ETHICAL AGENTS
VETERINARY MARKETING

# EA NEWS

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## Old Science Can Be Good Science

**Inside this issue:**





The latest NZVJ has some very interesting articles; in particular there is one querying recent science and another endorsing very old science.

The former is a literature review by Beasley, Cogger and Compton which examined the administration of 400–500 IU eCG as part of an oestrus synchronisation programme based on intravaginal progesterone-releasing devices, gonadotropin-releasing hormone and prostaglandin (P4-GPG programme).

They ultimately concluded that the results of published studies describing the effect of eCG in P4-GPG programmes on conception rate to fixed time artificial insemination are inconsistent and further well-designed, adequately powered studies with standardised outcome measures are required to investigate its effect.

Considering the still unresolved welfare aspects of collecting eCG from horses this is certainly food for thought.


As to the older science, Lawrence et al compared the performance of two predictive models for the survival of downer cows.

The first model had been developed in 1987 using a data set containing missing values, while the second, new model was developed on the same dataset but using modern data imputation and analytical methods.

Their conclusion was that the original prognostic formula published by Clark et al. in 1987 performed as well as a modern model built on an imputed data set so that the use of a prognostic test based on the Clark model should remain an important part of the clinical examination of downer cows by New Zealand veterinarians.

So the two points of interest are firstly, that old science can still be good science, and secondly scientists should always question accepted theories. For example social media may accept the 1997 findings of Andrew Wakefield but they have been totally discredited by science.

Beasley, Cogger and Compton sensibly did not outright reject the commonly held eCG theories but proposed further well-designed, adequately powered studies with standardised outcome measures.

# Drink Up is Back!

The old saying that you can lead a horse to water but you can't make it drink has more than just a ring of truth. Getting dehydrated horses to drink is one of the banes of the equine world, and the reasons are well documented.

When humans sweat it is predominantly from eccrine sweat glands so humans excrete mainly water, increasing the salt concentration in the body thus stimulating a thirst reflex. Horses, on the other hand, are covered in apocrine sweat glands so excrete high levels of sodium and chloride, i.e. salt, when they sweat so that there is no great salt concentration increase in the body hence no thirst stimulation. This has been a problem for horsemen and scientists for as long as time itself.

While a myriad of products to encourage horses to drink hit the market over the years none were very successful until around a decade ago the team at Kentucky Equine Research cracked it with the development of the highly successful Drink Up.

Since Covid and the later war in Ukraine supply of goods from overseas has been a nightmare for importers, from building supplies to pharmaceuticals. In almost any endeavour it has been common to blame shipping woes but that was not actually the case with Drink Up.

Drink-Up is a scientifically formulated, highly palatable, complex combination of ingredients, which increases a horse's acceptance of water and therefore aids in the prevention of dehydration.

