



ETHICAL AGENTS LTD
VETERINARY MARKETING

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Edited by:
Dennis Scott BVSc
MACVSc

Ethical Agents Ltd
54 Hobill Ave Wiri
PO Box 97-110 Manukau City
Manukau 2241

Ph 09-262-1388 Fax 09-262-1411
Freephone 0800 800-624
email eage@extra.co.nz
website www.ethicalagents.co.nz

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Special points of interest:

- * Why the long term outlook is fine for a food producing country.
- * Vétoquinol nutraceuticals, Lysine and Zentonic, both widely acclaimed overseas and now both available from EA - "The Source"

Fine Outlook - Thanks To Dairy

With the highest dairy payout in history Fonterra is already warning farmers that it may not last. They expect the commodity market to weaken a little in the next six months.

This is a cautionary tale however as long term the outlook for a food exporting country such as New Zealand must be sound. Whilst many farmers are concerned about debt reduction so that there is little overflow into the general economy this must change with time. One only needs to look at Mid and East Asia with its teeming millions and thus high demand for food.

The consumer price index (CPI) is meant to be a measure of the standard shopping basket of a country's consumers. The index is usually computed monthly, or quarterly in some countries, as a weighted average of sub-indices for different components of consumer expenditure, such as food, housing, clothing, each of which is in turn a weighted average of sub-sub-indices. For many

developed nations like Australia the CPI has a food content of 14%. For developing countries this percentage may be a lot higher, for example in India it is 43%. The demand for food is thus very high in Mid and East Asia and this continued demand for food in such a highly populated area makes the future of a food producing nation like New Zealand very secure, particularly the dairy sector.

While we only produce 2% of the world's total milk production we export most of it so that, in effect, New Zealand has close to 30% of the world export market in dairy products.

World demographics have changed dramatically over the last 250 years since the formation of the world's first veterinary school in Lyon, although the two events are in no way related.

Circa 1750 Eastern countries were self-sufficient in most goods and traded accordingly. From around that time the



United Kingdom started to have dramatic effects with colonisation and the industrial revolution, taking raw materials from the colonies and manufacturing them into products that dominated world trade.

What we are seeing now is not so much an Eastern takeover of world trade but a simple re-dressing of the balance, reallocating wealth to where the people are.

The first million people city was ancient Rome and, after its decline it was another 18 centuries before the second one arose, London. Now China alone has 139 cities of one million inhabitants or more.

There are now four main economic states in the World, the biggest still being the United States with China, India and a

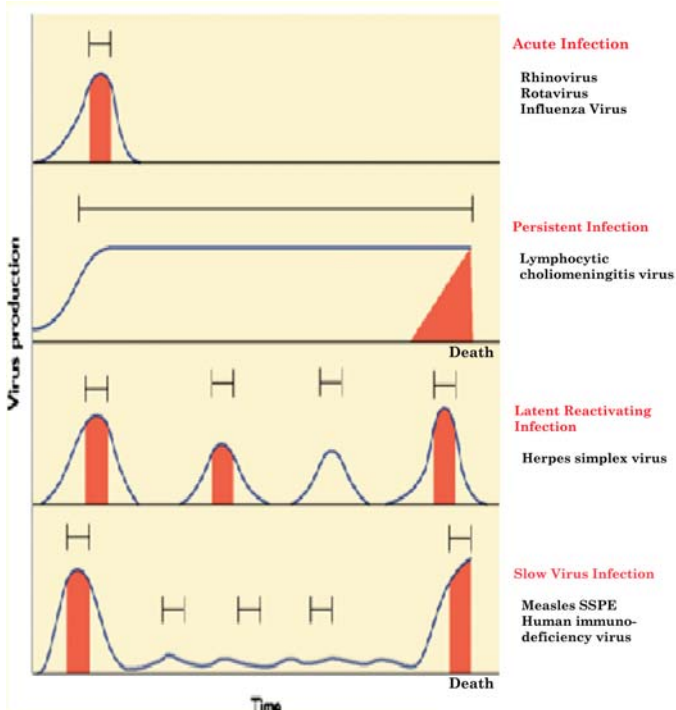
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Lysine and FHV

Viruses are in everything we touch, eat, breathe: they even become part of our genome! Every milliliter of sea water has >1 million virus particles.

