Introduction to problem-based clinical reasoning

What is problem-based clinical reasoning?

Problem-based vs "pattern" recognition
In problem-based medicine each significant clinico-pathological problem is considered separately before being related to the other problems that the patient may present with.

An alternative approach is to try to remember all diseases that fit the "pattern" of clinical signs/pathological abnormalities that the animal is showing. This may be relatively simple for common disorders, if a disorder has a unique pattern of clinical signs or if you have a huge amount of experience and knowledge as well as a photographic memory. However, using pattern recognition can also lead to errors of omission.

Pattern recognition is unsatisfactory when the clinician is faced with a patient exhibiting multiple clinical signs that are not immediately recognisable as a specific disease or, more commonly, if the pattern of clinical signs is suggestive of certain disorders but not specific for them - this can lead to dangerous tunnel vision where the vet pursues his/her initial diagnostic hunch to the exclusion of other diagnostic possibilities and interprets all subsequent data as favourable to their initial diagnosis including ignoring data that don’t “fit” their preferred diagnosis.

For experienced veterinarians, pattern recognition combined with ‘fishing expeditions’ (i.e."I have no idea what’s going on so I’ll just do bloods and hopefully something will come up!”) can result in a successful diagnostic or therapeutic outcome in perhaps 70-80% of medical cases.

But the other 20-30% of cases do not yield their secrets so readily using these approaches and it is these cases that frustrate the veterinarians and make practice less pleasant than it should be. It is for this reason we are going to work on enhancing your problem-solving skills and building your knowledge base.

Each problem is a building block
In problem-based clinical reasoning, the pathophysiological basis and differential diagnosis for the most specific clinical signs the patient is exhibiting are considered before a pattern is sought. This approach ensures that one’s mind remains more open to other diagnostic possibilities than what might seem to be initially the most obvious and helps prevent
pattern-based tunnel vision. Pattern-based tunnel vision can result at best in a speedy, correct diagnosis but, at worst, in wasted time, money, and it sometimes endangers the life of the patient.

If there are multiple clinical signs e.g. vomiting, polydipsia, and a pulse deficit, each problem is considered separately first and then in relation to the other problems to determine if there is a disorder (or disorders) that could explain all the clinical signs present. In this way, the clinician, if she/he has developed a logical approach to each clinical problem, will be able to easily assess the potential differentials for each problem and then relate them rather than trying to remember every disease process that could cause that pattern of particular signs.

Thus - one does look for patterns but not until we have put in place an intellectual framework that helps prevent tunnel vision too early in the diagnostic process.

Key elements to problem solving

Key element 1

*Construct problem list?*

The initial step in logical clinical problem-solving is to clarify and articulate the clinical problems the patient has presented with. This is best achieved by constructing a problem list – either in your head or in more complex cases, on paper or the computer.

*Why?*

Constructing a problem list:

- Helps makes explicit the clinical signs
- Transforms the vague to the more specific
- Helps prevent overlooking less obvious but nevertheless crucial clinical signs

*Identify the problems and "prioritise"*

Having identified the problems the animal has, assign them some sort of priority based on their specific nature (i.e. prioritise - dreadful word but unfortunately occasionally useful!).

For example, anorexia, depression, and lethargy are all fairly non-specific clinical problems, which do not suggest involvement of any body system in particular and can be clinical signs associated with a vast number of disease processes.

*Focus on the most specific problems*
However, persistent vomiting, polydipsia/polyuria, seizures, jaundice etc. are more specific clinical signs that give the clinician a "handle" with which to proceed with diagnosis.

As the clinician proceeds down the diagnostic path, the overall aim is to seek information, which allows her/him to define each problem more specifically (i.e. narrow down the diagnostic options) until a specific diagnosis is finally arrived at.

**Specificity is relative!**
The relative specificity of a problem will however, vary depending on the context. For example, for a dog that presents with intermittent vomiting and lethargy, *vomiting* is clearly the most specific problem and investigation of this problem will eventually result in a diagnosis.

In contrast, for the dog that presents with intermittent vomiting and lethargy and is found to be jaundiced on physical examination, *jaundice* is the most specific clinical problem. In this case, investigation of jaundice will lead more expediently to a diagnosis than investigation of vomiting, as the diagnostic options for jaundice are narrower than the diagnostic options for vomiting.

In other words, although you identify and consider to a certain degree each problem (at the very least by asking “Can I identify the problem” and “What system could be involved and how” – see later for further discussion of these concepts), you try to focus your diagnostic or therapeutic plans on the most specific problem IF you are comfortable that the other problems are most likely related to it. If you are NOT convinced e.g. the chronology of clinical signs is very different, the different problems just don’t fit easily together or there is some other clue that suggests to you that the problems may not be related, then you need to keep your problems separate and assess them thoroughly as separate entities.

**How do I decide what problems are specific?**
One of the most difficult steps in developing the problem-based approach is deciding which are the specific problems. As indicated above, specificity is a relative term and will vary with each patient. There are a few clues that you can look for when trying to decide what are the most specific problems the animal has:

- **Is there a clearly defined diagnostic pathway for the problem with a limited number of systems or differential diagnoses that could be involved?**

For example: **Vomiting vs Inappetence**
- The problem of vomiting has a very clearly defined diagnostic pathway (discussed later in this module) whereas there are almost an endless set of
diagnostic possibilities for causes of inappetence and there is no well defined
diagnostic approach
- Hence vomiting is more specific than inappetence

• Could one problem be explained by all the other problems but not vice versa or does the
differential diagnosis for one problem include many diagnoses that would explain the other
problems but not vice versa?

For example **Vomiting vs Jaundice**
- Jaundice is the more specific problem because most causes of jaundice could also
conceivably cause vomiting but there are many causes of vomiting that do not
cause jaundice.
- Hence the diagnostic pathway for jaundice is more clearly defined (discussed in
Module 5) and there is a more limited number of possible diagnoses.

**But don’t forget to relate each problem to the whole animal**
Once you have narrowed down your diagnostic options for the most specific problems, don’t
forget to consider the less specific problems in relation to your differential diagnosis.

**Example**
For example, your **specific** problem may be polyuria/polydipsia associated with a urine
specific gravity of 1.002 and your **non-specific** problem may be anorexia.

Hence when considering the potential differential diagnoses for polyuria/ polydipsia
associated with hyposthenuria, those diagnoses for which anorexia and lethargy are not
usually a feature e.g. psychogenic polydipsia, diabetes insipidus and hyperadrenocorticism,
are much less likely than those diagnoses where anorexia and lethargy are common such as
hypercalcaemia, pyometra and liver disease.

One doesn’t necessarily “rule out” the former diagnoses but they have a lower priority in
your investigation than the latter group.

Priority is also influenced by the relative likelihood of a diagnosis. Common things occur
commonly or to put it in more colourful terms “if you are living in Dorset the hoof beats in
the night are more likely to be a horse than a zebra”. So, although one doesn’t dismiss the
possibility of an unusual diagnosis by any means, the priority for investigation is usually to
pursue the most likely diagnosis first, provided it is consistent with the data available.

**Key element 2**
Logical Clinical Problem Solving

Ask "does this make sense?"
Always ask yourself, particularly when assessing clinical pathology or results of other diagnostic procedures in light of particular problems, - "Does this make sense - does this clinicopathological abnormality explain the problem that the animal has?" Be a detective!

Example 1
For example, a dog is depressed, anorectic, vomiting and polydipsic. Its blood glucose is 12 mmol/L, it has 3+ glucosuria and no ketones in the urine. Does this mean that diabetes mellitus explains all of the dog’s clinical signs? No - the dog may have diabetes mellitus but for it to be this unwell as a result of diabetes, it would need to have ketoacidosis, which it does not have. Hence you must look further for an explanation for the depression, anorexia and vomiting.

Example 2
Another example - an unwell dog (anorectic, vomiting, depressed) is found to have clinicopathological changes consistent with Cushing’s disease. Does this explain all of the dog’s clinical signs? No - dogs with uncomplicated Cushing’s disease are usually not unwell, so there is probably some other explanation for the dog’s malaise, which you will need to identify and resolve before definitive testing for Cushing’s disease is possible.

Key element 3
The essential question
Every clinical problem, be it identified in the history, on physical examination or from diagnostic tests, can be associated with an essential question, the answer to which will be invaluable in guiding further diagnostic procedures and which if not addressed will lead the unwary down dead ends and wasted diagnostic pathways. Through this course we will encounter many of these questions and you will soon be able to devise your own.

Example
• For example, an animal is determined to be anaemic - the essential question is "Is it regenerative or non-regenerative?"
• Why is this the essential question?
  o Because the list of differential diagnoses for regenerative and non-regenerative anaemia are different (though there are some commonalities). Once you know the answer to the question, you can focus on the appropriate differential diagnoses rather than having to consider all the causes of anaemia. This approach will also trigger you to seek the appropriate information i.e. a reticulocyte count.
Example

Another example, an animal is **polyuric** - the essential question is "**What is the specific gravity?**"

- Why is this the essential question?
  - Because once you know the answer you can concentrate on disorders that cause hyposthenuria (for example) rather than having to consider every disease that causes polyuria. Asking the question will also ensure that you do measure the urine SG - an absolutely essential step in working up an animal with polyuria.

**What are the consequences of failing to ask the essential question?**

The consequences of failing to identify and ask the essential question can be serious. For example, if one does not determine the urine SG in a patient with polyuria and polydipsia, one may waste time investigating diseases that couldn't possibly be the cause of the PU/PD e.g. renal disease if the urine SG is 1.001. In addition, in this example, it is very difficult to interpret the significance of increases in serum urea and creatinine values if you do not know the urine SG. As a result, renal failure may be erroneously diagnosed.

**Key element 4**

**Think "pathophysiologically"**

Another essential element is to think "pathophysiologically". An understanding of physiology and pathophysiology is essential to understanding internal medicine.

**Example**

For example, an animal has profound hypokalaemia: rather than trying to remember all the diseases that may cause hypokalaemia, think about how the body might lose potassium, or fail to acquire it, or even "use it up". By getting into the habit of thinking in this manner, you can potentially diagnose disorders that you may never have heard of (or that may never have been described before!).

Thinking pathophysiologically will also stimulate you to seek more knowledge about the pathophysiology of disease processes, which will lead to a greater understanding of internal medicine and ultimately to a better retention of knowledge.

**Problem, System, Location, Lesion**

The cornerstone of a problem-based approach to internal medicine is to always approach each problem logically and (usually) to rigorously pursue, as appropriate, some or all of the following questions:
Logical Clinical Problem Solving

Diagnostic approach

- What is the problem?
- What system is involved?
- Where within the system is the problem located?
- What is the lesion?

_These questions are often essential questions_

Often these questions can be defined as essential questions as discussed above. The answers to them or the pursuit of the answer will determine the appropriate questions to ask in the history, or alert you to pay particular attention to aspects of the physical examination, or will indicate the most appropriate and logical diagnostic test to use to answer the question.

**Identify the problem**

_Example:_ The owner reports that the dog is vomiting. Is the animal really vomiting or regurgitating?

Until the problem is appropriately defined, diagnosis is not possible. It is probably at this first step that many clinicians most commonly make mistakes e.g. assuming the animal is vomiting when in fact it is regurgitating. Failure to appropriately identify the problem can lead to wasted time and money.

**Other examples**
- The owner says the dog is having fits - is it having seizures or episodes of syncope?
- The owner says the dog has red urine - is it blood, haemoglobin or myoglobin?

**Identify the body system affected and how it is involved**

The question can be posed as “Do I have a primary (i.e. structural) problem of a body system or a secondary problem (i.e. the system is affected by other factors)?”

_Example:_ Is vomiting due to primary or extra-gastrointestinal disease?

Failure to appropriately identify the system involved can also lead to wasted time and money as well as client and veterinarian frustration.

In fact, if you do nothing else in assessing a case before seeking the diagnostic “pattern”, ask yourself for each of the specific problems - “what system could be involved and how?”. This simple question will immediately open up your mind to diagnostic possibilities you may never have contemplated if you were just focusing on the “pattern”.

_Failure to identify the system can be life threatening!_
Occasionally, the patient’s life may also be threatened by the delay that ensues in reaching the correct diagnosis. For example, if you do a barium meal to examine the gastrointestinal tract of a vomiting patient (or worse, an exploratory laparotomy) when in fact it has non-gastrointestinal tract disease such as pancreatitis, liver disease or hypoadrenocorticism.

Other examples
Other examples include:

- Hind limb weakness - is the neurological, skeletal or muscular system involved?
- Chronic cough - cardiac or respiratory system?
- Jaundice - due to haemopoietic or hepatobiliary disorder?
- Cardiac arrhythmia - is it due to primary (structural) cardiac disease or extra-cardiac disease e.g. GDV, splenic pathology?
- Polyuria/polydipsia - is it due to primary (structural) renal disease or extra-renal dysfunction?

An alternative, though closely related, question for some problems is “Is the problem local or systemic?”

- Epistaxis - due to local nasal disease or systemic disease e.g. coagulopathy, hyperviscosity?
- Melaena - GI bleeding due to local disease (ulceration – which in turn may be due to primary or secondary GI disease) or systemic disease e.g. coagulopathy

Identify the anatomical location of the lesion

Example: Having determined that vomiting is due to primary gastrointestinal disease, where in the gastrointestinal tract is the lesion located?

In this example, by asking this question you will select the most appropriate method to either answer the question or to move on to the next step.

For example, if you believe that your history and physical examination and other ancillary data indicate a lower small intestinal lesion, endoscopy is not going to be an appropriate method of visualising the area or obtain biopsies. On the other hand, if all information you have suggests a gastric lesion, endoscopy would be appropriate.

Other examples

- Hind limb weakness due to neurological dysfunction - is the lesion in the spinal cord (and where), peripheral nerves or brain?
- Diarrhoea due to primary GI disease - due to small bowel disease? large-bowel disease? both?
• Haematuria - from urethra, prostate, bladder or kidneys?

Identify the lesion

Example: The patient has a gastric lesion - Is it a tumour, foreign body, or ulcer?
• This question will require visualisation and/or biopsy to answer but it would have been a waste of time asking the question until you had arrived at the right location.

Other examples
• Spinal cord lesion visible on a myelogram - is it a tumour or granuloma or abscess?
• Haematuria due to lower urinary tract disease - infection, calculi or neoplasia?
• Large bowel diarrhoea - parasites, infection, ulceration, stricture, neoplasia, diet-related?

The final result
Instead of thinking, when faced with a vomiting patient, "I wonder if it has a gastric foreign body or renal failure or a liver tumour?" your initial energies are directed at defining the problem, then the system etc. In this way, the diagnosis is made logically and thoughtfully, and, during the process, all diagnostic options can be considered as the need arises.

Does pattern recognition have a place?
Having said all of this, it is important to reiterate that pattern recognition for many cases is appropriate and justified - depending on your level of experience. For example, if a potbellied terrier with bilaterally symmetrical alopecia, seborrhoea, hyperpigmentation and comedomes walked into your consulting room and the owner reported that the dog was drinking lots of water, was ravenously hungry and seemed to be panting excessively, obviously hyperadrenocorticism is the most obvious diagnosis and going through the motions of assessing each specific problem would be ridiculous (but not if you had never seen a dog with hyperadrenocorticism before!).

However, it is important to be aware that pattern recognition is only foolproof if the pattern is virtually unique to the disease or there are a very limited number of diagnostic options and its value is very dependent on the clinician's experience, depth of knowledge, ability to sort data quickly and efficiently etc.