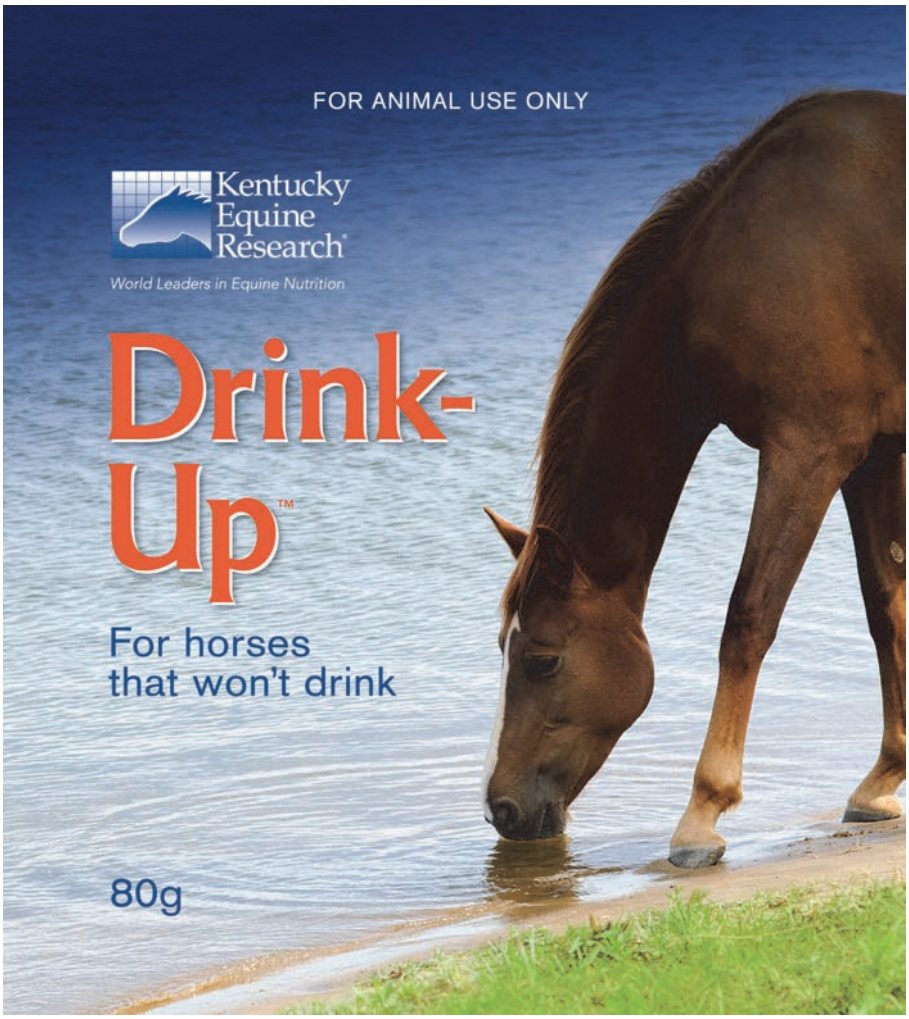
Launched in New Zealand in the summer of 2015/2016 the product rapidly caught on and dominated the market, until bureaucracy reared its head and MPI decided to stop shipments. The reason? Drink Up contains oats and MPI made the decision, despite the fact that oats have travelled back and forth across the Tasman for decades, that a whole shipment had to be sent back to Australia and no more could be imported unless the product was irradiated.

While we all fully endorse our country's biosecurity this did seem a little over the top. However in such a situation there is no option but to comply and so now, after a lull, we are able to once again import this highly effective 'hydration encourager'.

How does Drink-Up work? Drink-Up is a highly palatable blend designed to encourage horses to drink water. Drink-Up is a scientifically formulated blend containing floating, sinking and water flavouring ingredients which when combined encourages horses to drink to the bottom of their bucket!

As well as chasing the floating ingredients, Drink-Up contains KER Restore which helps stimulate the thirst response, encouraging a horse to drink every drop! Research has shown that 90% of horses increased water intake with Drink-Up.

Feeding recommendations: Drink-Up can be used at home, whilst travelling or during competition. Empty one 80g sachet of Drink-Up into 5 litres of clean, fresh water and stir to enhance flavour. Offer immediately or wait 30 minutes to further enhance flavour.



# Acetylsalicylic Acid and Foetal Loss

An interesting article appeared recently in a Kentucky Equine Research Newsletter regarding the use of acetylsalicylic acid to help prevent pregnancy loss in broodmares.

"Low uterine blood flow may contribute to pregnancy loss in mares. Despite the fact that aspirin, known also as acetylsalicylic acid or ASA, is often prescribed for certain conditions, including placentitis, few studies support its use. A new study revealed that ASA administered throughout mid and late gestation increased uterine blood flow and appeared safe for both the mare and foal.*

In that study, 16 pregnant Thoroughbred mares ranging in age from 9 to 17 years were included. All mares were considered high risk, as they had a history of placentitis or spontaneous abortion. From day 120 of gestation until parturition, mares were administered either a placebo or 5,000 mg of ASA once or twice daily. The ASA dose was chosen empirically, estimated from the few previously reported studies of ASA use in pregnant mares.