There are 10^{30} bacteriophage in the world's water supply, each particle weighing a femtogram. Thus, the planet's biomass of bacterial viruses alone exceeds that of elephants by more than 1000-fold. There are 10^{16} HIV particles on the planet. A whale secretes 10^{13} Caliciviruses (whale diarrhea) each day, and they can infect humans!

We encounter billions of virus particles everyday; the outcome is varied: Nothing, Infection and clearance, Infection and latency, Infection and persistence, Infection and death, Cancer.



The better the virus, the less disease it causes, the more it is "tolerated" by the host. A hallmark of all herpes viruses is the ability to establish latent infections. Viral latency and persistence is the reward for subverting detection and elimination.

In healthy individuals, herpetic pathologies are rarely fatal. Herpes is forever, a big bonus for the virus!

It is estimated that at least 80% of all the cats in the world are infected with Feline Herpes Virus (FHV-1), which is a major cause of the most severe and widespread respiratory infection in cats, Feline Viral Rhinotracheitis (FVR). Up to 80% of cats that contract FHV-1 remain lifelong carriers of this highly contagious virus and can pass it on to uninfected cats through shedding. Reactivation of the virus may occur spontaneously throughout an infected cat's lifetime, although it is often associated with stress.

FHV-1 presents a greater threat to kittens, in which it causes severe respiratory and ocular symptoms. While mortality is generally low in adult cats, it can reach 30% in kittens. In adult cats, FHV-1 flare-ups are often hard to differentiate from the other two main feline infectious respiratory diseases, calicivirus and chlamydiosis. As a first step in a differential diagnosis, clinical signs of upper respiratory infections and ocular symptoms, such as conjunctivitis, ulcerative keratitis and chemosis, are excellent indicators that FHV-1 is the causal agent.

In recently published studies cats receiving L-lysine supplementation experienced less severe clinical

signs of FHV-1 following experimental infection than the placebo group.¹ and oral administration of L-lysine to cats latently infected with FHV-1 was associated with reduced viral shedding in the face of stresses (such as changes in housing or husbandry) that are known to induce viral reactivation.²

"the planet's biomass of bacterial viruses alone exceeds that of elephants by more than 1000-fold."

"What I would expect in most cats is some improvement in clinical signs... One thing to remember about L-lysine, though, is that the earlier it can be started in the course of disease, the better... It doesn't mean you shouldn't use it in a severely affected cat, but the earlier you can get it started in an outbreak or in a primary disease, the better the outcome is going to be."

(Dr. Jean Stiles Diplomate, American College of Veterinary Ophthalmologists Associate Professor of Ophthalmology Purdue University)

Why Lysine? Lysine is an essential amino acid, i.e. it is not produced in the body. Lysine was shown to be beneficial in humans infected with Herpes simplex virus (HSV-1)

L-Lysine's Mode Of Action

Feline Herpes Virus is dependant on arginine, an essential amino acid without which the virus cannot replicate. When administered as a supplement, L-lysine – also an amino acid – competes with arginine, antagonizing its growth-promoting effect and inhibiting FHV-1 replication.

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Lysine and FHV

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Arginine restriction itself in cats is not recommended.¹ Arginine is an essential amino acid in cats and plays an active role in the urea cycle. Arginine is transformed to ornithine through the reduction of the enzyme arginase, giving off urea and thus disposing of ammonia. Reduction below the minimal requirement of 0.83% arginine in the diet of cats allows ammonia to increase to toxic concentrations.

Lysine is reported to be a potent arginase inducer, resulting in catabolic degeneration of arginine. In trial work¹ with orally administered lysine signs of arginine deficiency were not observed at any time. Although competition for arginine uptake into viral proteins

may be occurring at the cellular level suppression of arginine function in the urea cycle does not seem to be a concern in cats that received 1g of L-lysine daily.

