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The Toxicology of Plants in South Africa.

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I. DEFINITION OF A POISONOUS PLANT.

It is indeed a difficult task to define a poisonous plant in such terms as to comprise all plants which are considered detrimental to health. The most acceptable definition appears to be the following: A poisonous plant is a plant which, when consumed in such quantities as will be taken by animal or man over short or prolonged periods, exerts harmful effects on the system, or cause death by virtue of toxic substance(s) normally contained in that plant.

Many plants may at times constitute excellent feeds, whilst in certain circumstances they may prove deadly poisons. As examples mealie-stalks, sorghums, and a number of South African grasses may be mentioned. These plants are rightly considered valuable stock feeds, but in times of drought they may become deadly poisonous owing to the fact that they produce large amounts of prussic acid during the process of wilting.

Furthermore, many recognised valuable stock feeds are detrimental to health when fed in too large amounts over prolonged periods. As an example, cotton seed cakes and Lathyrus *sativus* L. may be quoted.

Another complicating factor in the definition of a poisonous plant is the fact that such quantities of a plant which are poisonous to one species of animal may not affect another species. Pigs are, for example, much more susceptible than sheep to poisoning with Syringa berries (*Melia azedarach* L.).

Again, some plants when eaten in small amounts may affect a certain organ or organs in such a way as not to cause immediate death or serious bodily harm, but may shorten life appreciably by decreasing the functions of such affected organs, and hence play an indirect rôle in the causation of death. Such plants are the species of *Senecio* concerned in stock poisoning and in bread poisoning in human beings. The seed heads and other parts of these plants become mixed with wheat threshed and milled in machines with deficient sieving and winnowing appliances and are then consumed with the bread. The active ingredients of these species of *Senecio* attack the liver and when taken in very small amounts over prolonged periods, cause cirrhosis of this organ. Apart from the ascites, which develops in human beings as a result of cirrhosis of the liver, the function of this organ, which is mainly a detoxicator, excretor and general protector of the system against all kinds of harmful substances, is markedly inhibited. Such affected subjects may, therefore, be much more susceptible to the effects of harmful substances which may find their way into the blood circulation via the liver, whether of exogenous or endogenous origin.

A part, or parts of a plant may be poisonous, whilst the remainder may be harmless and may even form part of the human or animal diet. This is the case in peach, apricot and prune kernels, which may frequently contain dangerous amounts of prussic acid, whilst the outer portion of the fruit is eaten with impunity. Similarly, the leaf-blades of rhubarb leaves are known to be poisonous, whilst the petioles are frequently used in the human diet.

The layman's idea of a poison is something that will cause death or disease when taken in small doses. The following examples will suffice to prove that plants may be the cause of serious bodily harm or even death in other ways than due to the poisonous constituents contained in them. In South Africa many plants are known to cause mechanical injury. The seeds of "steekgras" ("prick grass") (*Heteropogon contortus* R. & S., *Aristida congesta* R. & S., etc., etc.) may cause serious damage to the general health and condition of woolled sheep by irritating and piercing the skin, causing the penetration of pyogenic organisms which set up subcutaenous and in rare cases even intramuscular abscesses (Viljoen, 1918). From South West Africa cases have been reported where certain grass seeds have entered into the salivary ducts of cattle and have caused serious damage. Continuous ingestion of dry grasses rich in cellulose is prone to cause the formation of plant fibre balls in the stomach and intestines, especially in ruminants. This may lead to serious digestive disturbances and fatal obstruction of the gastro-intestinal canal. The seeds of burr-weed (*Xanthium* spp.) may cause partial or complete obstruction of the orifice of the sheath in oxen grazing on reaped lands overgrown with this weed. Such cases, if left unattended, may develop into severe inflammation of the sheath. The feeding of spiny prickly pear may lead to actinobacillosis and caseous lymphadenitis as was clearly proved by Thomas (1931). Some plants, for example lucerne, under certain conditions, cause death merely through the production of abnormal amounts of gas in the stomach, death apparently being due to asphyxia caused by high pressure on the diaphragm.

The constant feeding of plants deficient in minerals (stiffsickness, stywesiekte), proteins, lipoids (Jaffe, 1929), vitamins, etc., also lead to fatal results.

II. CLASSIFICATION OF POISONS.

Poisons may be classified as follows:—

(A) According to their origin: vegetable, mineral, animal, etc. This classification is obviously too vague to be of any value.