Prior to ASA administration, mares were examined through ultrasound, and uterine blood flow was evaluated on three separate occasions. During those examinations, maximum velocity of blood flowing in the uterine arteries and total blood flow volume were calculated.

Researchers repeated those tests every 21 days beginning on day 120 of pregnancy and ending at birth. The results showed increased uterine blood flow in mares treated with 5,000 mg ASA twice daily compared to the mares treated with ASA only once daily and to control mares.

Two doses of 5,000 mg ASA can enhance uterine perfusion by increasing blood flow velocity, according to the study.

"This team of researchers indicated that early detection of high-risk pregnancies and early intervention with ASA for mares with placentitis or placental insufficiency due to endometriosis, for example, may increase the likelihood of producing a live foal," said Kathleen Crandell, Ph.D., a nutritionist for Kentucky Equine Research.

Other ways of supporting mares during gestation are

(1) ensuring a balanced diet that supplies sufficient energy to support growth of the foal and prepare the mare for lactation, and

(2) (2) offering omega-3 fatty acids throughout pregnancy.

"In humans, research shows that increased intake of the omega-3 fatty acids DHA and EPA prevent premature labor [sic] and delivery through a reduction in prenatal stress.

Further, studies also report reduced perinatal mortality rate and higher birth weights in babies whose mothers were supplemented with omega-3 fatty acids during gestation," she explained.

Similar data are not yet available in pregnant mares. "However, we do know that mares supplemented with omega-3 fatty acids derived from fish oil, which is high in DHA and EPA, have improved colostrum quality and enhanced passive transfer of antibodies from colostrum," Crandell said.

In terms of safety, all 16 mares included in the study had normal pregnancies and delivered live foals. Gestation lengths, time to placental expulsion, and foal birth weight were all considered normal in mares treated with ASA.

*Sielhorst, J., U. Roggel-Buecker, K.-C. Neudeck, A. Kahler, K. Rohn, J. Luettgenau, H. Bollwein, F. Hollinshead, the and H. Sieme. 2022. Effect of acetylsalicylic acid on uterine blood flow, gestation length, foal birth weight and placental weight in pregnant Thoroughbred mares: A clinical pilot study. Journal of Equine Veterinary Science 118:104107."

# Late For Work

A young man was always late for work.

Finally his manager warned him, "Come in late again tomorrow and you will be fired."

The next morning he slept in again, arriving at the office half an hour late.

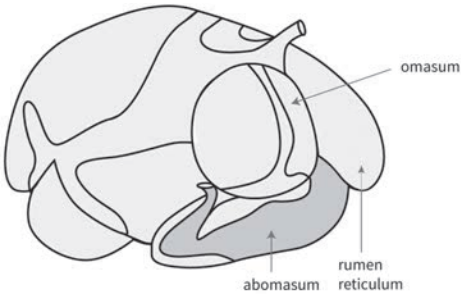
Remembering the threat he crept in surreptitiously wearing a hat and dark glasses and said as the manager walked in,

"Can I apply for the new vacancy please?"

He kept his job.

# Demystifying The Rumen

People often raise the issue of the effect of the rumen on drug absorption without ever really answering the question, thus bringing an air of mystique to this important but often misunderstood organ. It is a bit like listening to rugby pundits on TV, most of whom are ex-wingers, going on about the mysterious happenings in the front row that they never understand. To anyone who has played up front it is not that mysterious, in the vast majority of scrums the loosehead is trying to lift and the opposite tighthead is trying to force down.




It is similar with the rumen, there is no great mystique just certain anatomical features of which to be cognisant. While it is easy to be side-tracked by the fact that the reticulo-rumen apparatus functions as a giant fermentation vat, there are specific features that influence the absorption of drugs and nutrients. The most obvious is the size and volume of fluid contained in the rumen relative to the body mass of the animal, then there are features like the microflora, the pH and the oesophageal groove to consider.