Enisyl F

Enisyl F is a premium l-lysine supplement specifically developed for cats and kittens. It is a highly palatable paste that is easily accepted by most cats and the convenient dial-a-dose syringe enables precise dosing and easy administration (which may help promote client compliance).

There is no known cure for FHV-1. L-lysine can, however, lessen the severity of the symptoms and help control the spread of the disease by reducing viral shedding.

For cats that are prone to recurrences of FHV-1 (i.e., cats who have had more than two episodes of reactivation), the long-term prophylactic use of L-lysine is recommended.

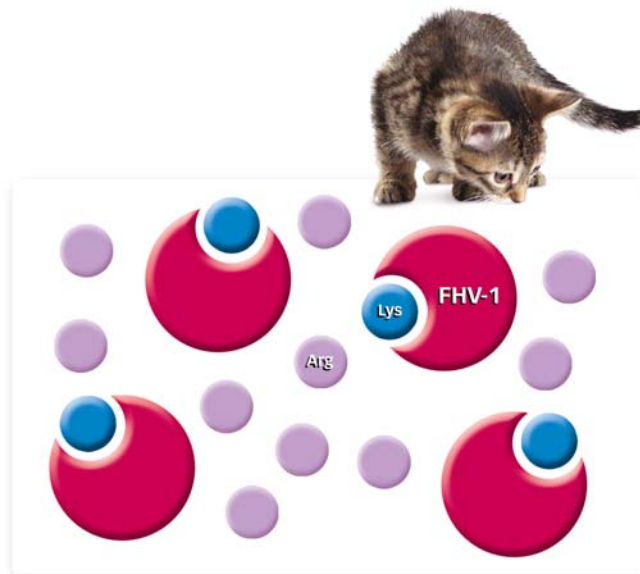
Developed specifically for veterinary use, highly palatable, easy-to-administer Enisyl-F also provides additional calories and

nutritional support to cats and kittens that may be reluctant to eat. Enisyl-F is manufactured according to IAW GMP standards, in a FDA-compliant facility, ensuring safety, quality and reliability.

L-lysine is an essential amino acid similar to arginine. Studies indicate that L-lysine competes with arginine and antagonizes its growth-promoting effect on FHV-1 (thereby inhibiting viral replication) without altering the plasma concentration of essential amino acids or causing arginine deficiency in cats.²

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Love The One You're With

1) Bob is sitting at home on his verandah with his wife Myrtle ... and he says ... "I love you."

She asks him ... "Is that you or the beer talking?"

He replies ... "It's me..... I'm talking to the beer."

2) After having both suffered from depression for a while, me and the wife decided we were going to commit suicide yesterday.

But strangely enough, once she killed herself I started to feel a hell of a lot better, so I thought 'stuff it – soldier on'.



Liver Detoxification

The liver, the body's largest organ (representing up to 7% of body weight), performs a vital role in a wide range of critical functions³ including carbohydrate metabolism, lipid metabolism, protein synthesis, detoxification of metabolites and xenobiotic.

The clinical and physical signs, as well as the clinicopathologic abnormalities that accompany liver disease, reflect deficiencies in these functions. The liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory and neoplastic insults.