Of course, once you have considered each individual problem you do in fact look for a pattern in the clinical signs. But the insertion of that initial step of considering each specific problem individually and then relating it to the other problems present should ensure that
you don't miss the less obvious possible diagnoses that you may not have initially been aware of.

There are some combinations/patterns of clinical signs that make the diagnostic options very limited. For example, a patient with PU/PD who is also polyphagic. If the PU/PD and polyphagia have been present for the same length of time then they are almost certainly due to the same disorder and it is quite appropriate to assess them together. There are very few conditions that will cause this pattern of clinical signs so it is quite appropriate to concentrate on these first. Even if the polyphagia is not due to the same pathology there are a number of causes of PU/PD that simply aren’t feasible in a dog that is also easting well (because they would decrease not increase appetite).

In addition, the process of developing a sound problem-orientated approach can enhance your ability to recognize patterns, because you have a greater understanding of the reasons why you believe a certain pattern suggests some disorders more than others.

*It may seem tedious!*
You may feel at times through the next few weeks that being asked to assess each individual specific problem is a tedious exercise when the diagnosis is obvious because you think you recognise the pattern of clinical signs. In some cases this will be true, in other cases you will be misled (I have a nasty habit of including cases with a bit of a twist to ensure the message gets across!).

*Practice, practice, practice!*
However, the most important point that I will try to get across is that if you don’t ‘practice’ your problem orientated approach on relatively simple clinical cases, when you are faced with the complex cases you will not be able to apply problem-orientated principles and will still left floundering for a diagnosis.

*Finding the right balance*
It is also useful to remember that medical diagnoses are often based on the ‘balance of probabilities’ rather than having to be proved ‘beyond reasonable doubt’. Striking the right balance between the diagnostic are skills/arts that are difficult to teach (but I’ll try!).

*Obtain best value from your “pathology pound”*
The aim of a logical and thorough approach to diagnosis is to reach the answer as expediently as possible and to get the best value from your “pathology pound” - i.e. not to waste the client’s money on unnecessary tests and procedures.
Client relations
An additional advantage is that you will have a very good idea why you are taking that blood or doing that x-ray or prescribing that medication. And because you know why you are doing it, you can explain it to the client clearly and they are much more likely to agree to spend the necessary money.

You are also in a much better position to explain the implications of "normal results" rather than being sent into a panic because you were hoping the blood tests would show something (because the dog looks really sick so it must have an abnormal blood test! - but its blood results are absolutely normal! - HELP! - what do I do now?)

What do I need to do to identify the problem, system, location or pathology?
The diagnostic methods used to identify the problem, then the system, then the anatomical location and then the lesion will vary depending on the problem.

For example, clinical pathology may be needed in some cases to identify the problem whereas in others (in fact most), the problem will be definable on the basis of history and clinical examination. Similarly, diagnostic tests or procedures may be required to identify the body system involved in some cases; for other problems the system involved will be evident from the physical examination. In other situations once the problem is defined e.g. regurgitation, the body system is immediately apparent and the anatomical location identified (upper GIT - oesophagus or pharynx).

Be the “boss”
Every time you do a diagnostic test or institute a therapeutic trial you should have a clear idea why you are doing that procedure AND the question you are trying to answer. In other words YOU should be in the driving seat and in control of your destiny as opposed to casting wildly around doing more and more tests to try to find an answer.

If you don’t know what question you are posing, then it can be very difficult to know if you have found the right answer. So, for example, you may be doing bloods to answer the question “Does this animal have primary or secondary GI disease as a cause of its vomiting?” If the patient is a dog and the bloods reveal severe pancreatitis you are lucky – the bloods have also answered your question “What is the lesion?” But if the bloods indicate hypercalcaemia as the cause of the vomiting, you may still not know what the lesion is – i.e. what is causing the hypercalcaemia. So you will need to do further tests with the aim to answering the question “What is the lesion?”

Does any of this make sense?
Time saver or time waster?
You will find that if you discipline yourself to think in this manner it will become second nature and almost sub-conscious and certainly not as laborious as it may seem at present. In fact, acquisition of these problem-solving skills will ultimately save time.

As with all skills, it takes time to develop the knowledge base and mental discipline required but, once developed, these will provide a firm base for the future and most importantly, will not "go out of date" no matter how many new diseases/disorders are discovered.

Now let’s try this approach on a clinical problem!
Vomiting

**Physiology of vomiting**

Vomiting or emesis is the forceful expulsion of gastric and/or intestinal contents through the oesophagus, mouth and sometimes nostrils. Vomiting results from the coordinated activity of a number of abdominal, pharyngeal and thoracic structures.

The essential components of the emetic reflex are:

- visceral receptors
- vagal and sympathetic afferent neurones
- the chemoreceptor trigger zone (CRTZ)
- the vomiting centre within the reticular formation of the medulla oblongata

The act of vomiting is controlled and coordinated by the vomiting centre in the medulla and cannot occur without an intact vomiting centre.

Stages in the act of vomition are:

**Nausea**

- reduced gastric tone
- duodenal and proximal jejunal tone is increased
- duodenal contents reflux into the stomach
- depression, hypersalivation, repeated swallowing

**Retching**

**Vomiting**

- glottis closed
- soft palate pressed up against nasopharynx
- abdominal muscles and diaphragm contracts contract
- cardia opens, pyloric stomach contracts

Reverse peristalsis, cardiac rhythm disturbances and changes in colonic motility also occur.
The closure of the glottis and pressing of the soft palate up against the nasopharynx protect against aspiration of gastric contents. In contrast, during regurgitation, which is a passive process without coordination, these actions do not occur, hence aspiration pneumonia is a common sequel to disorders that cause regurgitation.

Why do animals vomit?

Protective

Elimination of toxic or irritant substances from the GI tract. Important, especially in dogs due to their scavenging nature. Well-developed protective reflex in dogs and cats.

Stress induced in wild animals - against threats that can be more easily escaped on an empty stomach.

Defence e.g. camels

Vomiting may also act as an indicator or warning of disease - as does pain

Initiation of Vomiting

Vomiting is initiated by either humoral or neural pathways. The **humoral pathway** involves stimulation of the chemoreceptor trigger zone (CRTZ) by blood borne substances, the **neural pathway** involves activation of the vomiting centre.

Vomiting centre

All animal species that vomit have a brainstem ‘vomiting centre’, which is a group of several nuclei that act in concert to coordinate the somatomotor events involved in expelling gastric contents. Non-vomiting species such as rodents and rabbits also have the brainstem nuclei and motor systems necessary for emesis but lack the complex synaptic interaction among brainstem nuclei and viscera required for a coordinated reflex.

Is there a discrete vomiting centre?

The concept of a discrete emetic centre within the reticular formation of the medulla oblongata has been challenged recently. However, whether or not it is a discrete anatomical centre or simply represents a sequential activation of a series of effector nuclei, the important concept is that there is a central coordinating role for the medulla in emesis.

Input to the vomiting centre
The vomiting centre receives input from vagal and sympathetic neurones, the CRTZ, the vestibular apparatus and the cerebral cortex. It may also be stimulated directly by blood-borne toxins that can cross the blood-brain-barrier (BBB).

**Important receptors**
The receptors that have been identified to be important in the vomiting centre are $5\text{-HT}_{1A}$, $\alpha_2$-adrenergic and NK₁ receptors. Drugs such as buspirone act as anti-emetics by acting as antagonists at $5\text{-HT}_{1A}$ receptors, and anti-emetics such as prochlorperazine (Stemetil) act at $\alpha$-adrenergic receptors.

**Central Stimulation**
Central stimulation of the vomiting centre occurs via higher centres in the central nervous system. Stimuli include nervousness, unpleasant odours, pain and psychogenic factors. Opioids and benzodiazepine receptors have been implicated in centrally-initiated vomiting but have not been well characterised pharmacologically.

**Opioid receptors**
The role of opioid receptors in emesis is confusing. Various studies have demonstrated that opioids have an emetic action in dogs and cats but that there is a difference in the receptors involved, s-receptors in the dog and $\mu$-receptors in the cat. However, opioids have been used in humans and animals to reduce nausea and vomiting associated with cancer chemotherapy.

This apparent paradox is due to a differential effect of opioids on the CRTZ and the vomiting centre. If an opioid penetrates the vomiting centre it may cause strong blockade of the vomiting reflex. However, if an opioid penetrates the CRTZ first, it will initially cause vomiting before blocking the vomiting centre. Morphine has been demonstrated to have this dual effect (although it may also cause vomiting associated with histamine release).

**Direct stimuli**
Centrally-induced vomiting may also occur due to direct stimulation of the emetic centre by elevated cerebrospinal fluid pressure, encephalitis or CNS neoplasia.

**Vestibular Apparatus**
Labyrinthine dysfunction associated with motion sickness and middle ear infection also affects the vomiting centre via neural pathways arising from the vestibular system. The CRTZ is involved in this pathway in the dog but not the cat.
Receptors
The neuronal pathways for motion sickness have not been completely characterised. \(M_1\)-cholinergic and \(H_1\)-histaminergic receptors must be involved in the dog because antagonists at these receptors are very effective anti-emetic agents. \(D_2\)-dopaminergic, \(\alpha_2\)-adrenergic and \(5-HT_3\) receptors are not involved.

Chemoreceptor Trigger Zone (CRTZ)
The CRTZ is located in the area postrema in the floor of the 4th ventricle. The area postrema has no BBB, therefore allowing access to toxins and chemicals that would normally be excluded from the CNS by the BBB. The CRTZ is stimulated by endogenous toxic substances produced in acute infectious diseases or metabolic disorders such as uraemia, diabetic ketoacidosis and by drugs and exogenous toxins.

Receptors
A variety of neurotransmitters and their receptors are important in the CRTZ including dopamine, adrenaline, 5-HT, acetylcholine, histamine, encephalins and Substance P (through NK\(_1\) receptors).

Species differences
Species differ in the relative importance of some neurotransmitter-receptor systems. For example, apomorphine, a \(D_2\)-dopamine receptor agonist is a potent emetic agent in dog and man but not in the cat, monkey, pig, horse or domestic fowl. This suggests that \(D_2\)-dopamine receptor antagonists such as metoclopramide might not be very useful as anti-emetic agents in the cat.

In contrast, xylazine, an \(\alpha_2\)-adrenergic agonist is a more potent emetic agent in the cat than the dog suggesting that \(\alpha_2\)-adrenergic antagonists, e.g. prochlorperazine (Stemetil) might be more useful antiemetic agents than \(D_2\)-dopamine receptor antagonists. Cytotoxic-drug-induced emesis has been shown to be mediated by 5-HT\(_3\) receptors in the CRTZ of the cat in contrast to the dog where visceral and vagal afferent 5-HT\(_3\) receptors are activated.

Histamine receptors have not been demonstrated in the CRTZ of the cat. Studies based on eliminating the emetic response to parenterally administered compounds by lesioning the CRTZ suggest that the CRTZ may be less sensitive to emetic compounds in the cat than in the dog. Alternatively, other sites for the origin of emesis may be more sensitive in the cat than the dog.

Peripheral Receptors
Peripheral receptors are located mainly in the gastrointestinal tract, particularly the duodenum, but also in the biliary tract, peritoneum and urinary organs. The receptors may be stimulated by distension, irritation, inflammation or changes in osmolarity. There are a few receptors in the lower bowel, which explains why patients with inflammatory lower-bowel disease may occasionally vomit.

**Afferent receptors**

Of the many afferent receptors found in the gut, 5-HT₃ receptors play an important role in the initiation of vomiting by cytotoxic drugs. Cytotoxic drugs cause 5-HT release from enterochromaffin cells, which activates 5-HT₃ receptors on vagal afferent fibres. 5-HT₃ receptor antagonists are very effective anti-emetics for cytotoxic-drug-induced vomiting. However, the role of 5-HT₃ receptors in other disorders of the gut has yet to be ascertained.

**Efferent receptors**

Vagal efferent receptors and myenteric neurones initiate the complex excitation and inhibition of visceral smooth muscle that culminates in emesis. Receptors involved include D₂-dopaminergic, 5-HT₄-serotonergic, M₂-cholinergic, NK₁ (Substance P) and motilin receptors.
Problem-based assessment of vomiting

Identify the problem

It is important to differentiate vomiting from regurgitation, which involves the retrograde movement of food and fluid from the oesophagus, pharynx and oral cavity without initiation of reflex neural pathways other than the gag reflex.

It is also important to differentiate vomiting from coughing followed by gagging, which owners often confuse with vomiting.

Owners are often unable to differentiate vomiting, regurgitating and gagging and therefore one must ask specific questions to elicit appropriate information e.g. amount of effort involved, character of vomitus etc. If still uncertain, the veterinarian may need to observe the animal.
**Primary vs secondary gastrointestinal disorders**

Vomiting may occur due to primary gastrointestinal disease (diseases directly involving the gastrointestinal tract) or from secondary or non-gastrointestinal disease i.e. abnormalities of other systems that indirectly cause vomiting either due to the action of toxins on the CRTZ or by stimulation of peripheral non-GI associated vomiting receptors.

**Identify the body system**

It is important to determine whether primary or secondary gastrointestinal disease is occurring as much time and money can be wasted if the wrong system is investigated.

**Primary GI disease**

In general (there are always exceptions): in primary upper gastrointestinal disease the vomiting will often (but not always) relate in time to eating e.g. the animal always vomits half an hour after eating. Usually, the shorter the interval between eating and vomiting, the higher up the gastrointestinal tract the lesion is located.

However, vomiting may be delayed for some hours (up to 24 hours) in animals with non-inflammatory gastric disorders. Animals with foreign bodies or secretory disorders of the bowel often vomit despite not eating. Also in lower bowel disorders, vomiting more commonly occurs at variable times after eating.

Animals with primary gastrointestinal disorders may be normal in all respects, including appetite or may be depressed and inappetant due either to the particular lesion e.g. neoplasia or local effects of a foreign body, or to the secondary effects of prolonged vomiting e.g. dehydration, electrolyte disturbances, shock.

**When is primary GI disease most likely?**

Primary gastrointestinal disease should be strongly suspected if:

- An abnormality is palpable in the gut e.g. foreign body, intussusception,
- If the vomiting is associated with significant diarrhoea (but remember that primary GI causes of vomiting are frequently not associated with diarrhoea) or
- If the animal is clinically and historically normal in all other respects (the only secondary GI diseases that will cause vomiting without also causing the patient to be metabolically unwell are hyperthyroidism in cats and early pancreatitis in dogs).
Secondary GI disease

In animals with secondary gastrointestinal disease, who are vomiting due to the effect of toxins on the vomiting centre or CRTZ or because of stimulation of non-GI associated peripheral receptors, vomiting tends to be unrelated to eating (except pancreatitis).

They will often have evidence from the history and/or clinical examination of abnormalities affecting other organ systems. Vomiting is usually intermittent, unrelated to eating and may often occur after the onset of other signs of malaise. In general, animals that are vomiting due to extra gastrointestinal disease are metabolically ill.

The exception to these generalisations is pancreatitis which behaves like a primary GI disease – i.e. acute onset vomiting in an, often, otherwise well dog, vomiting immediately after eating, decreased appetite and depression develop and usually do not precede vomiting.

Diagnostic approach to the vomiting patient

Careful evaluation of the history and physical examination findings for any signs that may suggest secondary or primary gastrointestinal disease is imperative.