(B) According to their chemical constitution: alkaloids, glucosides, toxalbumins, picrotoxins, etc. Also this classification is too indefinite.

(C) According to similarity in pharmacological action, e.g.:—

(*a*) *Blood poisons:* acting on the blood.

(i) Poisons affecting cellular elements. Those acting on the red cells in particular and to a lesser extent on the white cells; for example, carbon monoxide, prussic acid, arsine, chlorates.

(ii) Poisons affecting the plasma. Those acting on the plasma as well as on the corpuscles or on the plasma only; for example, silver salts.

(*b*) *Neurotic poisons:* those acting on the nervous system.

(i) *Paralysomotor poisons.* Those affecting particularly the motor nerves, for example, curare and aconite.

(ii) *Spinal poisons;* for example, strychnine and yohimbin.

(iii) *cerebro-spinal poisons;* for example, morphine, chloroform and chloralhydrate.

(*c*) *Neuromuscular poisons:* those acting on the muscular system through the nerves controlling the muscles in question: for example, digitalis.

(*d*) *Muscular poisons:* those acting on the muscles without the intervention of nerves; for example, veratrin, lead and mercury.

(*e*) *Irritant or corrosive poisons;* for example, acids and alkalis in high concentrations, and corrosive sublimate.

To group C poisons, which attack certain organs only, may be added. The following might be cited as examples, *Senecio spp.*, which attack the liver, *Crotalaria dura* Wood & Evans, and *Crotalaria globifera* E. Mey, which attack the lungs in horses, and *Crotalaria burkeana* Benth which affect the hoofs in cattle.

Of the above schemes of classification, that given under group III appears most acceptable, although it is by no means satisfactory. Many poisons have complex actions and cannot be included under any one group to which a particular action is ascribed. It is for this reason that such great difficulty is experienced in the classification of poisonous plants, as many of them have most complex actions due to the presence of more than one substance, which is harmful to the system. In addition, the effects of one and the same plant may vary considerably according to the size of the dose administered and according to the method of administration.

Popularly poisonous plants are referred to as poisons to the brain, spinal cord, heart, liver, kidney, lungs and metabolism.

III. ACCESS OF POISONS TO THE ANIMAL BODY.

Poisons may find their way into the blood stream in the following ways:—

A. *Direct Introduction into Veins or Arteries.*

In this case symptoms of poisoning set in immediately or a short time after administration and death may occur instantaneously, as there is little or no time for elimination and inactivation of the poison. If a leathal dose of strychnine be injected intravenously the patient will in most cases succumb before the injection is completed (Steyn 1931d).

B. *Absorption from the Intraperitoneal and Intrathoracic Cavities.*

Serious membranes are very active absorbers, and fluids or substances in solution introduced intraperitoneally or intrathoracically are at once exposed to a large and active absorbing surface. Poisonous substances introduced into the body by this method will therefore exert their toxic effects very soon after administration, for the same reasons as mentioned above.

C. *Absorption from the Intramuscular Tissues.*

The rate of absorption of substances administered by this method is almost as quickly as in the case of intravenous injections. In the case of wounds brought about by poisoned arrows, blood vessels are ruptured and the poison is to a certain extent introduced directly into the blood circulation.

D. *Absorption from the Subcutaneous Tissues.*

Here the rate of absorption is slower than when the poison is administered intravenously or intramuscularly, as, unless the subcutaneous tissues are damaged over a large area with the consequent severing of bloodvessels, absorption into the blood circulation has to take place by way of osmosis. Irritant substances (oil of turpentine) introduced subcutaneously cause local inflammation with consequent necrosis in cases of severe irritants.

E. *Absorption from the Respiratory Tract.*

Absorption of gases and vapours by the lungs is practically instantaneous, the surface exposed to the action of inhaled gases being enormous, hence facilitating absorption. Also liquids are rapidly absorbed by the lungs, and even inhaled solids, when these are in a state of fine division, are allowed to pass into the lung tissues (silicosis). It is, for example, possible to cause death in guinea-pigs from ricinus (castor bean) poisoning by allowing these animals to inhale the dust of the beans (Ratnet and Gruehl, 1927-1928).