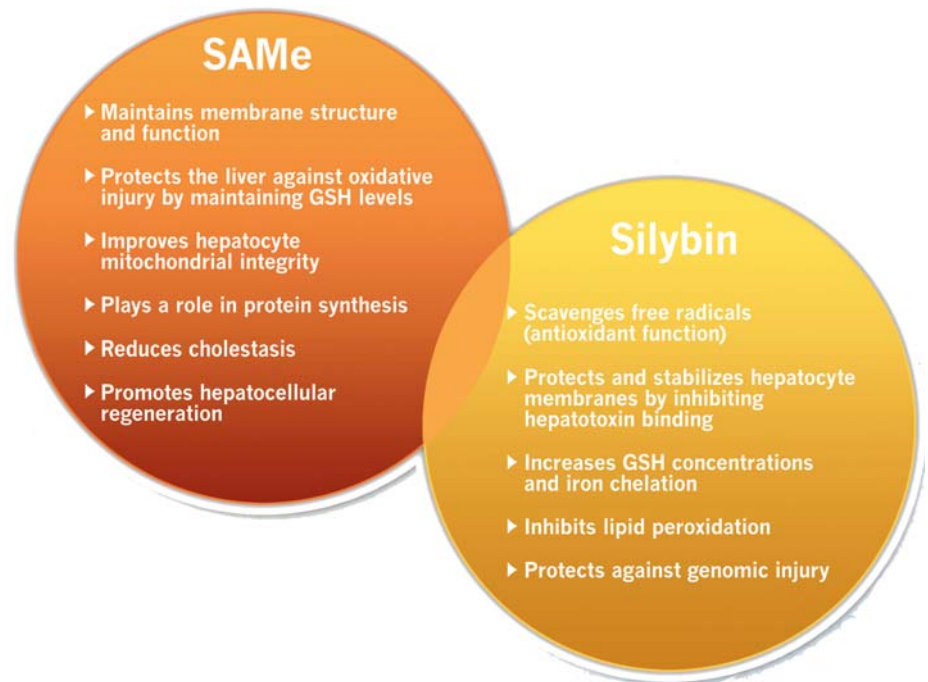
Because of the liver's ability to regenerate, specific signs of early hepatobiliary disease are often masked. However, with the progression of this diffuse disease or the disruption of bile flow, the consequences of hepatic distress can become life-threatening.⁶

With very rare exceptions, liver disease is an insidious process in which symptoms of hepatic decompensation may occur weeks or even years after the onset of injury.

The most common clinical signs of hepatic disease^{4, 5} include: inappetence, vomiting, constipation, diarrhea, intermittent anorexia, change in behaviour, exercise intolerance, weight loss, failure to groom, PU/PD, lethargy, possible abdominal tenderness, hepatic encephalopathy/effusion (in later stages of the disease) and/or icterus.

It is well established that oxidative stress plays a role in the pathogenesis of liver disease.² Oxidative stress results from the overproduction of toxic reactive oxygen intermediates or from the depletion of the body's endogenous antioxidant defense system.¹⁰

Oxidative stress usually occurs



when the number of free radicals exceeds the antioxidant capacity of the cell defense system.

Reactive oxygen intermediates (free radicals) are highly unstable and reactive molecules.

Oxidative stress is produced by many factors, both pathological and non-pathological.

Glutathione (GSH) is the primary antioxidant in living cells. It serves a protective function that is especially important to hepatocytes, as the liver metabolizes and detoxifies many compounds.¹²

The liver normally produces abundant SAME but evidence suggests that the conversion of methionine into SAME is hindered in liver disease, which results in depleted GSH concentrations.

What is SAME?

S-Adenosyl methionine, SAME, is an endogenous nucleotide-like molecule. It is naturally synthesized by the body from methionine, mainly in the liver.^{1, 2}

How does SAME work? SAME plays an important role in the intermediate metabolism because of its hepatoprotective and antioxidant properties.

Of particular importance to the liver, SAME is an essential factor in three metabolic pathways: transmethylation, transsulfuration and aminopropylation.

SAME is present in almost all body tissues and fluids. It is a naturally-occurring endogenous methyl-donor. In cases of hepatic impairment, the conversion of methionine into SAME seems to be reduced. Indeed, methionine supplements do not work if the SAME synthetase enzyme is not available to convert methionine into SAME.^{3,7}

For these reasons, SAME has proven to be a better choice as methyl-donor.²

Improvements in hepatocellular function, including cell membrane activity, bile flow and glutathione levels have been associated with

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Liver Detoxification

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the exogenous administration of SAME.¹²

Studies in humans and/or animals (disease models), as well as *in vitro*, suggest several main points of interest for the administration of SAME:⁵

It serves a cytoprotective function by maintaining membrane structure and function¹⁵, maintains hepatic GSH concentrations, protecting the liver from oxidative injury, improves hepatocyte mitochondrial integrity, ensuring an adequate energy supply, mitigates the pathological effect of certain inflammatory cytokines, reduces cholestasis, helps protect against bile acid-induced hepatotoxicity¹⁴ and promotes hepatocellular regeneration.