If indicated by the history and/or physical examination investigate extra gastrointestinal disease with appropriate tests. Only a proportion of vomiting animals will require a diagnostic work up but it is still important to consider whether primary or secondary GI disease is likely.

The most common causes of primary GI disease e.g. gastritis, will respond satisfactorily to symptomatic treatment. However, most secondary GI disease will not and further information is required for management and prognosis.

When is clinical pathology useful?

In general, clinical pathology is most useful in providing information about secondary gastrointestinal diseases causing vomiting. For most primary gastrointestinal disease, clinical pathology tests provide information about the systemic effects of vomiting but not about the aetiology of the disorder.

However, if you are unable to determine from the history and physical examination if the animal has primary or secondary GI disease, it is cheaper, less invasive and usually quicker to investigate secondary GI disease first with appropriate tests then investigate primary GI
disease (plain & contrast radiographs, endoscopy, exploratory laparotomy) if clinical pathology is normal.

When is a fuller work-up indicated?
A fuller work-up (either for diagnosis or to assess the systemic effects of vomiting) may be indicated if:

- There has been no response to symptomatic therapy
- Vomiting is persistent and severe
- Other clinical signs are present
  - e.g. polydipsia, icterus, inappetance (that started prior to the onset of vomiting), severe depression, palpable abnormalities in the gut.

Primary gastrointestinal disease
Clinical pathology will be of little value in the diagnosis of primary GIT disease and diagnostic procedures such as plain and/or contrast radiographs, exploratory laparotomy or endoscopy should be considered.

When primary GI disease is suspected, diagnostic procedures should be aimed at visualising the gastrointestinal tract.

However, it is important to do appropriate tests to assess the patient’s hydration and electrolyte/acid-base status as prolonged and severe vomiting may cause biochemical derangements such as alkalosis, acidosis, prerenal azotaemia, hypokalaemia, hyponatraemia, and hypochloraemia.

Identify the anatomical location
If primary gastrointestinal disease is determined to be present, the temporal relationship of vomiting to eating, the character of the vomitus etc. should be used to assess where the lesion is likely to be.

Diagnostic tools such as contrast radiography may be appropriate to localise the lesion. An assessment of the likely location of the lesion is important as this may determine what further diagnostic procedures are suitable. For example, endoscopy would be appropriate for examining the stomach and possibly duodenum but will be of little use if lower small bowel disease is suspected.

Identify the lesion
Primary GI disease
Once the lesion has been located (by radiography or visualised in some manner), it must now be identified. Thus biopsy may be appropriate or the type of lesion may be evident by visual inspection (e.g. foreign body).

In the gastrointestinal tract as elsewhere, neoplasia and inflammation often look grossly identical and biopsies should always be taken. Similarly, even if the gastrointestinal tract looks grossly normal, biopsies should be obtained.

- Gastritis
  - Garbage-induced
  - Drug-induced
  - Immune-mediated
  - Eosinophilic
  - Infection e.g. Helicobacter
- Gastric foreign bodies
- Gastric ulceration
  - Primary GI
  - Secondary to extra GI disease
    ♦ mastocytoma
    ♦ liver disease
    ♦ drugs e.g. NSAIDs
- Disorders of the pylorus
  - Pylorospasm
  - Pyloric obstruction
    ♦ congenital stenosis
    ♦ chronic hypertrophic gastropathy
    ♦ neoplasia
    ♦ foreign bodies
- Abnormal gastric motility

Intestinal disease
Those intestinal diseases for which vomiting is a predominant clinical feature include:

- Enteritis e.g. parvo, corona, garbage
- Intestinal obstruction
- foreign body
- intussusception
• Feline inflammatory bowel disease

The closer the obstruction is to the pylorus, the more frequent and severe the vomiting.

*Secondary GI disorders*

A large number of secondary gastrointestinal disorders can cause vomiting. However, most of these can be eliminated with relatively few tests. In Table 1 the most important non-gastrointestinal disorders are listed with tests that are useful in diagnosis.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CLINICAL PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Amylase*, lipase*, WBC count, ALP, PLI</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>ALT, ALP, bile acids, bilirubin</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Urea, creatinine, phosphate, urine SG</td>
</tr>
<tr>
<td>Hypoadrenocorticism</td>
<td>Na⁺, K⁺, urea, cortisol</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Blood and urine glucose, ketones</td>
</tr>
<tr>
<td>Toxaemia due to infection</td>
<td>WBC count</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>Serum Ca²⁺</td>
</tr>
<tr>
<td>Hypokalaemia/hyperkalaemia</td>
<td>Serum K⁺</td>
</tr>
<tr>
<td>CNS disease</td>
<td>CSF analysis (possibly)</td>
</tr>
<tr>
<td>Lead toxicity</td>
<td>Blood lead</td>
</tr>
</tbody>
</table>

*Not useful in cats
Diarrhoea

Identify the problem

Diarrhoea is defined as an alteration in the normal pattern of defecation resulting in the passage of soft, unformed stools with increased faecal water content, and/or in increased frequency of defecation.

It is important to consider the animal’s previous defecation pattern, as the frequency of defecation and the nature of faeces vary between individuals.

A rational diagnostic and therapeutic approach to chronic diarrhoea in the dog and cat is dependent on a basic understanding of the function of the gut and the classification of the type of diarrhoea that is present.

Classification of Diarrhoea

Identify the System

Diarrhoea can be due to disorders of the small bowel and/or large bowel or to other systemic disorders such as hepatic disease, pancreatic insufficiency, pancreatitis, hyperthyroidism or hypoadrenocorticism.

In cases of diarrhoea, the problem-orientated system we discussed in module 1 is applied, but in a slightly different order. Identification of the location occurs first (see below) which then assists you in identifying the system.

The reason for this is that almost always, large bowel diarrhoea reflects primary GI disease whereas small bowel diarrhoea can occur with either primary or secondary GI disease (e.g. liver disease, hyperthyroidism, exocrine pancreatic insufficiency, hypoadrenocorticism, severe systemic toxicity). In secondary gastrointestinal disease, with the exception of pancreatic insufficiency, diarrhoea is not usually the primary presenting complaint.

Severe systemic toxicity and uraemia can also cause large bowel diarrhoea, but this will be a very minor clinical sign in relation to the other problems the animal presents with. Thus it does not really pose a realistic diagnostic option when considering the work-up of a patient whose primary problem is large bowel diarrhoea.
**Identify the anatomical location of the lesion**

While symptomatic therapy is appropriate for the majority of animals with acute diarrhoea, chronic diarrhoea will often present the veterinarian with a diagnostic challenge where the more routine laboratory aids are not useful.

*Avoid frustration!*

Failure to elicit sufficient information from the client about the characteristics of the diarrhoea, so as to allow appropriate localisation of the pathology within the gastrointestinal tract, will result in inappropriate diagnostic procedures with increased expense to the client, and frustration of the veterinarian, client and patient.

**Essential first step**

The diagnostic work-up and therapy for small- and large bowel diarrhoea differ. Therefore, it is of the utmost importance that, prior to embarking on diagnostic procedures or therapy, an assessment is made as to whether the diarrhoea is:

- acute or chronic
- due to primary gastrointestinal or secondary gastrointestinal disease
- small bowel or large bowel origin, or mixed.

Diarrhoea may have features of both small and large bowel, which indicates either primary small bowel with secondary effects on the lower bowel, or diffuse disease involving both.

A thorough history is essential to differentiate small- from large-bowel disease. It is important to carefully question the owner as to the character of the faeces, and to elicit information regarding consistency, colour, frequency and presence of blood or mucus. Related abnormalities should also be assessed, such as whether there has been significant weight loss, loss of appetite or vomiting.

**Small bowel diarrhoea**

Characteristics of small-bowel diarrhoea:

- **Consistency**
  - Faecal bulk and/or water content is increased.

- **Pattern**
  - Diarrhoea may be projectile and does not involve tenesmus.
**Blood**  
- If blood is present it is usually digested (melaena).

**Colour**  
- Colour may be grey if large amounts of undigested fat are present or if the diarrhoea is due to lactose intolerance. A yellow-green coloration is common and due to malabsorbed bile salts.

**Weight loss**  
- Chronic small-bowel diarrhoea is often (but not always) associated with weight loss.

**Vomiting**  
- Vomiting may also be present (but need not be) - when present it is usually related to eating.

**Borborygmus and flatulence**  
- Gas commonly occurs with small bowel diarrhoea as malabsorbed carbohydrates are fermented by colonic bacteria producing CO₂ and H₂.

**Appetite**  
- Appetite may be variable depending on the underlying aetiology.

**Water balance**  
- If the diarrhoea is severe, the animal may be dehydrated. If the diarrhoea is very watery, the patient may have an increased water intake.

**Physical examination**  
- Physical examination may reveal increased gas or thickened loops of bowel but is often unrewarding. Always do a rectal examination to check for melaena or large bowel signs such as mucus and fresh blood that the owner may not be aware of.
Identify the Lesion

Table 2: Causes of acute small bowel diarrhoea in dogs and cats

| Diet related                      | • overeating (especially pups)   |
|                                  | • dietary change                 |
|                                  | • spoiled food                   |
|                                  | • ingestion of garbage           |
| Parasites                        | • parasites                      |
|                                  |   • most commonly ascarids, also hookworms |
|                                  |   • protozoa                      |
|                                  |     • *Giardia*                   |
|                                  |     • coccidia e.g. *Cystoisospora* spp. (formerly called *Isospora*) |
|                                  |     • *Cryptosporidium*           |
| Infection                        | • viral enteritis                |
|                                  |   • parvo                        |
|                                  |   • corona                       |
|                                  |   • distemper                     |
|                                  | • bacterial enteritis            |
|                                  |   • salmonellosis                 |
|                                  |     • *E. coli*                   |
|                                  |     • *Campylobacter* spp.        |
|                                  |     • *Clostridium*               |
| Toxins                           | • toxins                         |
| - lead       |
| - organophosphates |
| - plants     |
**Table 3: Causes of chronic small bowel diarrhoea in dogs and cats**

| Diet related          | • lactose intolerance  
|                      | • dietary hypersensitivity  
|                      | • gluten intolerance  

| Parasites            | • intestinal parasites (as above)  
|                      | • *Giardia*  
|                      | • coccidia e.g. *Cryptosporidium parvum, Isospora* spp.  

| ‘Infection’           | • antibiotic-responsive enteropathy  
|                      | • *Campylobacter/Salmonella*  
|                      | • FIV/FeLV  

| Infiltrative          | • eosinophilic enteritis  
|                      | • lymphocytic-plasmacytic enteritis  
|                      | • diffuse lymphosarcoma  
|                      | • adenocarcinoma  
|                      | • mast cell tumour (feline)  

| Miscellaneous and secondary GI causes | • lymphangiectasia (primary or secondary)  
|                                      | • brush border enzyme biochemical defects  
|                                      | • motility disorders e.g.  
|                                      | - hyperthyroidism  
|                                      | - lead toxicity  
|                                      | - dysautonomia  
|                                      | • hypoadrenocorticism  
|                                      | • exocrine pancreatic insufficiency  

**Protein-losing Enteropathy**

Protein-losing enteropathy is a syndrome rather than a specific disease. It occurs when diffuse small intestinal disease results in excessive loss of serum proteins into the gut, causing hypoproteinaemia.

**Cause**

The four causes of protein-losing enteropathy are:

- IBD
• lymphangiectasia
• lymphoma
• idiopathic crypt necrosis.

**Clinical signs**

Animals may present primarily with signs related to hypoproteinaemia (ascites, subcutaneous oedema), and the diarrhoea may not be severe, or occasionally may not even be present.

**Clinical pathology**

Both albumin and globulin are lost. Animals will often have **lymphopenia** due to loss of lymph into the gut, hypocholesterolaemia and hypocalcaemia.

**Hypocalcaemia** is due to a number of causes including decreased protein-bound fraction associated with hypoalbuminaemia, vitamin D malabsorption, and malabsorption of calcium complexed with fatty acids and proteins in the intestinal lumen. Steatorrhoea and abnormal absorption tests may be found inconsistently.

**Diagnosis**

Protein-losing enteropathy usually requires intestinal biopsy to determine the cause. The most common cause is lymphangiectasia due to blockage of lymph vessels and lacteals with granulomatous inflammation, usually consisting of plasma cells and lymphocytes. However, whether this inflammation is the primary cause or secondary is often not known.

**Identify the anatomical location of the lesion**

**Large bowel diarrhoea**

Large bowel diarrhoea is characterised by:

- **Amount**
  - Small amounts of faecal material are passed frequently.

- **Mucous**
  - Mucus is often present either on the surface (indicating the lesion is in the lower colon or rectum) or throughout the faeces (indicating a lesion in the higher colon).
Fresh blood

- If blood is present it will be undigested.

Tenesmus

- Tenesmus is often present, particularly if the lower colon or the rectum are involved.

Weight loss

- Usually there is no weight loss.

Appetite

- Usually the appetite is unaffected.

Vomiting

- Vomiting is infrequent and is unrelated to eating.

Physical examination

- Physical examination is often unremarkable but it is imperative to do a rectal examination to check for strictures, masses or thickened mucosa.

### Identify the Lesion

#### Table 4: Causes of acute and chronic large bowel diarrhoea in dogs and cats

| Parasites               | Trichuris vulpis       
|-------------------------|------------------------
|                         | Ancylostoma caninum    
|                         | Giardia sp. (more commonly small bowel) 
|                         | Entamoeba spp.         

| Infection               | Campylobacter sp.      
|-------------------------|------------------------
|                         | Clostridium perfringens; Clostridium difficile. 
|                         | Salmonella sp.         
|                         | Yersinia enterocolitica 
|                         | FIP                    
|                         | Tritrichomonas foetus(cats) 

| Diet related            | fibre deficiency       
|-------------------------|------------------------
|                         | dietary hypersensitivity  
|                         | passing foreign material 

| Inflammatory           | idiopathic ulcerative (plasmacytic-lymphocytic) |
Diagnostic Approach to the Patient with Diarrhoea

SMALL BOWEL DIARRHOEA

Acute vs chronic
It is important to ascertain the length of time the diarrhoea has been present. Acute diarrhoea that is not severe, fulminating and potentially life-threatening does not usually require extensive diagnostic investigation and will usually respond to non-specific therapy. Fulminating acute diarrhoea (e.g. viral) may not require extensive diagnosis but will require intense supportive therapy, and must be recognised and not treated on an outpatient basis. In contrast, chronic diarrhoea persisting for weeks to months indicates that a more thorough investigation is required.

When to investigate?
If the diarrhoea persists despite symptomatic treatment or is chronic, severe and associated with significant weight loss and/or evidence of dehydration or systemic illness, then a more detailed investigation is indicated.

Only a small proportion of diarrhoea cases require investigation as chronic disorders.

Identify the Lesion

Parasitology
The first diagnostic step is to investigate for intestinal parasites and treat appropriately, particularly in young animals, and to ensure that lactose intolerance is not present.
Giardia
Examination of fresh faeces for Giardia is useful, although a positive result may be coincidental as Giardia sp. can be found in the faeces of dogs without diarrhoea. Zinc sulphate flotation is a sensitive test provided three faecal samples are examined. A negative result does not necessarily exclude Giardia infection and some clinicians will treat with metronidazole regardless and proceed with further investigations only if the diarrhoea persists.