F. *Absorption from the Alimentary Canal.*

The amount of poison absorbed from the intact buccal cavity, pharynx and oesophagus is in most cases negligible, as it is rarely retained here for any length of time. Most poisons when retained for any length of time in the buccal cavity will be absorbed to a certain extent (Blume and Buchholz, 1932). Discussing absorption by the mouth Witthaus (1911, p. 83) writes: " Poisons of great activity, however, enter the circulation from the mouth or lips or the nasal mucous membrane with such rapidity that their contact with those surfaces may cause death before an act of swallowing is attempted, or even possible. Thus Preyer found that rabbits fell unconscious in twenty-three seconds after the application of hydrocyanic to the tongue, and in twelve seconds after its application to the nostrils. Nicotin also, when applied to the mouth in doses of two to four drops, may cause poisoning either immediately or within half a minute. In cases of tobacco poisoning from excessive smoking, in which the smoke is not inhaled, the absorption is by the buccal mucous membrane, except in so far as it may occur by swallowed

saliva. Arsenic is also absorbed from the mouth under exceptional circumstances, as in those instances in which arsenical symptoms were traced to smoking tobacco or cigars impregnated with arsenic. Gorochofzeff has shown that dogs after ligation of the oesophagus are killed by strychnine more rapidly by the mouth than by the stomach." Irritant poisons, which cause partial or complete destruction of the mucous membrane, will be absorbed in the same way as from wounds.

Absorption of poisons from the fore-stomachs of ruminants is negligible, except in case of gases and volatile substances, which will diffuse through the mucous membrane and in this way reach the blood circulation. In experiments conducted at Onderstepoort by the author it was found that sheep drenched by stomach tube with highly lethal amounts of *Dimorphotheca spectabilis* Schltr. (bietou) were already in a state of collapse by the time the stomach tube was withdrawn, thus indicating that the prussic acid contained in this plant passed through the ruminal wall as there was no time for the material drenched to find its way into the abomasum and small intestine. Volatile substances, like ether and alcohol, also to a large extent pass through the ruminal wall. Absorption by the stomach (abomasum in ruminants) is as a rule slow, depending on the diffusibility and solubility of the poison, and what has been said with regard to absorption by the fore-stomachs, also applies here. The following passage quoted from Witthaus (1911, p. 84) is of interest: "There are differences in the rates of absorption of certain substances from the stomach in the different kinds of animal. Thus strychnine is absorbed more slowly in cows and much more slowly in horses than in dogs, pigs or cats. Otto found that strychnine is absorbed from the ligated stomach in cats and dogs, but not in rabbits or guinea-pigs, while the reverse is the case with potassium iodide and sodium salicylate". Poisons insoluble in watery fluids but soluble in oils are not absorbed by the stomach. Such substances, for example phosphorus, are absorbed from the intestine and reach the blood circulation via the thoracic duct, provided the mucous membrane is not damaged, in which case we must accept that the phosphorus will be absorbed from the stomach.

The small intestine, being the most active organ of absorption, also very readily absorbs poisons. It is well known that foods, drugs and poisons in solution are rapidly absorbed by the rectum, some drugs and poisons (atropine, morphine) being even more rapidly absorbed than when given by the mouth.

G. *Absorption from the Skin.*

The intact skin also is an active absorber of most poisons soluble in lipoids and in water. The fact that the application to the skin of ointments and dipping fluids containing drugs, in too strong concentrations, or over prolonged periods, have been responsible for serious and even fatal poisoning, is too well known to be mentioned. It is also known that drugs incorporated in lanolin are more readily absorbed than when other fats are used as vehicles. The vapours of certain poisons (mercury) and even finely divided powders, especially when friction is applied, are also absorbed by the intact skin. Such

substances find their way into the blood circulation probably via the sebaceous glands. It stands to reason that absorption from the skin will be facilitated when friction is applied.

Absorption from the damaged skin will take place in a manner similar to that found in the case of wounds. Irritants, which will not penetrate the intact skin in normal circumstances, will do so readily after having destroyed the superficial layers of this organ.

H. *Absorption from the Genito-urinary Tract.*

The genito-urinary tract also is a fairly active absorber of poisons. In this connection many accidents have happened in the treatment of affections of the urinary bladder and uterus. In the post-parturient state the uterus which is a much more active absorber than the bladder, absorbs drugs much more readily than at other times. In olden times the introduction of arsenic into the vagina was not an uncommon method used in criminal poisoning. According to Witthaus (1911) atropine, but not strychnine, is absorbed from the urinary bladder. Here also absorption from the intact and damaged mucous membrane must be distinguished.