Finally there is the form of medication; unlike in humans and small animals any solid medication is not in the form of tablets to be dissolved in the stomach (abomasum) and/or the duodenum but in the form of bullets or boluses that remain in place in the reticulo-rumen and slowly release the active ingredients.

So, putting aside the treatment of rumen associated diseases such as ruminal acidosis and bloat, how do these features influence drug and nutrient administration to the body as a whole?

**Ruminal Size:**

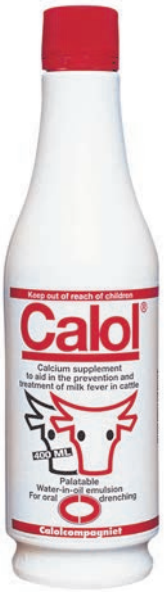
The rumen in the adult cow comprises approximately 80% of the abdominal cavity, with a capacity around 80 L (roughly 16% of body weight). Slow and inefficient mixing of drugs in the large volume of the ruminoreticular fluid delays attainment of uniform concentrations throughout the multiphasic ingesta and retards absorption from the ruminoreticulum. While the sheer size of ingesta is an impediment to absorption it is mainly an issue for drugs absorbed against a concentration gradient, something discussed below under the oesophageal groove.

**Oesophageal Groove:**

The oesophageal groove is present in all new-born ruminants but is still present and functions in the adult where it is often triggered by high concentrations of different salts; hence it has a highly important relationship to ruminal volume, especially in oral treatment and prevention of milk fever.

The high concentration of calcium mixtures triggers the oesophageal groove into depositing the administered salts directly into the abomasum where they rely on a concentration gradient for absorption.

However the oesophageal groove relies on smooth muscle function, thus it is one of the first reflexes lost in clinical and even subclinical milk fever. This results in the afore mentioned salts being deposited into the vast mass of the rumen so that there is no longer a concentration gradient driving absorption.



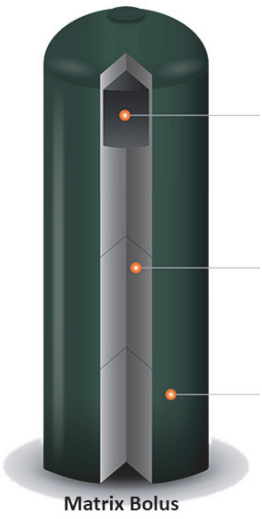

This is especially important for the all-important calcium chloride and other salts which are absorbed by passive diffusion.

With Calol, calcium chloride in a water in oil emulsion, this is not an issue as the oil-based product does not dissolve into the ruminal fluid mass but forms a film coat next to the mucosa hence absorption is not interrupted. On the other hand the mass of the ruminal fluid renders all water based salt mixtures ineffective.

If hypocalcaemia is not an issue, but it is preferable for the medication to be deposited directly to the abomasum, salts such as copper sulphate can be added to stimulate oesophageal closure.

**Bullets and Boluses:**

The other issue affected by both ruminal size and the oesophageal groove is that tablet administration as practiced in non-ruminant medication is not practical. Solid medication is usually done with boluses that sit in the reticulo-rumen area slowly dissolving over time.


Matrix Bolus

As with all medications, care needs to be taken with different actives to ensure they do not antagonise each oth-

# Demystifying The Rumen

er. A prime example is zinc boluses for facial eczema prevention that do impede absorption from copper boluses.

Fortunately zinc supplementation is generally early to mid-autumn, leaving a late autumn early winter window for copper supplementation in time for the traditional winter shortfall.

The vast majority of boluses are matrix boluses, which have the active ingredient coated with resin, apart from one open end through which the active is absorbed.