There is an ELISA test available which can identify Giardia antigen in faeces. The test is reported to be very sensitive and specific in human patients and is probably more sensitive than performing a single zinc sulphate flotation examination.

Faecal Examination
Evidence for malassimilation?
Despite the comments of some gastroenterologists, I believe that, in practice, microscopic examination of faeces for starch, split (digested) and unsplit (undigested) fats and muscle fibres is a useful albeit imprecise screen for evidence of malassimilation. Pancreatic insufficiency should be investigated in dogs (if clinical signs are appropriate) by determining plasma trypsin-like immuno-reactivity levels (TLI).

Fat assimilation is dependent on full integration of intestinal, pancreatic and hepatic function and is more complicated than carbohydrate or protein assimilation. It is therefore often affected earlier in pancreatic and small intestinal disease.

Unsplit fats (triglycerides) can be detected using Sudan III or IV staining of faeces. Split fat (fatty acids) can be detected using Sudan staining after acid treatment and heating. Although this method of detecting fat malassimilation is subjective and imprecise, it is a useful screening test as it is inexpensive and readily available at most veterinary laboratories.

What does a positive result mean?
A positive result will not assist in determining the aetiology of the disease process but will support your assessment that significant small bowel disease is present.

What does a negative result mean?
However, a negative result does not rule out the possibility of infiltrative or inflammatory small bowel disease.

Quantification of 72-hour faecal fat excretion is a more accurate method of documenting fat malassimilation but is not usually performed in practice.

**Evidence for EPI**

If there is starch, undigested muscle and predominantly unsplit fat in the faeces, pancreatic insufficiency should be suspected and the plasma trypsin-like immunoreactivity (TLI) level measured. Note that gut bacteria can split fats so, in cases of EPI, there may be evidence of split as well as unsplit fats. The presence of starch granules is the ‘hardest’ evidence that maldigestion rather than malabsorption is occurring.

**When are faecal trypsin levels useful?**

Determination of faecal trypsin levels are no longer needed in dogs to confirm EPI since the TLI test has become widely available. Although the test has been validated in cats its availability is variable and may require submission of samples to the US. Check with your lab.

**Evidence for small bowel disease**

If the faeces contain predominantly split fats, with no starch or undigested muscle, and the plasma TLI level is normal, then malabsorption is present. The presence of malabsorption is usually indicative of an infiltrative intestinal lesion or small intestinal bacterial overgrowth (see Table 2).

**Microbiology**

Microbial culture of faeces is often requested by practitioners but is often unrewarding due to the abundant normal flora in the gut and the predominance of anaerobes. *E. coli* and *Salmonella* are frequently isolated from faeces of normal animals, therefore their presence does not necessarily imply that they are the cause of the diarrhoea. Diarrhoea of any cause will alter the normal gut flora due to decreased transit time resulting in a decreased proportion of anaerobic bacteria.

**When is faecal culture of value?**

Faecal culture is of value if *Campylobacter, Salmonella*, or *Clostridium spp* are suspected causes of diarrhoea.

*But………*
A study of 132 dogs demonstrated that *Clostridium perfringens* and *Clostridium difficile* had equal prevalence in dogs with and without diarrhoea. However, there was a correlation between the presence of diarrhoea and the detection of toxins that are produced by these bacteria. In other words, a negative culture for Clostridia is likely to rule out this as a cause of diarrhoea. However a positive culture does not necessarily mean that the diarrhoea is due to Clostridia. Further tests would be required to determine whether the Clostridia present were producing toxins. Check with your lab whether they are able to offer these tests.

In the same study, *Salmonella* was isolated in only one dog – which didn’t have diarrhoea – suggesting that this is an uncommon cause of diarrhoea in dogs.

*How significant is Campylobacter?*

Whether *Campylobacter* spp. are a primary cause of diarrhoea in dogs remains controversial, and the bacteria can be isolated from the faeces of normal dogs or dogs with diarrhoea due to other causes. In the study discussed above, Campylobacter was isolated from > 65% of dogs regardless of whether they had diarrhoea or not.

Whilst any species of Campylobacter is considered pathogenic in man, only *C. jejuni* is really considered important in dogs, although it only causes mild disease in gnotobiotic dogs. It may even be an opportunist and not a true primary pathogen? It certainly makes experimental parvo infections worse.

Similarly other species (*C. coli, upsaliensis* etc.) may or may not be pathogenic and, as most commercial labs don’t bother to speciate the cultures, you don’t know which species you are dealing with.

However, it might be suspected as a primary pathogen in young dogs with acute or sub-acute diarrhoea that have the characteristics of both small and large bowel dysfunction. *Campylobacter* spp. require special culture media, therefore species differentiation must be specifically requested when submitting samples to a laboratory.

*SIBO and Idiopathic ARD*

*SIBO*

The normal small intestinal (SI) bacterial flora is a diverse mixture of aerobic, anaerobic and facultative anaerobic bacteria that are an integral part of the healthy SI. A stable enteric flora prevents colonization by pathogens and stimulates development of the enteric immune system.
Small intestinal bacterial overgrowth (SIBO) is the uncontrolled proliferation of resident bacteria and is defined by an increase in the absolute number of bacteria in the upper SI in the fasted state. There remains much controversy about what represents a normal resident bacterial flora in dogs and the exact numbers have not yet been adequately defined.

SIBO occurs secondary to some underlying problem such as exocrine pancreatic insufficiency, inflammatory bowel disease, partial obstruction or motility disorders.

It will often manifest as intermittent diarrhoea as bacteria build up and clinical signs develop, resulting in a flush out of bacteria and thus resolution of the clinical signs.

**Idiopathic ARD**

Idiopathic antibiotic-responsive diarrhoea (ARD) is the term now used for some patients (often German Shepherds) previously described as having SIBO. The clinical presentation is small intestinal diarrhoea that is responsive to antibacterials but no underlying cause can be identified (in contrast to SIBO).

Idiopathic ARD differs from SIBO in that patients do **not** have excessive numbers of bacteria in their small intestine. Rather, the host has an abnormal response to normal gut flora, either due to an abnormal mucosal barrier (IgA deficiency, permeability, brush border defects), immune dysregulation (e.g. loss of tolerance to the normal bacterial flora precipitating intestinal inflammation and abnormal intestinal function) or has an abnormal bacterial flora (but not increased numbers) or a combination of all these factors. German Shepherds are predisposed. Aside from occasional unpublished reports, idiopathic ARD has not been described in cats.

The bacteria causing idiopathic ARD and SIBO are usually present in mixed culture and are believed to originate in the oral cavity or food. *E. coli*, enterococci and anaerobes such as *Clostridium* spp. seem to be especially common in symptomatic dogs. Enterocytes are damaged by deconjugation of bile acids, fatty acid hydroxylation and generation of alcohols. Anaerobic bacteria may cause greater damage because of the enzymes they produce.

**Diagnosis**

Diagnosis of SIBO is difficult and, in practice, the most common method is observation of response to therapy.
Culture of multiple duodenal aspirates obtained via a laparotomy or endoscopy is the gold standard. Breath hydrogen analysis is usually not available in general practice and is unreliable. Measurement of serum cobalamin (decreased) and folate (increased) concentrations is reported by some to be specific but not sensitive for the disorder. However, other studies have not found this. Bacteria may be identified on examination of duodenal mucosal smears but the test is not sensitive. Bacteria are rarely identified on histopathology of affected tissues. Measurement of canine unconjugated bile acids is a new test that may have value in the diagnosis of SIBO. Certain bacteria deconjugate bile acids excreted into the intestine via the biliary tract. Note this is not the same test as the bile acids used to assess liver function – these are conjugated bile acids.

*When to suspect SIBO or ARD*

Occasionally patients will have diarrhoea that rapidly resolves with antibacterial therapy only to return fairly soon after therapy ceases. These cases probably have SIBO or idiopathic ARD but the key question is why? There may be an underlying predisposing cause (thus causing SIBO) and the clinical challenge is to find it. If there is no underlying cause identifiable then the diagnosis is idiopathic ARD.

*Treatment*

Four to six weeks of therapy with oxytetracycline is usually the recommended treatment. Other drugs that have been used include tylosin and metronidazole. However, the most appropriate drug has not been determined by controlled clinical trials.

Occasionally these patients respond to increased fibre diets (commercial or adding unprocessed bran) – presumably because fibre improves intestinal mucosal health, can alter the balance of gut bacteria beneficially or … who knows! The role of probiotics in cases of idiopathic ARD has yet to be determined but anecdotal reports suggest such therapy is unrewarding. This may be related to the fact that appropriate (e.g. host species-specific) agents have yet to be used.

*Prognosis*

The prognosis of SIBO depends on the nature of the underlying cause. The prognosis for idiopathic ARD is guarded. Although some patients never relapse after treatment, many relapse when therapy is discontinued. If this occurs, restart treatment then wean down to find the lowest dose that will control the signs – occasionally this may require very long-term treatment, even life-long. Although there are concerns that chronic low dose antibacterial therapy might induce resistance, this doesn’t seem to be the case.
Diarrhoea

One study suggested that rm long-term oxytetracycline therapy does not ‘sterilise’ the small intestine. Instead it may be providing a selection pressure on the bacterial microflora (a qualitative rather than quantitative effect) or may be having other (immunomodulatory?) effects. Some cases may improve spontaneously as the animal enters adulthood.

**Haematology and Biochemistry**

**What can a full blood count tell you?**
Haematology may provide evidence of blood loss anaemia, inflammatory changes (leucocytosis), leucopenia (particularly in viral diarrhoea), lymphopenia (stress or lymphangiectasia), eosinophilia (suggesting parasites, eosinophilic enteritis, hypoadrenocorticism). But remember that mild eosinophilia may also occur with any enteritis as a result of increased transfer of antigens through the damaged mucosa.

**Is biochemistry useful?**
Serum biochemistry is usually not helpful in diagnosing primary gastrointestinal disease except in the determination of electrolyte abnormalities that may occur as a consequence of diarrhoea (hypokalaemia), or in the determination of protein levels (protein-losing enteropathy), or as a possible indicator of neoplasia (hypercalcaemia in lymphoma).

**Serum Folate and Cobalamin (vitamin B₁₂) Concentrations**
The value of vitamin B₁₂ (cobalamin) and folate levels in the diagnostic work-up for the dog with chronic diarrhoea is controversial. There are many factors that will increase and decrease both vitamins, making the tests insensitive and non-specific even for bacterial overgrowth.

Some gastroenterologists currently recommend doing vitamin B₁₂ levels only when there is chronic small bowel diarrhoea or exocrine pancreatic insufficiency, to determine if parenteral supplementation is necessary. Low vitamin B₁₂ adds to ongoing poor intestinal health as it is important for crypt cell turnover and epithelial renewal. Supplementation with cobalamin improves GI health – injectable, not oral administration is required.

Only preliminary work has been done in this area in cats. A recent paper indicated that almost 50 per cent of cats with chronic GI disease, especially lymphoma, had cobalamin deficiency. This prevalence has not been seen at other centres to date and the observation has yet to be validated.

**Dietary Trial**
Dietary hypersensitivity or intolerance (no immunological basis) can be the cause of chronic diarrhoea in dogs and cats. Diagnosis is usually a process of trial and error by using elimination diets, as there is no sensitive or specific diagnostic test. True dietary hypersensitivity may or may not be associated with peripheral eosinophilia (i.e. hypersensitivity should not be ruled out if the eosinophil count is normal). Current evidence would suggest that blood tests for anti-food antibodies are not specific.

The aim of an elimination diet is to feed the animal a single protein source to which it has not previously been exposed (sometimes this can be very difficult to find – fish is often good for dogs but not cats) and ideally a single carbohydrate source that is gluten-free (i.e. rice). Both commercial prescription and homemade diets can be utilised for this purpose. The diet should be fed for several weeks – if the diarrhoea does not resolve, then a dietary cause is unlikely. Although a 12-week dietary trial has been recommended in some texts, most animals that have hypersensitivity will respond in two to three weeks – and most owners will not tolerate diarrhoea and dietary trials for 12 weeks! If the diarrhoea does resolve, then single items are added to the diet to attempt to identify the offending food/s.

The newer commercial diets that contain fragments of protein (i.e. supposedly too small to be immunogenic) can be useful especially in patients who have had a wide and varied diet so that finding a novel protein is almost impossible. However, these diets may not be entirely hypoallergenic as the hydrolysates will occasionally still trigger an allergic reaction in very susceptible patients. Apparently, if proteins are completely hydrolysed so that their capacity to induce an allergic reaction is entirely eliminated, the taste is so bitter the diet is unpalatable.

*When is an elimination diet useful?*
I will recommend an elimination diet prior to biopsy if the animal is essentially well, has not lost a large amount of weight and is not hypoproteinaemic. If the diet is unsuccessful then biopsy is the next step.

*Is radiology useful?*
I believe the ‘pathology pound’ is more wisely spent obtaining biopsies than performing a barium meal on the patient with chronic diarrhoea, as a specific tissue diagnosis cannot be obtained from radiology and performing a good quality barium meal is time consuming and relatively expensive. Ideally, however, plain radiographs or ultrasound should be performed prior to endoscopy to rule out partial obstruction or foreign material.

*Ultrasonography*
Ultrasonography has been shown to be of diagnostic value in cases of chronic diarrhoea provided (as always) the ultrasonographer is appropriately trained, skilled and experienced.

Ultrasonography is particularly useful in an older animal as, sometimes, localised ileal thickening due to neoplasia is seen – in these cases, exploratory laparotomy would be the next diagnostic step rather than endoscopy. Ultrasonography will also help identify whether it is the mucosa that is thickened (in which case endoscopic biopsies will be useful) or the muscularis that is thickened (in which case full thickness biopsies via laparotomy are required.

**Biopsy**

*When should you biopsy?*

Intestinal biopsy is indicated if small intestinal disease is confirmed by appropriate means and factors such as parasites, lactose intolerance, bacterial or dietary causes are ruled out.

**Remember** that only a biopsy will allow you to differentiate the different inflammatory and infiltrative small intestinal disorders. If you have eliminated other diagnostic possibilities (see Table 3) either by specific tests or by therapeutic trial, biopsy is required to obtain a diagnosis.

Intestinal biopsy is primarily required to characterise infiltrative inflammatory gut disease (Table 3) and/or protein-losing enteropathy. It is important, however, to be aware of the limitations of histopathology – there can be quite significant disagreement between experienced pathologists asked to assess the same tissue sample. Thus results should always be interpreted in light of clinical presentation. For example, a patient can have severe clinical signs due to inflammatory bowel disease yet the histopathological changes can be mild and even occasionally read out as normal. All results that don't fit the clinical presentation should be questioned.

**Brush cytology**

Brush cytology provides superior cytological information to histopathology and may aid in the diagnosis of GI disease. However, it cannot replace histopathology because it does not provide architectural information. Its greatest benefit may be for the differentiation of severe lymphocytic-plasmacytic enteritis from alimentary lymphoma, where the cellular and nuclear characteristics of malignancy can be better assessed.

**Laparotomy vs endoscopy**
Fibreoptic endoscopy may be used to obtain gastric and duodenal biopsies and to obtain duodenal aspirates for culture. This method of obtaining biopsies has a number of advantages over exploratory laparotomy, particularly in cases of protein-losing enteropathy when the presence of hypoproteinaemia can impair wound healing. It also permits biopsies at multiple sites to be taken, which can assist the pathologist in making a diagnosis.