I. *Absorption from the Ear.*

Non-irritant substances (atropine) in solution may be absorbed from the auditory canal. In criminal poisoning mineral acids and solutions containing arsenic were poured into the ear of sleeping victims. In these cases absorption was very rapid as the mucous membrane was corroded. Accidents have frequently occurred in the treatment of ear parasites in animals, especially with arsenical solutions.

J. *Absorption from the Eye.*

It has been established that atropine is absorbed from the intact palpebral and corneal conjunctiva, absorption is, however, slower than from mucous surfaces.

K. *Absorption from the Nasal Mucous Membrane.*

The intact mucous membrane of the nose may also absorb drugs and poisons although absorption will in most cases be very slow and never, or very rarely, lead to poisoning unless poisonous substances are applied over prolonged periods or to the damaged mucosa.

Mechanism of Absorption.

The principle underlying absorption is osmosis. Crystalloids (salts, sugar) readily diffusing through the cell membranes, whilst colloids as such (mucilages, proteins) pass through thee membranes very slow or not at all. Most gases (prussic acid) diffuse extremely rapidly through the cell membrane.

Poisons absorbed from surfaces other than that of the gastro-intestinal tract find their way directly into the main circulation. whilst those absorbed from the stomach and intestines (with the exception of fat soluble substances, which enter the blood circulation through the thoracic duct) enter the liver by way of the portal vein.

Many plants contain active ingredients, which have an irritating effect on the gastro-intestinal mucosa. In these cases the mechanism of absorption is rendered abnormal owing to damage done to the mucous membrane, and the poisoning is further complicated by the fact that harmful substances, which are present in the gastro-intestinal tract in normal circumstances, will find their way into the blood circulation. It is for this reason that a certain proportion of the phosphorus dissolved in oil in such concentrations as would damage the gastro-intestinal mucosa, will find its way into the liver through the gastric and mesenteric veins.

IV. THE FATE OF PLANT POISONS IN THE BODY.

The action of body fluids on the toxic constituents of plants from the time they enter the mouth up to the point of absorption by the gastro-intestinal mucosa will be discussed under " Factors concerned in the Determination of the Toxicity of Plants ". Very little is known about the changes induced in the toxic constituents of plants and of their fate after absorption into the blood circulation. In this respect more definite information is available in connection with the mineral poisons.

In discussing the fate of poisons in the body we have to consider that there are two ways in which poisons absorbed by the intact gastro-intestinal mucosa may find their way into the general circulation. Most of these poisons find their way directly into the liver through the gastric, mesenteric and portal veins, whilst those, which are soluble in fats only, enter the general circulation via the thoracic duct. These poisons passing through the liver undergo, as a rule, certain changes. The liver, as the main protector of the body against the effects of poisons, arrests, retains, modifies and excretes poisons, and the higher its glycogen content the greater its detoxicating capacity. The toxic constituents of plants may be deposited in the liver by the formation of insoluble or slightly soluble compounds (for example, combinations of alkaloids and biliary acids). In addition, processes of neutralisation, oxidation, reduction, synthesis and decomposition may play an important rôle in the detoxication of poisonous substances in the liver and other organs, and also in the tissues and fluids of the body. Some poisons are deposited in one or other of the organs, for example, strychnine in the central nervous system.

Witthaus (1911, p. 104), referring to experiments conducted by Czylharz and Donath said that they concluded, " that the subcutaneous cellular tissue, the muscles, or the body or lymph has the power to neutralise strychnine during life ". Dold (1914) found that fresh serum detoxicates all extracts of organs and that this detoxicating effect of serum is lost by heating it to 60° C. or by filtering it and Beutner (1926) established the fact that bovine and rabbit serum binds pilocarpine in such a manner that it can again be recovered by precipitating the serum. It is a well established fact that the body produces specific antitoxins to toxalbumins (ricin, modeccin, abrin, etc.).