This can result in uneven absorption as the bolus gets older. This can be compounded if more than one bolus, the general practice, is administered as they rub together mechanically resulting in loss of the resin coating, further altering absorption rate.

Irish company Bimeda has overcome this problem by manufacturing glass boluses that are absorbed at a very even rate over time.

**Microflora:**

Rumen microbes are anaerobic and make vitamin K and all B vitamins. Microbes make enough of these vitamins for cattle growth and maintenance. Thus, under most conditions, cattle with healthy rumens don't need added B vitamins or vitamin K in their diet. An exception is on cobalt deficient areas of the country as cobalt is required for the micro-organisms to manufacture vitamin $B_{12}$. In such areas acute shortage is treated by vitamin $B_{12}$ injections, longer term prevention can manifest by cobalt containing boluses.


Amino acid supplementation is also at the mercy of these microbes. Certain amino acids, in particular choline and methionine, when administered *per os* are completely scavenged by the rumen microorganisms and so are completely unavailable to the animal. This can only be overcome by feeding rumen protected choline and methionine, as in the nutritional

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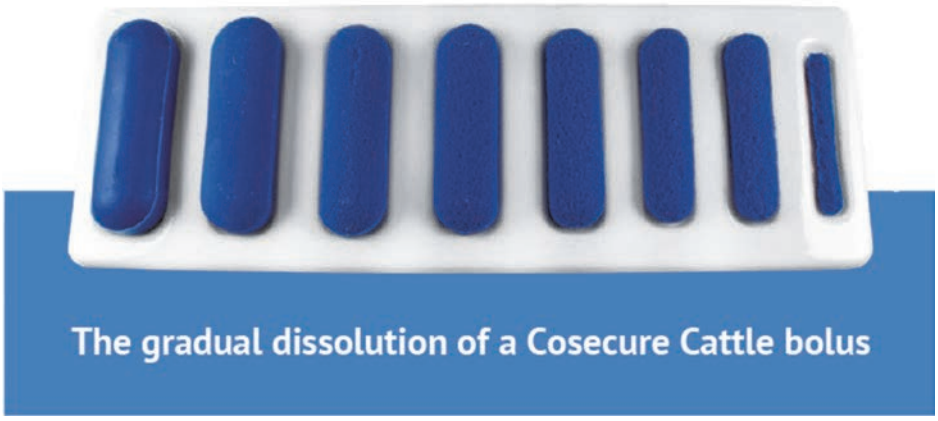


The gradual dissolution of a Cosecure Cattle bolus

# The Transplant

A married couple was in a terrible accident where the man's face was severely burned. The doctor told the husband that they couldn't graft any skin from his body because he was too skinny. So the wife offered to donate some of her own skin.

However, the only skin on her body that the doctor felt was suitable would have to come from her buttocks.

The husband and wife agreed that they would tell no one about where the skin came from, and they requested that the doctor also honour their secret. After all, this was a very delicate matter.

After the surgery was completed, everyone was astounded at the man's new face. He looked more handsome than he ever had before! All his friends and relatives raved about his youthful beauty!

One day, he was alone with his wife, and he was overcome with emotion at her sacrifice. He said, "Dear, I just want to thank you for everything you did for me. How can I possibly repay you?"

"My darling," she replied, "I get all the thanks I need every time I see your mother kiss you on the cheeks.

# Demystifying The Rumen

*(Continued from page 5)*
supplement especially designed for ruminants, Hep-Ora.

The anaerobic and reductive environment of the ruminoreticulum and the presence of many microbial enzymes result in inactivation of drugs such as trimethoprim and cardiac glycosides.

Aside from the many effects that the ruminoreticular environment can have on the activity and disposition of drugs, the drugs themselves may have unintended effects on ruminoreticular function. In particular, broad-spectrum antibacterial agents and antiprotozoal agents can disrupt the normal balance of microflora in the ruminoreticulum.

Thus there is little indication for oral antibiotic therapy in cattle except for pre-ruminant calves.