However, endoscopy is not available in a lot of practices and it is not useful for biopsying lesions in the jejunum or ileum. You also cannot obtain full thickness biopsies, which may be necessary for the diagnosis of some infiltrative conditions. Laparotomy has the advantage of allowing visualisation of the entire GI tract and is a procedure that can be performed in any veterinary practice.

It is essential to always obtain biopsies from several sites if a laparotomy is performed, even if the intestine looks normal.

**LARGE BOWEL DIARRHOEA**

**Identify the Lesion**

There are a limited number of diagnostic options in determining the aetiology of large bowel diarrhoea. Physical examination is often unremarkable although rectal examination may reveal evidence of strictures or masses.

*Treat for parasites*

Anthelmintic treatment for *Trichuris* infection in dogs is usually recommended regardless of faecal flotation results, as the parasite produces eggs intermittently and in low numbers. Examination of fresh faeces for *Giardia* sp. is also indicated and I usually treat with metronidazole prior to initiating further diagnostic procedures.

*Faecal culture*

Faecal culture is occasionally of value in diagnosing campylobacteriosis or clostridial diarrhoea (however see comments previously).

*Faecal examination?*

Faecal examination for evidence of fat or carbohydrate malassimilation is of **no value** in the diagnosis of large bowel diarrhoea, as assimilation of digestible nutrients is not impaired.

*Dietary trial*
In my experience, in general practice dietary manipulation will often resolve chronic large bowel diarrhoea - particularly by adding bran or soluble fibre (e.g. metamucil) to the diet.

**Radiology useful?**
As for the investigation of small bowel diarrhoea, contrast radiology (barium enema) can be useful in identifying the location of lesions in the large bowel lesions, but I prefer to go straight to proctoscopy and biopsy rather than mess around with contrast radiology.

**Biopsy**
If the procedures described above do not lead to a diagnosis or resolution of clinical signs, colonic biopsy is required. Ideally, biopsies should be obtained via a proctoscope. If proctoscopy is not available, biopsies can be obtained via a laparotomy.

**Practical Diagnostic/Therapeutic Approach to Diarrhoea**

The following is an outline of the approach I usually take to cases of diarrhoea in adult dogs or cats I see in general practice. It is my own personal approach and I am sure there are all sorts of variations possible (and I’m sure some would disagree especially ‘proper’ gastroenterologists!) but it usually works for me.

1. Always advise fasting for 24 hours and then feeding small, more frequent meals of a bland, low residue diet.

2. Ensure worming history is up to date and if in doubt treat with Drontal. If large bowel diarrhoea is present, do a faecal flotation if possible. If *Trichuris* is present, the patient will need to be wormed at two-monthly intervals indefinitely due to the robust nature of the eggs in the environment.

3. If the diarrhoea is very watery and smelly (small bowel) or very haemorrhagic (large bowel) I will usually prescribe metronidazole (10-20 mg/kg bid).

4. At this point the vast majority of cases have resolved. However ……..

5. If small bowel diarrhoea persists after points 1-3, I will consider treating for antibiotic-responsive diarrhoea with oxytetracycline, tylosin, amoxycillin or occasionally enrofloxacin (used in people for ARD).

6. If large bowel diarrhoea persists I will request a faecal culture for *Campylobacter*, *Salmonella* and *E. coli* and if available request tests for Clostridial toxins.

7. And/or (depends on the severity of the diarrhoea, client factors such as finances etc.) recommend commencement of a hyposensitivity diet (commercial or home made).
Discussion with the owner will include the fact that dietary hypersensitivity is uncommon but worth checking for as (a) the next step will be gut biopsy and (b) it is the first management decision when some of the inflammatory bowel disorders are diagnosed by biopsy (lymphocytic-plasmacytic or eosinophilic enteritis/colitis). Diet will be recommended for four to six weeks but if there is absolutely no response after two weeks then the prognosis for a good response is reduced.

8. And/or (if the owner will not/cannot comply with the dietary trial and/or the patient has large bowel diarrhoea but with not a lot of fresh blood – just mucus and tenesmus) advise adding fibre to the diet (unprocessed bran or soluble). I personally don’t combine a hypoallergenic diet with fibre addition because if the patient responds I don’t know which component it has responded to – the diet or the fibre – which has significant implications for future dietary recommendations (not to mention the wallet of the client!).

9. If all the above fails or if the patient is hypoproteinaemic or if the patient has really bloody large bowel diarrhoea and severe tenesmus, or if there is any other clue that neoplasia may be the cause, I will recommend ultrasound by a specialist and/or biopsy – either by endoscopy, if equipment and expertise are available, or by exploratory laparotomy.
Polyuria and polydipsia

Before we begin......................
Reflect on these statements and indicate whether you believe they are true or false. We will revisit these statements at the end of the notes.

1. Medullary hypertonicity is primarily determined by the sodium concentration in the renal medulla.
   True ❍ False ❍

2. If an animal has a urine specific gravity of 1.002, primary structural renal disease is a possible diagnosis.
   True ❍ False ❍

3. A urine SG of 1.020 in a dehydrated patient indicates adequate urine concentration.
   True ❍ False ❍

4. A water-deprivation test is useful to differentiate diabetes insipidus and other causes of hyposthenuria such as hyperadrenocorticism.
   True ❍ False ❍

5. Prerenal azotaemia is never associated with hyperphosphataemia. If hyperphosphataemia is present in an adult animal, it must have structural renal disease.
   True ❍ False ❍

6. A dog that is polydipsic, clinically dehydrated, has a urea concentration of 30 mmol/L (normal range 5-10), creatinine of 250 µmol/L (normal range 55-100) and a urine SG of 1.010 must have primary structural renal failure.
   True ❍ False ❍

7. A dog that is polydipsic but NOT clinically dehydrated, has a urea concentration of 30 mmol/L (normal range 5-10), creatinine of 250 µmol/L (normal range 55-100) and a urine SG of 1.010 must have primary structural renal failure.
   True ❍ False ❍

Polyuria/polydipsia is a relatively frequent presenting complaint in small animal medicine. A variety of disorders may cause polydipsia or polyuria and an ordered, rational diagnostic approach to the problem is important.

Identify the Problem

The initial step is to ensure that true polyuria/polydipsia is present.
Physiological response?

Animals with profuse watery diarrhoea will often drink more than usual to maintain their hydration status – an appropriate physiological response. In addition, animals with gastritis will often drink large amounts of water but will vomit immediately hence are not truly polydipsic. Exercise and high ambient temperatures may also induce an animal to drink more than usual – another appropriate physiological response.

However, those animals that drink excessively and subsequently urinate excessively (or vice versa) require investigation to determine the cause of their disordered water intake.

Beware of the incontinent animal!

It is important to be aware that a polyuric animal may present for urinary incontinence and the owner may not be aware or may not volunteer that the animal is drinking more than usual. On the other hand, owners will often confuse pollakiuria with polyuria.

Urinary tract infections

Animals with lower urinary tract infections can present with polydipsia. Some of these patients probably do have pyelonephritis in addition to their lower urinary tract infection but in other patients it does not appear to be due to a urinary concentrating defect – i.e. it may be a primary polydipsia. Do these animals know in some way that if they drink more they will dilute their urine and perhaps ameliorate the discomfort of the UTI? Whatever the reason, it is advisable always to ensure that a UTI is not present before embarking on a more complex workup for PU/PD.

How can I confirm polydipsia?

Polydipsia is usually defined as a water intake that is twice maintenance requirements i.e. approximately 100 mls / kg day. (However, note that, in cats, ingestion of greater than 50 mls / kg day is probably excessive and indicative of PU/PD). It may be necessary to measure the animal’s water intake to ensure that it is polydipsic. However, particularly in the stressful hospital environment, a polydipsic animal may reduce its water intake for a period of time and it is therefore desirable, if possible, to get the owner to measure intake at home.

If the owner has noticed that the dog or cat is drinking substantially more (especially cats), they can estimate roughly what the patient is drinking (e.g. “I normally only have to fill the ice cream container once per day but now I have to fill it three times per day”) and the urine is not well concentrated, you can usually be fairly comfortable that the patient is polydipsic, without having to accurately measure water intake.
Renal Physiology

In order to fully understand pathophysiologic mechanisms that cause polyuria/polydipsia, we should review some basic renal physiology.

Overview of kidney function

The kidney has several functions:

1. To remove waste materials that are either ingested or produced by metabolism
   a. Urea (produced from amino acid metabolism)
   b. Creatinine (produced from muscle creatine)
   c. Uric acid (from nucleic acids)
   d. End products of haemoglobin breakdown (e.g. bilirubin)
   e. Metabolites of various hormones
   f. Toxins produced by the body or ingested and ingested foreign materials

2. To control the volume and composition of body fluids (water and electrolyte balance, body fluid osmolality, electrolyte concentrations)

3. Regulate arterial blood pressure

4. Regulate acid-base balance

5. Secretion, metabolism and excretion of hormones


It is the first two functions that we are primarily interested in reviewing in this module as they related to the pathophysiology of PU/PD.

The nephron

The nephron is the functional unit of the kidney. The kidney cannot regenerate new nephrons therefore with renal disease, injury or normal ageing there is a gradual decline in nephron number. Each nephron unit in the kidney consists of a glomerulus, proximal tubule, loop of Henle, distal tubule and collecting duct (Figure 1). The function of each is outlined below.
Substances that are freely filtered by the glomerular capillaries may be handled in one of 4 ways by the nephron:

a. Neither reabsorbed or secreted (e.g. creatinine)
b. Partly reabsorbed back into blood thus urinary excretion is less than the rate of filtration (e.g. electrolytes)
c. Not excreted into urine because all of the filtered substance is reabsorbed back into blood (e.g. in normal animals - amino acids, glucose)
d. Not reabsorbed and additional quantities secreted from peritubular capillaries into the renal tubules (e.g. organic acids and bases – permitting them to be rapidly cleared from the blood and excreted)

In general, tubular reabsorption is quantitatively more important than tubular secretion in the formation of urine but secretion plays an important role in the amounts of potassium, hydrogen and a few other substances that are excreted into urine. Most substances that must be cleared from the blood, especially the end products of metabolism such as urea and creatinine, uric acids and urates, are poorly reabsorbed and are therefore excreted in large amounts in the urine. Conversely electrolytes such as sodium, bicarbonate and chloride ions are highly reabsorbed so that only small amounts appear in the urine.
The glomerulus acts to form an ultra-filtrate of plasma. The filtration barrier excludes molecules from the filtrate on the basis of size but also charge – cationic particles are more easily filtered than anionic particles.

GFR is determined by: The rate at which plasma is filtered by the glomerulus (the glomerular filtration rate - GFR) is determined by the ratio of afferent (into the glomerular capillary bed) and efferent (out of the capillary bed) arteriolar tone, the pressure in glomerular capillaries and the glomerular surface area.

**Proximal Tubule**

The proximal tubule is permeable to water and isotonically absorbs 70% of filtered Na+ and H₂O as well as K+, glucose, amino acids, Ca²⁺, Mg²⁺, HPO₄²⁻, urea and uric acid. Ca²⁺ reabsorption is linked to Na⁺ absorption hence if Na⁺ excretion increases so does Ca²⁺ excretion – this is the basis for treating hypercalcaemia with isotonic saline fluids.

The proximal tubule secretes H⁺, ammonia and organic acids and bases.

**Loop of Henle**

*Thin loop*

The thin descending and ascending section of the loop of Henle primarily reside in the renal medulla. Water passively moves out of the descending thin loop of Henle (which is permeable to water) because the medullary interstitium is hypertonic. Medullary hypertonicity is predominantly due to high urea and sodium concentrations in the medullary interstitium. The ascending thin loop however is impermeable to water.

*Effect of osmotic solutes*

Any solute in the lumen of the descending thin loop of Henle to which the loop is impermeable (e.g. glucose, mannitol) will oppose water extraction and increase the delivery of salt and water to more distal sites within the nephron.

*Thick ascending limb*

The thick ascending limb is impermeable to water – sodium chloride is actively pumped out of the lumen. This is the site of action of the diuretic frusemide, which inhibits the sodium chloride pump hence causing a greater solute concentration in the filtrate, which results in increased water excretion. This segment is impermeable to water and therefore can be regarded as a diluting segment.

*What is the concentration of the filtrate when it leaves the loop of Henle?*
An important concept to understand is that in the normal nephron the filtrate that leaves the loop of Henle is hypotonic because of the active removal of NaCl. Thus if there is no ADH or the action of ADH is impaired, the final urine concentration will be less than the glomerular filtrate i.e. hyposthenuric.

The counter current mechanism and the vasa recta

The term “counter-current mechanism” refers to the exchange of water and solutes between the loop of Henle and the medullary interstitium, which is responsible for urine concentration. Medullary portions of the thick ascending limb contribute to medullary hypertonicity and thereby are important in urine concentration. The major factors that contribute to the buildup of solute concentration in the renal medulla are:

- Active transport of Na⁺ and co-transport of K⁺, Cl⁻ and other ions out of the thick portion of the ascending limb of the loop of Henle into the medullary interstitium
- Active transports of ions from the collecting duct into the medullary interstitium
- Facilitated diffusion of large amounts of urea from the inner medullary collecting ducts into the medullary interstitium
- Diffusion of only small amounts of water from the medullary tubules into the medullary interstitium, far less than the reabsorption of solutes into the medullary interstitium

There are two special features of renal medullary blood flow that contribute to the preservation of the high solute concentration

- The medullary blood flow is low – accounting for less than 5% of total renal blood flow. This rate of flow is sufficient to supply the metabolic needs of the tissues but helps minimize solute loss from the medullary interstitium
- The vasa recta is the system of medullary blood vessels that are in a hairpin configuration. The vasa recta serve as countercurrent exchangers minimizing washout from the medullary interstitium. Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla. As blood descends into the medulla toward the papillae it becomes progressively more concentrated, partly by solute entering from the interstitium and partly by loss of water into the interstitium. By the time it reaches the tips of the vasa recta it has the same concentration as the medullary interstitium. As blood ascends back toward the cortex it becomes progressively less concentrated as solutes diffuse back out into the medullary interstitium and as water moves into the vasa recta. As a result, there is little net dilution of the concentration of the interstitial fluid as each level of the renal medulla because of the U shape of the vasa recta capillaries which act as countercurrent exchangers. Thus the vasa recta do not create the medullary
hypertonicity but they do prevent it from being dissipated – under steady state conditions, the vasa recta carry away only as much solute and water as is absorbed from the medullary tubules.

The rate of blood flow in the vasa recta is slow, which contributes to maintaining medullary hypertonicity – if flow is increased (for example by increased renal perfusion associated with intravenous fluid volume overload), medullary wash-out can occur and hence urine concentration is impaired because less water will passively leave the thin loop of Henle.

NaCl reabsorbed from cortical portions of the thick ascending limb does not provide a driving force for water abstraction from medullary structures and therefore does not participate in the concentration of urine.

The reabsorption of Mg\(^{2+}\), Ca\(^{2+}\) and K\(^{+}\) is also important in the thick ascending loop of Henle and inhibition of the NaCl pump causes increased urinary loss of these cations in addition to NaCl.

**Distal Convoluted Tubule**
Although only 5-10% of the filtered load of sodium is reabsorbed in the distal tubule it is very important in overall sodium and water balance. *Sodium reabsorption from the distal tubule is regulated by aldosterone* and is dependent on blood volume perceived by renal receptors.