Our knowledge of the distribution in the body and elimination from the body of plant poisons, especially those of South African origin, is very limited. A poison may be eliminated by certain or all organs depending on the nature of the poison. The rate of elimination, which is of so much importance in the determination of the toxicity of a substance, depends on the nature of the poison, on the organ or organs concerned in the elimination, and on the state in which these organs are. Gaseous and volatile poisons (prussic acid, ether, etc.) are mainly excreted by the lungs and skin, whilst in the elimination of other poisons the kidneys, liver, mucosa of the alimentary canal (salivary glands, gastro-intestinal glands), skin (talc and sweat glands), bronchial glands and lactating glands are concerned. Many poisons are eliminated as such (prussic acid) whilst others (carbolic preparations) are changed in the body and then excreted. Oxalic acid forms insoluble calcium oxalate in the blood, and the biliary acids from salts with alkaloids, which, being soluble in bile, are passed out with the bile and may be reabsorbed or passed out with the faeces. Again, some poisons (gases) are eliminated at a very quick rate, whilst others may take months to leave the body. This fact brings us to the cumulative effects of poisons. It is difficult to determine exactly which poisons have a cumulative effect and which not, as this effect is determined by the rate of absorption and elimination of a poison. Substances, which are absorbed quickly and eliminated slowly, will naturally have a tendency to accumulate in the body. The size of the dose and the intervals of dosage must therefore be considered when ascertaining whether a poison will have a cumulative effect or not. Poisons, which are fixed for a time by certain organs will have a tendency to exert cumulative effects. It is well known that digitalis has cumulative effects and that care must be exercised in the treatment of chronic heart diseases with this drug. It should also be mentioned here that all poisons are likely to have cumulative effects, when the organs of excretion especially the liver and kidneys are diseased, thus allowing of very slow excretion. According to Seni (1929) prussic acid is to a certain extent destroyed by blood.

Weese (1930) states that Cloetta and his collaborators have shown that striated muscle has a highly specific capacity for the fixation of digitoxin. This glucoside is bound irreversibly and is slowly decomposed into aglycon and sugar by the action of ferments. Weese holds that the cumulative action of digitoxin is attributable to the fact that it is fixed in the heart muscle, while that portion of the digitoxin that is bound extra-cardiacally is decomposed or excreted.

V. MODES OF ACTION OF PLANT POISONS.

A. Local Action.

We must distinguish between local and remote action of poisons. The local action is that which is exerted at the point of application, whilst the remote action of a poison occurs only after absorption into the blood circulation. Many plants taken per os have an irritating effect on the gastro-intestinal mucosa. This effect may be due to the toxic ingredient or ingredients (digitalis glucosides), or to one or other substances (acids) which such plants may contain in addition

to the active principle, which is mainly responsible for death. *Psilocaulon absimile* N.E. Br. contains a large amount of acid oxalates and also a narcotic alkaloid (Rimington and Steyn, 1933). Some plants (*Moraea* spp. *Homeria* spp.) cause severe irritation and even destruction of the mucosa of the gastro-intestinal tract, with the result that the mechanism of absorption is rendered abnormal. Noxious substances, which are present in the digestive tract in normal circumstances and which are not absorbed by the intact mucosa, may find their way into the blood circulation and will exert their harmful effects on the system, thus aggravating the condition of the already poisoned victim. It is, therefore, possible that a plant may cause death by virtue of its irritating properties only. Death in such cases is probably not due to some or other deadly poison contained in the plant, but to poisonous substances normally present in the digestive tract and which are not allowed to pass through the intact mucous membrane. In addition, the disturbed digestion may be the cause of the production of further harmful substances in the gastro-intestinal tract. Before concluding the remarks on local action, it must be mentioned that many plants (*Euphorbia* spp.) contain irritant juices, which, even when applied to the skin, cause severe inflammation.

B. Remote Action.

It is hardly necessary to state that it is an impossibility to cover fully the vast ground of the remote actions of all plant poisons. Therefore only a few of the most outstanding examples will be referred to under this heading.

After absorption into the blood stream plant poisons may exert their effects on the body in many ways. The rôle played by the liver in the inactivation and elimination of poisons has already been referred to under " The Fate of Plant Poisons in the Body ". Some poisons have a special affinity for and may be fixed by certain organs; hence we speak of liver, kidney, heart and nerve poisons. Poisons fixed by certain organs are inclined to have cumulative effects (digitoxin). Most poisons exert their effects on all the organs to a certain extent. As an example of the manner in which poisons may affect the system, the following instances may be quoted:—

(*a*) *Poisons Affecting the Blood.*

(1) *Red blood corpuscles.*—Poisons may change the blood by causing haemolysis (saponins), methaemoglobinaemia (nitrites, chlorates) or by attaching themselves to the red blood corpuscles and replacing the oxygen (carbon monoxide).

In these cases death is due to asphyxia as the oxygen-carrying capacity of the blood is destroyed.