Silybin

The best-known and most widely recommended herb for the treatment of liver impairment, *Silybum marianum*, has a long history of medicinal use and contains silybin (silibinin), the most active isomer.²

How does Silybin work? Pharmacokinetic studies show that silybin is absorbed through oral administration and is distributed in the

gastrointestinal tract (liver, stomach, intestine and pancreas)¹⁶. It is excreted mainly as metabolites in the bile and it is subject to enterohepatic circulation.

Even though the hepatoprotective properties of silybin are quite well documented, its action pathways are still poorly understood. However, a review of literature suggests a number of possibilities, including the following:

The hepatoprotection provided by silybin appears to rest on the following properties: the ability to protect against lipid peroxidation as a result of free-radical scavenging and to increase/regulate the cellular content of GSH, the ability to regulate membrane permeability and to increase membrane stability in the presence of hepatotoxic agents, the ability to minimize toxin absorption by inhibiting membrane transport systems, the ability to inhibit the accumulation of collagen fibers that leads to fibrosis.

The oral uptake and bioavailability of silybin are low – up to 4% recovery in the bile,¹⁶ depending on the authors – but it can be significantly increased when silybin is



complexed with phosphatidylcholine,²³ which enhances gastrointestinal absorption. Compared to silymarin, the silybin/phosphatidylcholine complex has a superior bioavailability – up to 10 times higher than that of the extract.²⁵

Phosphatidylcholine is a major constituent of cell membranes. It is also a component of bile that is essential for normal bile acid transport. Its hepatoprotective activity appears to be associated with the improvement of membrane integrity and function.^{22, 17}

Silybin therapeutic activity

In several studies (on humans, rats and dogs) silybin has been shown to provide protection and support in cases of liver impairment.¹⁶

Acute viral hepatitis: Silybin may help reduce disease duration and complications, as well as promote recovery.

Hepatitis induced by toxins or drugs: Silybin has been shown to reduce hepatic injury resulting from poisoning by *A. phalloides*, phenothiazines and butyropheones.

Chronic hepatitis and cirrhosis: Silybin helps improve enzyme levels and reduce liver fibrosis in chronic hepatic injury.

Alcohol-related liver disease: Silybin has been associated with an improvement in histological findings.

Mildred

Mildred, the church gossip, and self-appointed monitor of the church's morals, kept sticking her nose into other people's business. Several members did not approve of her extra-curricular activities, but feared her enough to maintain their silence.

She made a mistake, however, accusing Frank, a new member, of being an alcoholic after she saw his old pickup parked in front of the town's only bar one afternoon.

She emphatically told Frank (and several others) that every one seeing it there would know what he was doing!

Frank, a man of few words, stared at her for a moment and just turned and walked away. He didn't explain; he said nothing..

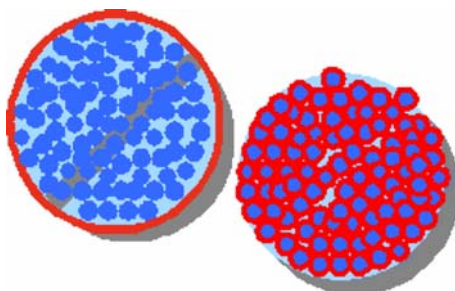
Later that evening, Frank quietly parked his pickup in front of Mildred's house ... walked home and left it there all night.

Administering SAMe

Giving SAMe can be quite difficult; tablets have to be coated to protect them from the harmful effects of stomach acid, therefore traditionally tablets are coated on the outside which means they cannot be split/crushed or chewed or the ingredients will become exposed

Tablets should be given on an empty stomach and therefore not with food. This means the owner has to force whole tablets down the animal's throat. In addition the inability to split tablets due to enteric coating makes administration expensive for certain weights of animal and leads to a wide variation in SAMe levels received between different weights.