**Increased aldosterone**
Activation of the renin-angiotensin system regulates aldosterone secretion – if hypovolaemia is detected (reduced blood flow to the kidneys → activation of renin-angiotensin system) aldosterone secretion is stimulated which enhances sodium retention. This increased sodium retention increases medullary hypertonicity and hence increases water absorption from the thin loop of Henle and also the collecting duct (under the influence of antidiuretic hormone – ADH).

**Lack of aldosterone**
Lack of aldosterone (i.e. in hypoadrenocorticism) causes (a) sodium wasting from the proximal convoluted tubule and hence concurrent water loss (as water follows sodium) and (b) sodium loss and potassium retention in the distal convoluted tubule. Reduced sodium delivery to all parts of the nephron also contributes to reduced medullary hypertonicity and hence impaired urine concentration.
**Potassium secretion**
The distal tubule also secretes K⁺ and H⁺ ions and is the primary determinant of final urinary K⁺ excretion.

Tubular flow rate is an important factor in the control of K⁺ secretion. Increased flow rate causes increased K⁺ secretion and hence urinary loss of K⁺. Thus many diuretics may cause excessive K⁺ loss.

Post-obstructive diuresis also results in marked loss of K⁺, which may cause hypokalaemia if the intravenous fluids are not appropriately supplemented with potassium. Polyuria induced by over-enthusiastic fluid administration can also cause hypokalaemia by this mechanism.

**Diluting segment**
Water permeability in the distal tubule is relatively low and is not affected by ADH. Thus the distal convoluted tubule is regarded as a cortical diluting segment.

**Collecting Ducts**

**Sodium and potassium**
Only 5-7% of the filtered load of sodium is reabsorbed in the collecting ducts but this can be the major determinant in daily fluctuation of sodium balance. Sodium reabsorption is under the influence of aldosterone in this segment. K⁺ is absorbed or secreted depending on the overall K⁺ balance.

**Permeability to water**
A particularly important facet of collecting duct function is its permeability to water (and also urea) in the presence and absence of ADH. ADH (vasopressin) binds to receptors (V₂), which leads to activation of adenyl cyclase, which ultimately leads to formation of water channels called aquaporins. ADH function can be impaired by conditions such as hypercalcaemia (causes resistance to ADH – exact mechanism unknown – see later for details) and hypokalaemia (which down regulates aquaporin formation) and hypercortisolaemia (which interferes with the action of ADH at a renal tubular level).

In the cortical collecting duct, the presence of ADH increases the permeability of the duct to water but not to urea; hence the urea concentration of the tubular filtrate increases.

In the medullary collecting duct, in the presence of ADH, the duct is permeable both to water and urea hence as water is reabsorbed urea also passively diffuses into the
interstitium and then moves into the thin loop of Henle, doubling the amount of urea in the tubular fluid. Thus, in the presence of ADH, both urine and medullary urea concentrations are maintained.

The urea concentration in the interstitium is responsible for approximately 50% of the osmolarity of the interstitium. In the absence of ADH, no urea moves out of the collecting duct. There is therefore decreased accumulation of urea in the interstitium and therefore decreased ability to concentrate urine.

**Final Urine Concentration**

Glomerular filtrate has a fixed urine SG of 1.008 – 1.012 (probably 1.006 – 1.012 in cats). If there is no active concentration or dilution of the glomerular filtrate in its passage through the nephron, the final urine concentration will be in this range. If urine has a SG less than 1.006, active dilution of glomerular filtrate in the distal nephron has occurred (i.e. the animal is excreting more free water than solutes); if it has a SG greater than 1.012, active concentration to a variable degree has occurred.

**Classifying the Mechanisms of Polyuria/Polydipsia**

The mechanisms that result in polyuria and polydipsia can be classified according to the primary defect.

Thus polyuria/polydipsia can be due to:

1. **Primary polydipsia**
   a. Psychogenic
   b. Hyperadrenocorticism (partly)
   c. Hepatic encephalopathy (partly)
   d. Hypothalamic lesion affect thirst receptors (extremely rare)

2. **Absence or interference with ADH function**
   a. Diabetes insipidus
   b. Hyperadrenocorticism
   c. Hypercalcaemia
   d. Hypokalaemia
   e. Pyometra

3. **Increased metabolism and renal blood flow rate**
a. Hyperthyroidism

4. **Osmotic diuresis**
a. Glucosuria

5. **Reduced medullary hypertonicity**
a. Hyponatraemia
   i. Hypoadrenocorticism
   ii. Profound gut sodium loss
b. Liver disease? (possibly due to decreased urea?)

6. **Structural renal tubule damage**

**Diagnostic Approach to the Polyuric/Polydipsic Patient**

**Determine urine SG**

Having confirmed that an animal is truly polydipsic or polyuric, the initial and most important diagnostic step is to determine the urine specific gravity (SG) - without this information, appropriate interpretation of other pathology results can be difficult.

- Urine with an **SG of < 1.008**, (1.006 in cats) has been actively diluted
- Urine with an **SG of 1.008 - 1.012** has neither been diluted or concentrated
- Urine with an **SG of >1.012** has been concentrated to some degree - however whether the degree of concentration is appropriate must now be determined for the patient

**Normal animals may have a urine SG of any value depending on the physiological circumstances**

**Always interpret urine SG in relation to the hydration status of the patient**

Although urine with a SG greater than 1.012 has been concentrated, the degree of concentration may not be appropriate.

If an animal is **dehydrated** or **hypovolaemic**, the appropriate renal response is to produce urine that is concentrated to at least a SG of 1.030 (dogs) or 1.035 (cats).
If a **dehydrated** animal has a urine SG less than 1.030, it has by definition *inadequate urine concentration* and it must have some degree of renal dysfunction (primary structural renal dysfunction or extra-renal dysfunction).

If an **azotaemic** animal has a urine SG less than 1.030, then the patient **must** have impaired urine concentrating ability because if the azotaemia was due to prerenal factors only and the patient had normal renal concentrating ability the urine SG would be >1.030 or 1.035.

**Identify the System - Primary Renal (structural) or Extra-Renal (functional)?**

*Structural vs Functional*

Persistent polyuria (primary or secondary to polydipsia) or failure to concentrate urine appropriately in the presence of dehydration or azotaemia may be the result of a **structural renal abnormality** (i.e. primary renal disease) or a **functional renal abnormality** (extra-renal disease).

A functional (extra-renal) abnormality occurs when the kidney is structurally normal but urine concentration is impaired as a result of alterations in, for example, medullary hypertonicity (e.g. hyponatraemia) or ADH function (ADH deficiency, impaired ADH function secondary to hypercalcaemia).

If the urine is very dilute (hyposthenuria) there are a limited number of diagnostic possibilities (see Table 5) and differentiation of the possible causes is relatively simple.

If the urine SG is between 1.008 and 1.030 the first consideration is whether the urine is inappropriately dilute. If a patient is dehydrated and renal function is normal, the urine SG should be greater then 1.030 (dog) or 1.035 (cat). If it is not, then renal dysfunction **must** be present - this can either be due to a structural or functional renal abnormality. If the urine is concentrated the patient is either **not** polyuric or if it is definitely polyuric then there must be an osmotic solute in the urine that is creating polyuria - the most common of these would be glucose.

Table 5 outlines the differential diagnoses for polyuria/polydipsia.
### Table 5: Differential diagnosis of Polyuria/Polydipsia

<table>
<thead>
<tr>
<th>Urine concentration</th>
<th>Differential diagnosis</th>
<th>Useful tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOSTHENURIA</td>
<td>Psychological polydipsia</td>
<td>Water deprivation</td>
</tr>
<tr>
<td>Urine SG &lt;1.008</td>
<td>Diabetes insipidus*</td>
<td>Water deprivation/ADH response test</td>
</tr>
<tr>
<td></td>
<td>Hypercalcaemia</td>
<td>Serum Ca^{2+}</td>
</tr>
<tr>
<td></td>
<td>Hyperadrenocorticism</td>
<td>WBC, ALP, cholesterol Low-dose dexamethasone suppression</td>
</tr>
<tr>
<td></td>
<td>Pyometra</td>
<td>WBC</td>
</tr>
<tr>
<td></td>
<td>Hepatic disease</td>
<td>ALT, ALP, bile acids</td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia</td>
<td>Serum K^{+}</td>
</tr>
<tr>
<td></td>
<td>Hypoadrenocorticism (usually associated with isosthenuria or hypersthenuria but very occasionally can cause hyposmoticuria)</td>
<td>Serum Na^{2+}, Na^{+}:K^{+} ratio, resting cortisol, ACTH stim test</td>
</tr>
<tr>
<td>LACK OF APPROPRIATE</td>
<td>Renal disease</td>
<td>Urea, creatinine, PO^{4}</td>
</tr>
</tbody>
</table>
### CONCENTRATION (if patient is not normally hydrated)

<table>
<thead>
<tr>
<th>Urine SG 1.008 - 1.030</th>
<th>Hypercalcaemia</th>
<th>Serum Ca²⁺</th>
<th>WBC, ALP, cholesterol, low-dose dexamethasone suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperadrenocorticism</td>
<td>ALT, ALP, GGT bile acids</td>
<td>Blood and urine glucose</td>
</tr>
<tr>
<td></td>
<td>Hepatic disease</td>
<td>Na⁺:K⁺, cortisol, ACTH response test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>WBC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyometra</td>
<td>Serum K⁺</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyponatraemia (often but not always due to hypoadrenocorticism)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CONCENTRATED

<table>
<thead>
<tr>
<th>Urine SG &gt; 1.030</th>
<th>Diabetes mellitus</th>
<th>Urine and blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal glucosuria</td>
<td>Urine and blood glucose</td>
</tr>
</tbody>
</table>

### Further comments related to Table 5

- Animals with partial central diabetes insipidus (low but not total lack of ADH) can have isosthenuric urine if they are dehydrated.
- Animals with partial diabetes insipidus (central or nephrogenic) may on occasions have both hypostenuria and isosthenuria.
- Other disorders that may be associated with polyuria/polydipsia, and SG values ranging from hypostenuric to concentrated, include hyperthyroidism, polycythaemia and pheochromocytoma.

Having ascertained the urine concentration of the patient, the clinician can now concentrate on differentiating disorders that may be associated with each category.

### Identify the System or Organ Involved

**Hypostenuria**

Animals with persistent hypostenuria **cannot have primary renal disease**. Hypostenuric urine has been actively diluted, a function that animals with renal disease cannot perform. However, it is my observation that cats with renal failure can occasionally have urine concentration values of between 1.006 and 1.008.

Persistent hypostenuria is a consistent feature of **diabetes insipidus** and **psychogenic polydipsia**. Note however, that a patient with partial central diabetes insipidus may present with urine in the isosthenuric range if, but only if, they are dehydrated.
**Hyperadrenocorticism, liver disease, pyometra, hyperthyroidism, hyponatraemia and hypercalcaemia** may all be associated with hyposthenuria but, as Table 5 illustrates, can also be associated with isosthenuria or minimally concentrated urine.

Dogs with **internal haemorrhage** e.g. due to splenic haemangiosarcoma, can present with profound PU/PD and hyposthenuria. This is paradoxical because haemorrhage is a potent stimulus for ADH release as ADH at high doses has a vasopressor function (hence its other name, vasopressin). This should cause increased urine concentration and haemodilution due to water retention. Perhaps the observed polyuria and hyposthenuria are a compensatory measure: the initial hemodilution may result in excretion of excess water, and profound blood loss may stimulate the thirst mechanism.

*Water-deprivation useful?*

A water-deprivation test should **not** be the first procedure performed once hyposthenuria is confirmed. Animals with hepatic disease, hypercalcaemia, hyperadrenocorticism, hyperthyroidism, hyponatraemia and pyometra may or may not be able to concentrate urine, to a certain extent, and a water-deprivation test will be of little discriminative value.

In addition, water deprivation and delay in diagnosis may be detrimental, particularly to animals with hypercalcaemia (we can probably assume that an animal with pyometra will have sufficient other clinical signs to ensure a diagnosis is made relatively easily). Therefore, the first step should be directed at determining whether hepatic disease, hyperadrenocorticism, pyometra, hyperthyroidism or hypercalcaemia exist.

Note that azotaemia is an **ABSOLUTE** contraindication to doing a water deprivation test - if the patient is azotaemic; it has in essence failed this test.

A diagnosis of polydipsia/polyuria associated with hepatic disease (most often hepatic encephalopathy), hypercalcaemia, hyperthyroidism, hypoadrenocorticism or pyometra can be made relatively easily, based on the history, physical examination and selected tests.

If you are considering a water deprivation test to rule out psychogenic polydipsia it is often a good idea to get the owner to collect multiple urine samples from different times of day. Often these dogs will only have low urine SGs some of the time (because they can concentrate their urine if they are not drinking excessively). For example, after a long walk is a good time to get a concentrated sample. Then you have no need to do a water deprivation test.
**Hepatic disease**

Hepatic disease is usually associated with other clinical signs in addition to polydipsia/polyuria and can be investigated by measurement of serum enzymes, and of bile acids if serum enzymology is only slightly abnormal.

**Hypercalcaemia**

Hypercalcaemia can be diagnosed by a serum calcium level. It is usually associated with systematic signs such as inappetence and/or GI signs.

**Pyometra**

Patients with pyometra will have other clinical signs as well as polyuria/polydipsia and should not pose a diagnostic dilemma.

**Hyperthyroidism**

Hyperthyroidism is primarily of consideration in cats and will usually be associated with other clinical signs and increased serum T4 values.

**HyperA**

Diagnosis of hyperadrenocorticism may prove more problematical as animals may not have any other clinical signs (although many will have characteristic signs such as alopecia, thin skin, pot belly and hepatomegaly).

Although a low-dose dexamethasone suppression test is necessary to definitively diagnose or exclude hyperadrenocorticism, the vast majority of animals with the disorder will have increased ALP and/or cholesterol and/or stress leukogram. Thus a polydipsic animal which has no other clinical signs and no changes in these haematological or biochemical parameters is unlikely to have hyperadrenocorticism although the diagnosis cannot be completely excluded without provocative testing of the adrenal gland.

Measurement of the corticosteroid-induced ALP isoenzyme is only useful for ruling out hyperA i.e. if the enzyme is not elevated then the animal does not have hyperA. Despite initial assumptions to the contrary, an increase in the isoenzyme is not specific for hyperA and does not assist in differentiating hyperA from liver disease.

Dogs with hyperadrenocorticism are usually systematically well (i.e. they eat well and are bright and alert). If the dog is systematically unwell then non-adrenal illness should be suspected (even if there is also concurrent hyper A).
The low-dose dexamethasone suppression test and ACTH stimulation test can be abnormal in systematically unwell animals with non-adrenal disease hence it is very important to interpret these tests light of the dog’s overall well-being. If there is concurrent illness but you still suspect that hyperA may be present, delay provocative testing of the adrenal gland until the concurrent disease has been resolved and the dog appears systematically well.

What if all tests are normal?
If an animal with hypothenuria and no other clinical signs has a normal white blood cell count, serum calcium, serum ALP, serum T4 and serum cholesterol then closed pyometra, hypercalcaemia, hyperthyroidism and hepatic disease can be eliminated from the differential diagnosis. Hyperadrenocorticism is unlikely but is theoretically possible and should be investigated by a low-dose dexamethasone suppression test or ACTH stimulation test.