**pH:**

Absorption is also affected by the polarity and ionization status of the drug, which is determined by the pKa of the drug and the pH of the ruminoreticular fluid. The latter depends on the diet and the relative contributions of alkaline saliva and acidic ruminoreticular fluid.

A cow's salivary glands can make and add 45 to 75 litres of saliva to the rumen daily. Saliva has several functions in cows. It provides liquid for the microbes. It recirculates nitrogen and minerals. It buffers the rumen. Saliva keeps the rumen pH between 6.2 and 6.8 for best digestion of forage and feedstuffs.

That is not however the ideal pH for drugs such as weak acids which are not ionized at the higher pH, thus able to be absorbed across a membrane, until they reach the much lower pH of the abomasum.

For many drugs and nutrients this is not really an issue as they are absorbed once they reach the lower pH levels of the abomasum where they can dissociate. However for two minerals in particular, cobalt and copper, this is of vital importance.

Both are commonly supplied in boluses as copper oxide and cobalt carbonate, both of which are unionized at the normal ruminal pH. Thus neither are readily available until they reach the much lower pH of the abomasum where they dissociate into their respective ions. In the case of cobalt this means lower availability to the microflora who need cobalt to manufacture vitamin $B_{12}$. By the time the cobalt reaches the abomasum it is already past the site of utilisation.

In the case of copper one problem is the presence of thiomolybdates in the rumen. These combine irreversibly with copper ions and render them unavailable. If there is not enough copper to cancel them out they can migrate into the blood stream and bind to copper there, thus creating a secondary copper deficiency.


Cosecure glass boluses, from Bimeda, are manufactured at high temperatures that burn off the oxide and carbonate ions resulting in both copper and cobalt being embedded in the glass bolus in the ionic state so that they are released into the rumen already ionised and thus freely available to the microorganisms in the case of cobalt and to neutralise thiomolybdates in the case of copper, thus making dietary copper available to the animal.


# Texting

**Daughter's text to Dad:**

Daddy, I'm coming home to get married soon , so get your chequebook ready. LOLI As you know, I'm in Australia and he's in the US. We met on a dating site, became friends on Facebook, and had long chats on WhatsApp. He proposed to me on Skype and now we've had a 2-month relationship through Viber. Dad, I need your blessing, good wishes, and a really big wedding. Lots of love, Lilly.

**Dad's reply:**

My dear Lilly, Like Wowl Really? Cooll Whatever ... l suggest you two get married on Twitter, have fun on Tango, register for your stuff on Amazon , and pay for it all through PayPal. And when you get fed up with this new husband, sell him on Ebay. Lots of love, Dad .

# The Role of Antihistamines

In general antihistamines, very much like opioids, have a relatively short duration of action leading them to perhaps being underutilized in veterinary medicine. They are however very useful drugs in giving immediate relief to allergic and itchy conditions.

Just like opioids are the go to drugs after surgery, before following up with NSAIDs for a longer action after recovery, antihistamines are ideal in the initial inflammatory stages of allergies with the slower acting corticosteroids taking over later (only if required) for prolonged activity.

Mepyramine maleate, the active ingredient of Antimine, is a first generation antihistamine, targeting the $H_1$ receptor as an inverse agonist, a drug that binds to the same receptor as an agonist but induces a pharmacological response opposite to that of the agonist. This is different from an antagonist which occupies a receptor and simply blocks a response.

An agonist increases the activity of a receptor above its basal level, whereas an inverse agonist decreases the activity below the basal level. The efficacy of a full agonist is by definition 100%, a neutral antagonist has 0% efficacy, and an inverse agonist has < 0% (i.e., negative) efficacy.