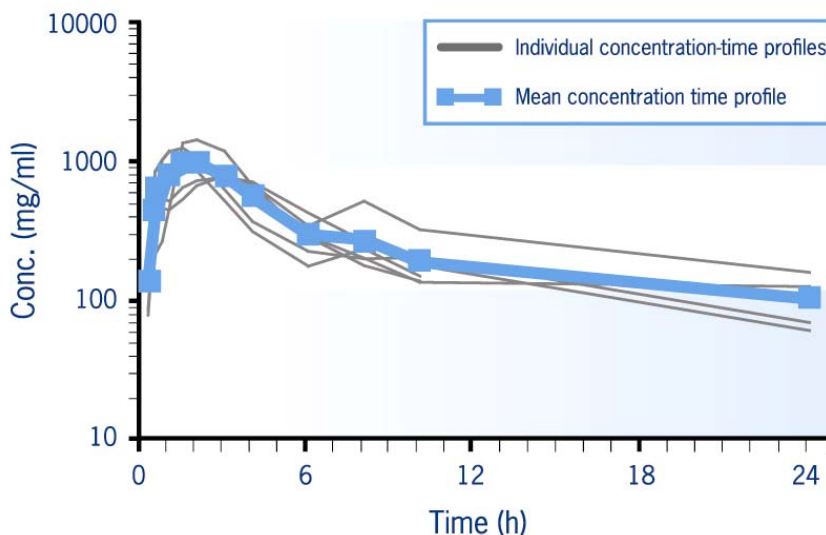
Vétoquinol's patent pending microencapsulation technique coats tiny particles of SAMe rather than just the surface of the tablet thus allowing the tablet to be split and chewed whilst protecting the SAMe from the harmful effects of stomach acid. This also means that tablets can be split to increase accuracy of administration and decrease costs.



The microencapsulation also takes care of the palatability problem as SAMe has an extremely bitter taste.

After oral administration of Zentonil®, SAMe is available for use by the body within 10 minutes of administration and peak levels are achieved between 1 to 4 hours after administration. The bioavailability curves were constant between test

Profile of S-Adenosyl methionine in dog plasma after administration of a Zentonil® Advanced tablet



subjects.

SAMe should be given on an empty stomach for optimal effectiveness. Feeding one hour after administration of Zentonil® allows optimal SAMe absorption and the levels will be at their highest to support the liver through the time when digestion is occurring.

Zentonil® Advanced is a *divisible, palatable* formulation of SAMe with the *additional benefits* of silybin.

Silybin in Zentonil® Advanced is complexed with phosphatidylcholine. The oral bioavailability of silybin is very low but is significantly increased when complexed with phosphatidylcholine (PC). PC coats the silybin and makes it easier to be absorbed across the intestines.

By providing silybin in this form, bioavailability of silybin is up to 10 times higher than that achieved by giving silymarin.

Zentonil® can be used in all cases when the liver is known or expected to require support in both dogs and cats.

Tablets should be given on an empty stomach at least one hour

before or two hours after feeding for optimal effectiveness.

Other SAMe products are enterically coated – the whole tablet is coated not the particles – as soon as the tablet is split the raw ingredients are exposed. Zentonil is microencapsulated – tiny particles are coated then clumped together in a tablet this allows splitting and crushing.

Compounded products should not be trusted as the highly reactive SAMe may become denatured. With Zentonil the SAMe is microencapsulated before addition of silybin and this technique has been proven to preserve the bioavailability of the SAMe.



Fine Outlook - Thanks To Dairy (continued)

(Continued from page 1)

conglomeration of states in Western Europe making up the remainder.

This reallocation of wealth and the demand for food can only be beneficial for an economy such as New Zealand's, which has been expanding into this area over the last decade or two.

On the second tier there is the ANZ-ASEAN free trade agreement,

a trading bloc that connects New Zealand and Australia with 10 economies such as Indonesia, etc.