Diabetes insipidus vs psychogenic polydipsia
The clinician can now concentrate on differentiating diabetes insipidus from psychogenic polydipsia. If other clinical signs suggest the possibility of hyperadrenocorticism or hepatic encephalopathy, further tests may be required such as: a low-dose dexamethasone suppression test; fasting and postprandial bile acids; or blood ammonia concentrations.

Diabetes insipidus and psychogenic polydipsia may be differentiated by a water-deprivation test. It is important to recognise that the end point must be detectable dehydration, which may take many hours in an animal with normal urine concentrating capacity.

BEWARE!
In contrast, the animal with diabetes insipidus has no capacity to concentrate urine in the face of water deprivation and, hence, can become dehydrated extremely quickly (within hours). Close monitoring of body weight, PCV, plasma protein and blood urea is essential to prevent catastrophic hypernatraemia occurring. It is not acceptable, for example, to deprive the animal of water overnight and see what its urine SG is in the morning - the chances are you’ll have a moribund patient with a brain as dry as a crisp if it does have diabetes insipidus.

Animals with psychogenic polydipsia will usually be able to concentrate urine appropriately although occasionally medullary washout secondary to profound polyuria
may impair concentration. A partial water-deprivation test with or without salt administration may be necessary in some cases.

**ADH response test**
If the patient has been water-deprived for sufficient time to induce dehydration, its urine SG remains in the hyposthenuric range, and hyperadrenocorticism, hypercalcaemia, hepatic disease, hyperthyroidism and pyometra have been ruled out by appropriate testing, diabetes insipidus is the most probable diagnosis and response to ADH should be assessed.

A positive response to ADH (2.5-5.0 units Pitressin tannate i.m. or 0.5 U/kg aqueous ADH i.m) confirms central diabetes insipidus. If pitressin tannate is unavailable, desmopressin acetate (Minirin) drops can be instilled in the eye. A negative response suggests a diagnosis of nephrogenic diabetes insipidus (a very rare and controversial diagnosis).

**Impaired Urine Concentrating Ability**

A urine specific gravity from 1.008-1.035 is only evidence of a urine concentrating defect if the patient is:
- definitely PU/PD
  - or
- dehydrated or azotaemic

As Table 5 illustrates, the differential diagnoses for the animal with inappropriately dilute urine when the urine concentration is 1.008-1.035 includes renal disease, hyperadrenocorticism, diabetes mellitus, hypercalcaemia, pyometra, hyperthyroidism, hypokalaemia, hypoadrenocorticism and hepatic disease (or very occasionally consider diabetes insipidus if the patient is dehydrated).

**What tests are required?**
As discussed in the previous section, hepatic disease, pyometra, hypercalcaemia, hyperthyroidism and hyperadrenocorticism can be excluded relatively easily from the list of differential diagnoses. Animals with hypoadrenocorticism rarely present with PU/PD as their major clinical sign.
Diabetes mellitus is also easily investigated utilising urine and/or blood glucose levels. (Note that cats may have substantial hyperglycaemia associated with stress and other disease and animals with proximal renal tubular defects may have glucosuria without hyperglycaemia). Hypokalaemia may be investigated by measuring serum potassium concentrations.

**Are all animals with renal disease azotaemic?**

Dogs with impaired urine concentration due to renal disease may or may not be azotaemic depending on the percentage of nephron loss – loss of 67% of nephron function results in impaired concentration ability, loss of 75% results in azotaemia. This rarely occurs in cats – i.e. cats with impaired concentrating ability due to renal disease are almost always azotaemic as well.

**Is a water-deprivation test useful?**

Although it is often assumed that a water-deprivation test is useful in diagnosing compensated renal disease, it should be remembered that the animal with compensated renal disease may become seriously azotaemic if water is deprived and dehydration ensues.

As previously mentioned, disorders such as hyperadrenocorticism may also impair the animal’s ability to concentrate urine in the face of dehydration and hence the test may not be particularly discriminatory. It is preferable to rule out other possible disorders with appropriate tests (urea, creatinine, liver enzymes, calcium, electrolytes, T4 and WBC).

If these tests are all normal and there are no other clinical signs, compensated renal disease is the probable diagnosis. Confirmation requires more sophisticated tests to measure glomerular filtration rate such as endogenous or exogenous creatinine clearance (not usually feasible in practice).

It is important to recognise that hypercalcaemia and hypoadrenocorticism (or hyponatraemia due to other causes) as well as renal disease may be associated with impaired urine concentration and azotaemia (see Table 6).

**Concentrated Urine**

The most common diagnosis in this category is diabetes mellitus.

Note that polyuria in diabetes mellitus is due to the osmotic effect of glucose in the renal tubules, which decreases water reabsorption from, for example, the thin loop of Henle.
Urine concentration *per se* however is not impaired as the extra water excreted is accompanied by a solute (glucose) and there is no disturbance to medullary hypertonicity.

This is in contrast to drugs/disorders causing sodium wasting which as well as causing increased water loss to accompany the sodium, result in reduced medullary hypertonicity.

*Renal glucosuria vs diabetes*

Renal tubular defects causing glucosuria should also be considered and differentiated from diabetes mellitus by measuring blood glucose.

Cats with stress-related hyperglycaemia may also have glucosuria that could conceivably be of sufficient magnitude to cause polyuria. Diagnosis of the underlying disorder can present a diagnostic challenge in these patients. However, measurement of serum fructosamine levels appears to be useful in differentiating most cases of stress hyperglycaemia from true diabetes mellitus.

Animals with hyperadrenocorticism, hypercalcaemia and hypoadrenocorticism may not be consistently polyuric and therefore may have concentrated urine at certain times.

**Pathophysiology of impaired urine concentration**

**Diabetes Insipidus**
Lack of ADH impairs water and urea re-absorption from the distal collecting duct. This causes increased water loss and reduced osmolarity of the medullary interstitium, which further reduces water reabsorption from the thin loop of Henle.

**Psychogenic Polydipsia**
Primary polydipsia (cause unknown) causes compensatory (and appropriate) polyuria.

**Hypercalcaemia**
Hypercalcaemia impairs the action of ADH on the collecting duct, although the exact mechanism has not been identified. A protein called the apical extracellular calcium sensing receptor (CaSR) is believed to be involved. When luminal calcium increases CaSR decreases ADH-induced permeability of the collecting duct. In addition there may be down-regulation of the formation of water channels (aquasporin 2) in the collecting duct. The effect may be partial or total. Hypercalcaemia will also decrease the glomerular filtration rate by causing vasoconstriction of afferent arterioles, which results initially in reversible
azotaemia. Eventually tubular function becomes permanently impaired, causing azotaemia due to nephrocalcinosis.

**Hypokalaemia**
Hypokalaemia results in mild to moderate impairment of urinary concentrating ability through ADH resistance. Aquaposrin-2 is down-regulated in hypokalaemia resulting in decreased permeability of the collecting duct to water.

**Hyperadrenocorticism**
The mechanism by which hyperadrenocorticism causes PU/PD in dogs is not well understood. It is thought that cortisol may interfere with ADH function. However, frequently dogs with hyperadrenocorticism can reduce their water intake and urine output when initially hospitalized, which would suggest that other factors are important. PU/PD does not occur in humans with hyperadrenocorticism nor in humans or corticosteroid medication, which is a fascinating species difference.

Cats become polydipsic after corticosteroid treatment much less frequently than dogs, which also suggests an interesting species difference.

**Liver Disease**
The mechanism by which hepatic disease, especially portosystemic encephalopathy, causes polyuria is also unknown. Various theories have been proposed - decreased urea concentration in the medullary interstitium may be a factor. However, some dogs with portosystemic shunts can concentrate their urine when challenged, whereas other can’t. It is possible that the polydipsia, rather than the polyuria, may be primary and a consequence of the encephalopathy.

**Hyperthyroidism**
The mechanism by which hyperthyroidism causes PU/PD is multifactorial. Thyroxine increases the effective renal blood flow due to dilation of the preglomerular arterial vessel which leads to increased GFR and hyperfiltration. It has been suggested that increased renal blood flow may also impair urine concentrating ability by causing medullary solute washout. It is also possible that thyrotoxicosis produces a primary, compulsive polydipsia due to disturbance of hypothalamic function.

**Pyometra**
Bacterial infection (*E. coli*) in pyometra causes decreased responsiveness to ADH although urine dilution is still possible.

**Hypoadrenocorticism**

Hyponatraemia due to any cause will impair urine concentration although PU/PD may not be an overt clinical sign. The cause is presumably related to decreased medullary osmolarity as a result of sodium wasting.

**Diabetes Mellitus**

Primary polyuria is caused by the osmotic effect of glucose in the urine.

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**Interpreting serum urea and creatinine levels**

**Azotaemia**

*Azotaemia* is the laboratory finding of increased concentrations of non-protein nitrogenous wastes, measured as blood urea or serum creatinine.

**Azotaemia can result from primary renal disease, prerenal or post-renal processes.**

Extensive renal lesions result in azotaemia when there is a loss of 75% or greater of functioning nephrons.

**Prerenal azotaemia**

Prerenal processes include hypovolaemia and severe dehydration. Mild azotaemia may also occur after a large meat meal and when there is GI bleeding.

**Urine SG?**

A *dehydrated* animal with normal renal function should have highly concentrated urine (>1.030-1.035) and if they do not it is possible that they have renal azotaemia i.e. impaired renal function. However, if an animal with a polyuric disorder such as pyometra, hyper A or liver disease becomes dehydrated they may become azotaemic due to the prerenal factor of dehydration but they may still have inappropriately dilute urine (because of the factors discussed previously that interfere with urine concentration). Thus while a high urine SG in a dehydrated patient confirms that prerenal factors are responsible for the azotaemia, an inappropriately low SG does **not** necessarily rule out prerenal azotaemia if that patient has a polyuric disorder.

**Renal azotaemia**
If the patient is dehydrated:
If azotaemia is found in association with inappropriately dilute urine, it is usually defined as renal azotaemia. The question then becomes “Does the animal have structural renal disease or a functional problem?” As discussed above, dehydrated patients which have an impaired ability to concentrate urine may become azotaemic due to prerenal factors. They thus have renal dysfunction at that time but do not have structural renal disease.

If the patient is not dehydrated:
If non-renal sources of increased urea or creatinine (e.g. GI bleeding, large meal) can be ruled out, the only disorders other than primary renal disease that can cause azotaemia in a non-dehydrated, apparently normovolaemic patient are:

- **hyponatraemia** (due to hypovolaemia - sodium is the osmotic backbone of the plasma – thus loss of sodium reduces total body water and blood volume which in turn reduces GFR and therefore results in azotaemia)
- **hypercalcaemia** (as calcium causes constriction of the afferent arteriole in the glomerulus thus decreasing GFR and hence causing azotaemia).

It is therefore imperative that, before a diagnosis of primary renal disease is made, sodium and calcium levels are checked in any azotaemic patient with inappropriately dilute urine, especially if they are not dehydrated and there is no evidence for other polyuric disorders such as liver disease, pyometra and hyper A.

**Postrenal azotaemia**
Postrenal azotaemia results from either obstruction to urine flow or traumatic rupture of the excretory pathway resulting in accumulation of urine in the body.

**Uraemia**
Uraemia refers to the constellation of clinical signs and biochemical abnormalities associated with a critical loss of functioning nephrons (e.g. anorexia and vomiting).

<table>
<thead>
<tr>
<th>An animal may have azotaemia but not be uraemic</th>
</tr>
</thead>
</table>

That is, the animal may have an elevated blood urea or serum creatinine but does not have clinical signs of uraemia because the degree of increase is not sufficient to cause clinical signs of uraemia.
Table 6: Interpretation of laboratory data relevant to renal function

<table>
<thead>
<tr>
<th>Laboratory abnormalities</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal urea and creatinine</strong></td>
<td></td>
</tr>
<tr>
<td><em>Urine adequately concentrated</em></td>
<td>• Non-renal disease</td>
</tr>
<tr>
<td>(urine SG &gt;1.030 dog, 1.035 cat)</td>
<td>• Glomerular disease (if +++ proteinuria)</td>
</tr>
<tr>
<td><strong>Isosthenuric or poorly concentrated urine</strong></td>
<td></td>
</tr>
<tr>
<td>(urine SG 1.008–1.030)</td>
<td>• Normal animal</td>
</tr>
<tr>
<td></td>
<td>• Non-renal disease</td>
</tr>
<tr>
<td></td>
<td>• Glomerular disease (if +++ proteinuria)</td>
</tr>
<tr>
<td></td>
<td>• Non-azotaemic renal disease (dogs only)</td>
</tr>
<tr>
<td><strong>Normal or slightly increased urea and creatinine</strong></td>
<td></td>
</tr>
<tr>
<td><em>Inadequate urine concentration</em></td>
<td>• Although the animal may have renal disease → inadequate urine concentration, clinical signs such as anorexia and vomiting cannot be attributed to renal disease and non-renal disease must be investigated.</td>
</tr>
<tr>
<td>(urine SG &lt;1.030 dog, 1.035 cat)</td>
<td></td>
</tr>
<tr>
<td><strong>Urea increased, creatinine normal</strong></td>
<td>• Usually prerenal azotaemia but urine concentration must be &gt;1.030. Consider also GI haemorrhage or hyperthyroidism.</td>
</tr>
<tr>
<td><strong>Urea and creatinine increased</strong></td>
<td></td>
</tr>
<tr>
<td><em>Urine adequately concentrated</em></td>
<td>• Prerenal azotaemia</td>
</tr>
<tr>
<td>(urine SG &gt;1.030 dog, 1.035 cat)</td>
<td></td>
</tr>
<tr>
<td><em>Inadequate urine concentration</em></td>
<td>• Structural renal disease</td>
</tr>
<tr>
<td>(urine SG &lt;1.030 dog, 1.035 cat)</td>
<td>• Hypercalcaemia</td>
</tr>
<tr>
<td><strong>Patient not dehydrated</strong></td>
<td>• Hyponatraemia</td>
</tr>
<tr>
<td><strong>Patient is dehydrated</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Structural renal disease</td>
</tr>
<tr>
<td></td>
<td>• Hypercalcaemia</td>
</tr>
<tr>
<td></td>
<td>• Hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>• Diuretic therapy</td>
</tr>
<tr>
<td></td>
<td>• Any other polyuric disorder if the patient is <strong>also</strong> dehydrated/hypovolaemic for some reason</td>
</tr>
<tr>
<td><strong>Hyperphosphataemia</strong></td>
<td>• Renal disease (GFR &lt;25%)</td>
</tr>
<tr>
<td></td>
<td>• Hypercalcaemia (some but not all causes)</td>
</tr>
<tr>
<td></td>
<td>• Vitamin D toxicosis</td>
</tr>
<tr>
<td></td>
<td>• Severe prerenal azotaemia (differentiate by urine SG)</td>
</tr>
</tbody>
</table>
Before we go further.....................

1. Medullary hypertonicity is primarily determined by the sodium concentration in the renal medulla.
   True  False  My answer has changed

2. If an animal has a urine specific gravity of 1.002, primary structural renal disease is a possible diagnosis.
   True  False  My answer has changed

3. A urine SG of 1.020 in a dehydrated patient indicates adequate urine concentration.
   True  False  My answer has changed

4. A water-deprivation test is useful to differentiate diabetes insipidus and other causes of hyposthenuria such as hyperadrenocorticism.
   True  False  My answer has changed

5. Prerenal azotaemia is never associated with hyperphosphataemia. If hyperphosphataemia is present in an adult animal, it must have structural renal disease.
   True  False  My answer has changed

6. A dog that is polydipsic, clinically dehydrated, has a urea concentration of 30 mmol/L (normal range 5-10), creatinine of 250µmol/L (normal range 55-100) and a urine SG of 1.010 must have primary structural renal failure.
   True  False  My answer has changed

   What disorders could create this scenario?
   ................................................................................................................