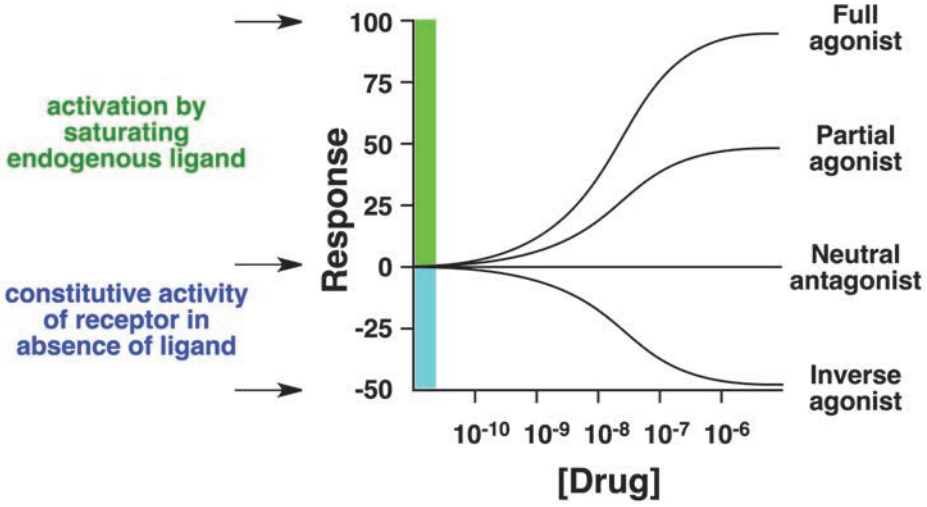
In the case of antihistamines, although designated as inverse agonists, their main function is to stabilize the histamine $H_1$ receptors in the tissue cells rather than have a direct cellular action.

The mechanism of action is described as being based on quantitative considerations, which simply means that histamine in excess may displace antihistamines.

The $H_1$ receptor is expressed in smooth muscles, on vascular endothelial cells, in the heart, and in the central nervous system. Antihistamines, which act on this receptor, are used as anti-allergy drugs.


Antihistamines in general cause drowsiness with overdosage but have a reasonably short duration of action (a few hours) and have a high safety threshold.

Overall antihistamines are a useful adjunct to veterinary medicine and, apart from antihistamines in some ointments, Antimine, in injectable form, is the only available antihistamine registered in New Zealand for use in animals.




**Idealized dose response curves of an agonist, partial agonist, neutral antagonist, and inverse agonist.** *By Boghog - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=34657034*

# Proud Mums

Three women were boasting about their sons. "What a birthday I had last year," exclaimed the first, "My son, that wonderful boy, threw me a big party in a fancy restaurant. He even paid for my friends."

"That's very nice, but listen to this," said the second, "Last winter my son gave me an all expenses paid holiday to the Greek Islands, first class."

"That's nothing," interrupted the third.

"For five years now my son has been seeing a psychiatrist, three times a week. And the whole time he talks about nothing but me."

# Prayers Answered

The pastor asked if anyone in the congregation would like to express praise for answered prayers.

Suzie stood and walked to the podium.

She said, "I have a praise. Two months ago, my husband, Phil, had a terrible bicycle wreck and his scrotum was completely crushed. The pain was excruciating and the doctors didn't know if they could help him."

You could hear a muffled gasp from the men in the congregation as they imagine the pain that poor Phil must have experienced.

"Phil was unable to hold me or the children," she went on, "and every move caused him terrible pain."

We prayed as the doctors performed a delicate operation, and it turned out they were able to piece together the crushed remnants of Phil's scrotum, and wrap wire around it to hold it in place."

Again, the men in the congregation cringed and squirmed uncomfortably as they imagined the horrible surgery performed on Phil.

"Now," she announced in a quivering voice, "thank the Lord, Phil is out of the hospital and the doctors say that with time, his scrotum should recover completely."

All the men sighed with unified relief. The pastor rose and tentatively asked if anyone else had something to say.

A man stood up and walked slowly to the podium. He said, "I'm Phil." The entire congregation held its breath.

"I just want to tell my wife the word is sternum."