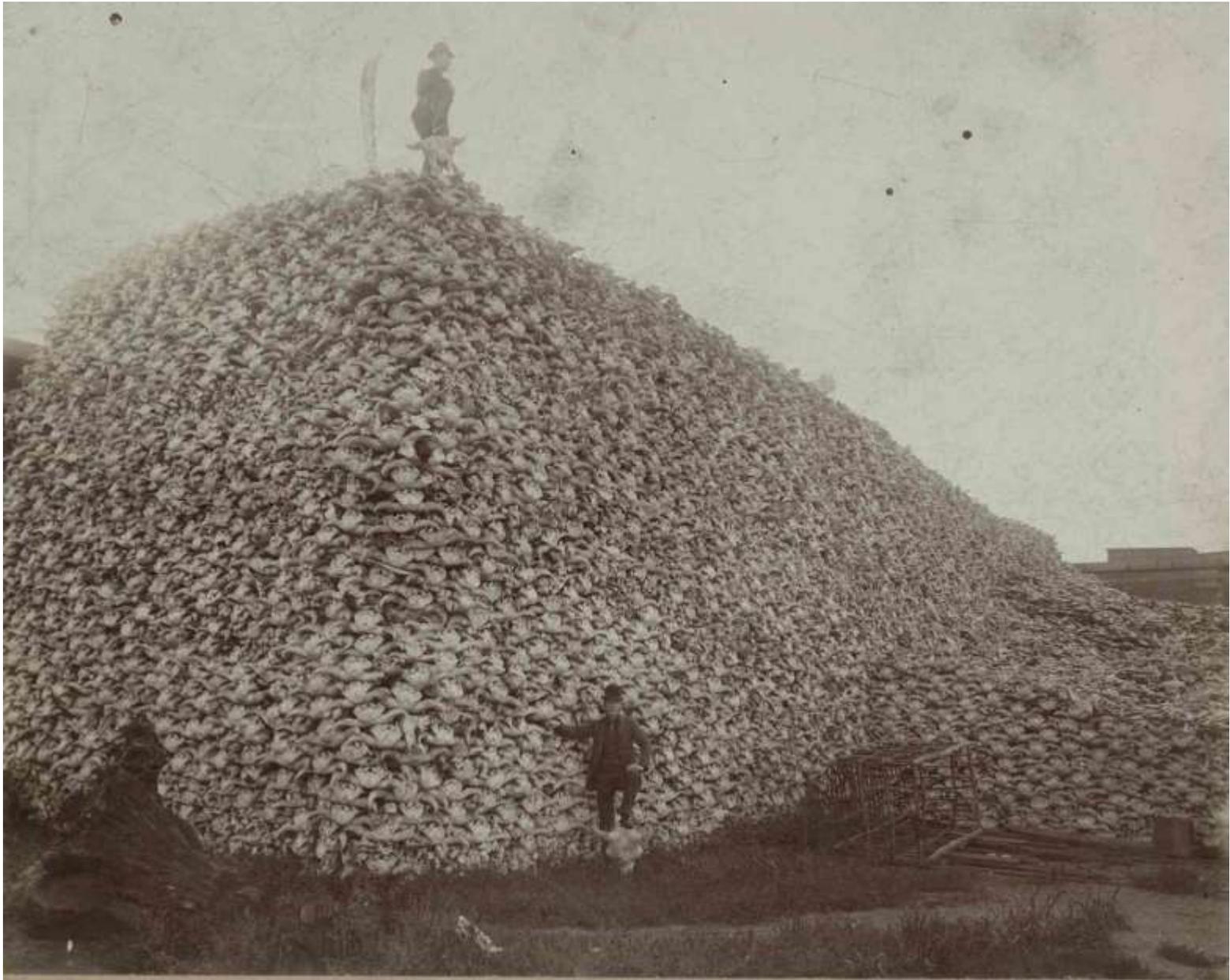
Dilute in sodium chloride 0.9 % and give over not less than 5 minutes or infuse at 25 mg/hour over 2 hours. <sup>4</sup>

## Appendix 1

### The Gastric Proton Pump:



*The Proton Pump, (School of Biochemistry and Microbiology University of Leeds).*



*Buffalo skulls at the Michigan Carbon Works, Detroit, 1892. (Detroit Public Library)*

*“...I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered without a struggle....We should preserve every scrap ....while we learn to use it and come to understand what it means to humanity”.*

*Edward O Wilson.*

*For millennia Native Americans lived in harmony with herds of America bison so immense they seemed to stretch unending to the horizon. Then in the Nineteenth century, in the blink of an eye, Europeans with modern weapons hunted the animal to the very brink of extinction, partly out of greed, partly in order to bring Indian tribes warring against them in defence of their lands, into submission.*

*Humanity would do well to heed the urgent pleas of the magisterial Edward O. Wilson. We are in the midst of a sixth great extinction of biodiversity on planet Earth. Many species are disappearing before we even fully understand them and the consequences for the planet and the potential benefits to humanity remain completely unknown. At the very least, if humanity can live without the magnificent bison, impoverished planet that this would represent, one lesson could relate to the profound consequences of our casual disregard for life in general. In the century that followed this casual disregard saw mountains of bones a commonplace image in the horrific wars fought on the industrial scale in that century - bones not of bison, but of Homo Sapiens.*

### References

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2. Ranitidine Tablets in MIMs, 1 February 2006.
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4. Ranitidine in Australian Medicine's Handbook, Website, Accessed May 2017
5. Ranitidine in RWH Pregnancy & Breastfeeding Guidelines, 19 July 2017.

Further reading:

Andrew Isenberg, *The Destruction of the Bison: An Environmental History*, Cambridge University Press, 2001.

Dr J. Hayes  
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