7. A dog that is polydipsic but NOT clinically dehydrated, has a urea concentration of 30 mmol/L (normal range 5-10), creatinine of 250µmol/L (normal range 55-100) and a urine SG of 1.010 must have primary structural renal failure.
   True  False  My answer has changed

   What disorders could create this scenario?
   ................................................................................................................
Seizures, syncope and weakness

Define the Problem

When an animal presents with a history of episodic weakness, fatigability or collapse, appropriately defining the problem is essential although sometimes difficult.

An owner may state that their dog is having collapsing episodes, but it is imperative that the clinician ascertains whether:

- the animal loses consciousness (indicating syncope or seizures)
- there is evidence of convulsive activity (more likely seizures than syncope)
- the animal is normal in between the episodes, whether weakness is precipitated by exercise (fatigability) or the animal is consistently weak.

Think pathophysiologically!

Thinking ‘pathophysiologically’ is also important - i.e. considering the function of each body system and how disturbances of its function might manifest clinically e.g. it's obvious that if an animal is persistently weak and has episodes of loss of consciousness, primary muscle disease is unlikely.

System ranking

Although system dysfunctions that may cause collapse (without loss of consciousness), syncope and seizures are similar, appropriately defining the problem will assist the clinician in ranking the systems in order of priority, the rank being different with each problem. In this way, diagnostic procedures can be rationally, economically and usefully utilised.

Define the System

Weakness, syncope or seizures implies dysfunction of the central nervous system (CNS), or the neuromuscular system (peripheral nervous system [PNS], neuromuscular junction abnormalities or muscle dysfunction). However, the cause of such failure can either be a primary structural disorder of the CNS or components of the neuromuscular system or can
result from dysfunction of a number of other systems that result in impaired CNS or neuromuscular function. This impairment may result in either:

• reduced delivery of nutrients to the brain, nerves or muscles (e.g. glucose, oxygen) or impairment of vascular function (e.g. polycythaemia, hyperglobulinaemia)
• change in the internal milieu of muscles and nerves that alter their function (e.g. calcium and potassium imbalances)
• production of endogenous toxins e.g. uraemia.

Hence it is apparent that weakness, collapse or seizures may be caused by:

- primary structural nervous system or muscle disease
- functional nervous system or muscle disease induced by cardiovascular, respiratory or metabolic derangements.

The following systems need to be considered in all animals with a history of collapse although depending on the precise problem, the systems will be ranked in different orders of priority:

- cardiovascular
  - heart, vessels, blood
- nervous system/muscular
  - neurological (central or peripheral)
  - neuromuscular junction (junctionopathies)
  - muscles
- metabolic
  - electrolytes
  - glucose
  - endogenous toxins (e.g. sepsis)
- respiratory
- skeletal

Other clinical signs that have been noted or physical abnormalities detected on physical examination will often assist in defining the system of involvement. In other cases, further investigation may be required to determine which system is involved.

Collapse (without loss of consciousness)

Collapse without loss of consciousness will usually involve:
• neuromuscular dysfunction
• cardiovascular dysfunction
• metabolic derangements
  o hypoglycaemia
  o hypo/hyperkalaemia
  o hypo/hypercalcaemia
  o endogenous toxaemia

It is important to determine whether the animal is always weak (persistent weakness) or is normal between episodes (episodic weakness).

**Persistent weakness**
Persistent weakness is more likely to be due to:
• primary peripheral nerve dysfunction
• primary muscle dysfunction
• neuromuscular junction abnormalities
• derangements in calcium or potassium homeostasis
• endogenous toxaemia.

**Episodic weakness**
True episodic weakness (i.e. the animal has relatively normal strength in between episodes and the weakness is usually exacerbated by exercise - otherwise known as fatigability) is usually due to:
• neuromuscular junction abnormalities
• cardiovascular disorders
• metabolic muscle disorders
• disturbances of glucose or potassium homeostasis.
• cataplexy, usually associated with the central nervous system disorder narcolepsy

The direction of your diagnostic procedures will depend on other clinical signs and abnormalities that are present.

See Table 7 for specific causes of persistent and episodic weakness.

**Weakness in Cats**
Cats in contrast to dogs tend not to present often with episodic weakness - they will usually ‘self-regulate’ their activity and more commonly present with persistent weakness. This is usually manifested by ventral flexion of the neck and lying with their head on their paws (i.e.
Looking really relaxed) even in the middle of a consulting room or other strange and stressful environment.

Interpreting Serum CPK Levels
Creatine phosphokinase levels in serum are often measured in dogs and cats when a myopathy is suspected because the enzyme is a relatively specific indicator of muscle damage. It is important to note, however, that even relatively minor muscle damage associated, for example, with a recumbent animal or with an intramuscular injection will result in increased CPK levels in serum. It is therefore important not to overinterpret mild to moderate (<1000 IU/L) increases in enzyme levels. Even levels greater than 1000 IU/L may be associated with secondary muscle damage and are not necessarily indicative of primary muscle disease.

Syncope

Syncope (or fainting) implies disruption of fuel (oxygen, glucose) supply to the brain.

This may be due to interruption in delivery of oxygenated blood (cardiovascular disease, respiratory disease) or insufficient glucose delivery to maintain brain function (hypoglycaemia).

Syncope does not usually occur with primary CNS disease and can usually be distinguished from seizures by the lack of tonic-clonic movements and absence of urination/defaecation. In addition, there is not an aura detectable preceding a syncopal episode and recovery of consciousness is immediate and not accompanied by post-ictal signs. However, it can sometimes be difficult to reliably confirm whether syncope or seizures is occurring.

Seizures

Tonic-clonic generalised seizures (previously known as grand mal seizures, particularly in humans) are characterised by lateral recumbency, tonic (increased muscle tone) and clonic (rhythmic muscle contraction) phases, loss of consciousness and are sometimes but not always accompanied by urination and defaecation. They are thought to be sometimes preceded by an aura, which actually indicates a partial onset of the seizure, during which an observant/experienced owner may detect unusual behaviour or mentation in their pet. Generalised seizures are followed by a post-ictal period of variable length (minutes/hours or days) where the animal may appear dazed and disorientated.
Classic seizure activity is not difficult to differentiate from syncope but may require careful questioning of the owner as owners will often describe all episodes of collapse as ‘fits’.

**Define the System**

**Intra- vs extra- cranial**

Seizures are caused by either primary cerebral hemisphere (forebrain) dysfunction (intra-cranial) or extra-cranial disease which impinges on cerebral function.

Structural intra-cranial disease may be associated with other neurological abnormalities (e.g. weakness, blindness, abnormal behaviour). However, intra-cranial disease cannot be ruled out if the animal is completely normal between seizures.

Structural lesions that are not sufficiently large to cause neurological dysfunction other than seizures or are in a relatively ‘silent’ area of the cerebrum may not manifest in any way other than seizures (for example in the most rostral parts of the cerebrum such as the olfactory lobe).

NB Recurrent seizures associated with structural cerebral disease are referred to as **symptomatic epilepsy** in humans and this term is now more commonly being used in the veterinary literature too.

**Metabolic causes**

Extra-cranial disease may or may not cause clinical signs in addition to seizures. Metabolic disturbances such as hyperkalaemia and hypocalcaemia most commonly will also cause signs of malaise such as gastrointestinal dysfunction but there are occasional reports of dogs with hypoadrenocorticism or hypocalcaemia where seizures were the only presenting signs.

NB Recurrent seizures secondary to metabolic disturbance are called **reactive seizures** in humans and this term is now also being used in the veterinary literature.

**Hypoglycaemia**

Hypoglycaemia will frequently cause seizures with no other clinical signs. However, chronic hypoglycaemia can also cause peripheral neuropathy and so may also be associated with neuromuscular weakness. Confirmation of hypoglycaemia may be problematical as
homeostatic mechanisms (adrenaline and cortisol release) will come into play when the blood glucose falls to a critical level and increase the blood glucose temporarily.

It is important to obtain a fasting blood glucose sample when investigating metabolic causes of seizures.

**Toxins**
Acute exogenous toxicity will often cause status epilepticus. If the history of toxin exposure is known, or other clinical signs are present, diagnosis is usually not difficult. However, it should be remembered that dogs with epilepsy may present in status epilepticus without a prior history of seizures. This possibility should be considered if there is no evidence for intoxication and the dog or cat is of the appropriate age. Chronic toxicity e.g. lead should be considered if the geographical area is appropriate.

**Intra-cranial vs extra-cranial**
Table 8 lists the intra-cranial and extra-cranial causes of seizures. It should be clear from this list that it is not particularly difficult to rule out extra-cranial causes of seizures with selected biochemical tests. Consideration of age and breed is obviously important - a 14 year old animal without a prior history of seizures is very unlikely to have idiopathic epilepsy.

**How to work up?**
A reasonable work-up for the seizuring animal is to rule out extra-cranial causes with selected tests then consider, based on the animal's age, breed and concurrent clinical signs as well as the owner's economic circumstances, whether investigation of intra-cranial disease is appropriate.

A CT scan or MRI possibly followed by CSF tap are the next diagnostic steps but will often need to be performed at a referral centre. MRI is more useful than CT in most patients with seizures due to the excellent soft tissue contrast acquired with this technique. There are no 'hard and fast' rules about when these investigations are appropriate and it will depend on the owner's wishes and geographic location.

In a young (six months to five years) animal with no interictal signs, the most likely diagnosis is idiopathic epilepsy and institution of antiepileptic drug therapy is reasonable if the owner chooses not to 'go the whole hog'. On the other hand, in an older animal, seizures indicate a more sinister prognosis although antiepileptic drug therapy may be beneficial for some time.
The presence of interictal abnormalities indicates significant structural disease for which CSF analysis and/or MRI or CT scan are needed to follow the diagnosis further. Treatable (although not necessarily curable) intra-cranial diseases include granulomatous meningo-encephalomyelitis, surgically-accessible tumours (requires referral) and hydrocephalus.

### Identify the Lesion

**Table 7: Differential diagnoses for weakness and syncope**

<table>
<thead>
<tr>
<th>Episodic or Exercise-induced Weakness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cardiovascular system</em></td>
<td></td>
</tr>
<tr>
<td>• structural cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>• arrhythmias</td>
<td></td>
</tr>
<tr>
<td>• anaemia</td>
<td></td>
</tr>
<tr>
<td>• hyperviscosity syndromes</td>
<td></td>
</tr>
<tr>
<td>• polycythaemia</td>
<td></td>
</tr>
<tr>
<td>• acute haemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• heartworm disease</td>
<td></td>
</tr>
<tr>
<td>• upper respiratory tract dysfunction (laryngeal paralysis)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• hypoglycaemia (insulinoma)</td>
<td></td>
</tr>
<tr>
<td>• hyperkalaemia (occasionally)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Junctionopathy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• myasthenia gravis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myopathy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• metabolic myopathy (exercise-induced hyperthermia)</td>
<td></td>
</tr>
<tr>
<td>• polymyositis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cataplectic attacks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• narcolepsy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Persistent Weakness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cardiovascular</em></td>
<td></td>
</tr>
<tr>
<td>• cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>• anaemia</td>
<td></td>
</tr>
<tr>
<td>• polycythaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>• hypokalaemia</td>
</tr>
<tr>
<td></td>
<td>• hyperkalaemia (e.g. hypoadrenocorticism)</td>
</tr>
<tr>
<td></td>
<td>• hypocalcaemia/hypercalcaemia</td>
</tr>
<tr>
<td></td>
<td>• hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>• endogenous toxaemia (e.g. sepsis)</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>• peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Myopathy</strong></td>
<td>• myopathy</td>
</tr>
<tr>
<td><strong>Junctionopathy</strong></td>
<td>• neuromuscular junctionopathy</td>
</tr>
<tr>
<td></td>
<td>e.g. OP toxicity, spider bite, tick paralysis, botulism, snake envenomation)</td>
</tr>
</tbody>
</table>

### Syncope

| **Cardiovascular**        | • left-sided heart failure |
|                          | • heartworm disease       |
|                          | • paroxysmal arrhythmias  |
|                          | • anaemia (if severe or associated with exercise/excitement) |
|                          | • polycythaemia           |
| **Respiratory**           | • severe coughing         |
|                          | • laryngeal paralysis     |
| **Metabolic**             | • hypoglycaemia           |
### Table 8: Causes of Seizures in Small Animals

<table>
<thead>
<tr>
<th>Intra-cranial Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epilepsy</strong></td>
<td></td>
</tr>
<tr>
<td>- idiopathic</td>
<td></td>
</tr>
<tr>
<td>- acquired epilepsy (trauma, &quot;old dog distemper&quot;)</td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasia</strong></td>
<td></td>
</tr>
<tr>
<td>- primary</td>
<td></td>
</tr>
<tr>
<td>- metastatic</td>
<td></td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>- granulomatous meningoencephalomyelitis</td>
<td></td>
</tr>
<tr>
<td>- feline polioencephalomyelitis</td>
<td></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>- toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>- neosporosis</td>
<td></td>
</tr>
<tr>
<td>- FIP</td>
<td></td>
</tr>
<tr>
<td>- cryptococcosis</td>
<td></td>
</tr>
<tr>
<td>- abscess</td>
<td></td>
</tr>
<tr>
<td><strong>Structural developmental abnormality</strong></td>
<td></td>
</tr>
<tr>
<td>- hydrocephalus</td>
<td></td>
</tr>
<tr>
<td><strong>Functional developmental abnormality</strong></td>
<td></td>
</tr>
<tr>
<td>- metabolic storage diseases</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td></td>
</tr>
<tr>
<td>- haemorrhage</td>
<td></td>
</tr>
<tr>
<td>- infarct</td>
<td></td>
</tr>
<tr>
<td><strong>Nutritional</strong></td>
<td></td>
</tr>
<tr>
<td>- thiamine deficiency</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extra-cranial Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>- hypoglycaemia</td>
<td></td>
</tr>
<tr>
<td>- hyperkalaemia</td>
<td></td>
</tr>
<tr>
<td>- hypo/hypercalcaemia</td>
<td></td>
</tr>
<tr>
<td>- hyperosmolarity</td>
<td></td>
</tr>
<tr>
<td><strong>Endogenous toxins</strong></td>
<td></td>
</tr>
<tr>
<td>- hepatic encephalopathy (particularly cats)</td>
<td></td>
</tr>
<tr>
<td>- renal failure (end stage - will always have other signs of uraemia)</td>
<td></td>
</tr>
<tr>
<td><strong>Exogenous toxins</strong></td>
<td></td>
</tr>
<tr>
<td>- lead toxicity, snail bait, strychnine etc.</td>
<td></td>
</tr>
<tr>
<td><strong>Disturbance of vascular perfusion</strong></td>
<td></td>
</tr>
<tr>
<td>- polycythaemia</td>
<td></td>
</tr>
<tr>
<td>- hyperviscosity syndromes</td>
<td></td>
</tr>
<tr>
<td>- anaemia (if associated with excitement etc)</td>
<td></td>
</tr>
<tr>
<td>- rarely cardiovascular disease may result in seizure activity (although syncope is far more common)</td>
<td></td>
</tr>
</tbody>
</table>