In 1949 99% of our overseas exports went to the UK and there was a missive from the British Government expressing concern that it was not 100% and that they did not want to see a trend developing.

However in 1973 we were suddenly no longer a firm favourite if the

UK as that country merged with Europe to join what was then called the European Common Market.

Necessity breeds invention and today only 4% of our produce goes to Britain with 23% going to Australia and 11% to China.

The growing economic potential and food demands of Mid and East Asia means more markets coming on board for our primary produce.

Hunting

Tony and Nagy flew to Canada on a hunting trip. They chartered a small plane to take them into the Rockies for a week hunting moose. They managed to bag six.

As they were loading the plane to return, the pilot said the plane could take only four moose.

The two lads objected strongly. "Last year we shot six. The pilot let us take them all and he had the same plane as yours."

Reluctantly, the pilot gave in, all six moose were loaded and the plane took off.

However, while attempting to cross some mountains even on full power the little plane couldn't handle the load and went down.

Somehow, surrounded by the moose bodies, only Tony and Nagy survived the crash.

After climbing out of the wreckage, Tony asked Nagy, "Any idea where we are?"

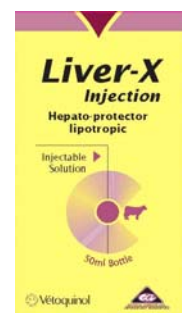
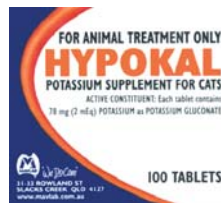
Nagy replied, "I think we're pretty close to where we crashed last year."



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An Ancient Story

In ancient Israel, it came to pass that a trader by the name of Abraham Com did take unto himself a young wife by the name of Dot. And Dot Com was a comely woman, broad of shoulder and long of leg. Indeed, she was often called Amazon Dot Com.

And she said unto Abraham, her husband: "Why dost thou travel so far from town to town with thy goods when thou canst trade without ever leaving thy tent?"

And Abraham did look at her - as though she were several saddle bags short of a camel load, but simply said: "How, dear?"

And Dot replied: "I will place drums in all the towns and drums in between to send messages saying what you have for sale, and they will reply telling you who hath the best price.

And the sale can be made on the drums and delivery made by Uriah's Pony Stable (UPS)."

Abraham thought long and decided he would let Dot have her way with the drums. And the drums rang out and were

an immediate success. Abraham sold all the goods he had at the top price, without ever having to move from his tent.

To prevent neighbouring countries from overhearing what the drums were saying, Dot devised a system that only she and the drummers knew. It was called Must Send Drum Over Sound (MSDOS), and she also developed a language to transmit ideas and pictures - Hebrew To The People (HTTP)

But this success did arouse envy. A man named Maccabia did secrete himself inside Abraham's drum and began to siphon off some of Abraham's business. But he was soon discovered, arrested and prosecuted - for insider trading. And the young men did take to Dot Com's trading as doth the greedy horsefly take to camel dung. They were called Nomadic Ecclesiastical Rich Dominican Sybarites, or NERDS.

And lo, the land was so feverish with joy at the new riches and the deafening sound of drums that no one noticed that the real riches were going to that enterprising drum dealer, Brother William of

Gates, who bought off every drum maker in the land.

And indeed did insist on drums to be made that would work only with Brother Gates' drumheads and drumsticks. And Dot did say: "Oh, Abraham, what we have started is being taken over by others."

And Abraham looked out over the Bay of Ezekiel, or eBay as it came to be known. He said: "We need a name that reflects what we are."

And Dot replied: "Young Ambitious Hebrew Owner Operators." "YAHOO," said Abraham. And because it was Dot's idea, they named it YAHOO Dot Com.

Abraham's cousin, Joshua, being the young Gregarious Energetic Educated Kid (GEEK) that he was, soon started using Dot's drums to locate things around the countryside. It soon became known as God's Own Official Guide to Locating Everything (GOOGLE).

And that is how it all began.