Annau and Hergloz (1928) found that chronic strychnine poisoning in rabbits was accompanied by a diminution of 35 per cent. in the total red count, whilst in splenectomized rabbits suffering from chronic strychnine poisoning there was an increase of about 35 per cent. in the total red count. The latter increase is considered by them to be due to stimulation of the reticulo-endothelial apparatus.

(2) *Leucocytes and lymphocytes.*—The movements of these blood corpuscles are paralysed by some poisons (quinine), while other poisons (strychnine) again cause a hypoleucocytosis.

(3) *Serum.*—The serum is coagulated by some poisons (ricin, abrin), the result being the formation of emboli and thrombosis.

(*b*) *Poisons Affecting the Heart.*

Of the indigenous South African poisonous plants, which are heart poisons, *Dichapetalum cymosum* (Hook) Engl. (gifblaar) and *Pachystigma pygmaea* Schltr. Robyns (gousiekte bossie) may be mentioned, the latter plant causing a chronic indurative myocarditis.

Heart poisons may directly affect the heart muscle, or may affect it through the vagus and accelerator nerves, or they may affect both. Digitalis affects both the heart muscle and the vagus nerve.

(*c*) *Poisons Affecting the Blood Vessels.*

Blood vessels may be dilated or constricted by poisons. Ephedrine and histamine cause contraction of some vessels, and dilation of others, whilst digitalis causes constriction. These effects are caused by the action of the poisons either on the centres of vasodilation and vasoconstriction, or on the nerve-endings, or on the muscles in the walls of the blood vessels.

(*d*) *Poisons Affecting the Respiratory System.*

These include poisons either affecting the centre of respiration, or the vagus-endings in the lungs, or the bronchial glands or the muscles, larynx muscles, muscles of respiration (intercostal muscles and diaphragm), on the blood vessels in the lungs, etc., etc. Slowing and weakening of the respiration may be brought about in the following ways: (1) Paralysis of the centre of respiration (prussic acid); (2) paralysis of the muscles of respiration (curare); (3) paralysis of the vagus-endings in the lung (atropine), or (4) stimulation of the inhibiting centre of respiration. Stimulation of respiration can be achieved in the reverse way. Oedema of the lungs may be effected by one or more of the following conditions: (i) increased secretion of the bronchial glands (pilocarpine, arecoline); (ii) hyperaemia of the lungs; and (iii) increased permeability of the vessels in the lung. As an example of plants exerting a local effect on the lungs or the liver or both *Crotalaria dura* Wood and Evans and *Crotalaria globifera* E. Mey. may be mentioned.

(*e*) *Poisons Affecting the Nervous System.*

Different poisons may affect different parts of the central nervous system and their effects may be of a stimulatory or inhibitory (narcotic) nature. The brain is stimulated by atropine producing hallucinations, excitement, and epileptiform convulsions, whilst morphine, after a preliminary stage of excitement, which varies in different individuals, cause depression, sleep and coma. The centres (heat regulation, respiration) situated in the medulla oblongata are affected by many poisons.

Strychnine is known to exert its main effects on the spinal cord.

The following plants indigenous to South Africa exert their effects mainly on the central nervous system: *Cynanchum africanum* R. Br., *Cynanchum capense* Thunb., *Cynanchum obtusifolium* L.f., *Matricaria nigellaefolia* DC., and various *Cotyledon* spp.

A typical example of poison affecting the peripheral nerves is curare, a South American arrow poison.

(*f*) *Poisons Affecting the Gastro-intestinal Canal.*

Poisons may affect the digestive tract in various ways. Many substances cause severe irritation of the mucosa and even perforation of the gastro-intestinal wall, while others decrease or increase the gastro-intestinal movements and secretions either through acting on the wall directly or through the nerves, or nerve endings. Stimulation of the vagus causes increased movements of the stomach, whilst splanchnic stimulation retards intestinal peristalsis. Many of the South African poisonous plants are gastro-intestinal irritants in addition to causing other symptoms of poisoning.

(*g*) *Poisons Affecting the Kidney.*

Harmful substances may stimulate, irritate or even cause necrosis of the epithelium in the uriniferous tubules. If the epithelium is stimulated or irritated diuresis occurs, whilst in the case of glomerulonephritis oliguria and anuria may supervene. Irritant substances excreted by the kidneys may cause irritation of the mucosa of the ureters, urinary bladder and urethra. Haemolytic poisons, in themselves harmless to the kidneys, cause irritation of the epithelium through the excreted haemoglobin. Chronic irritation of the kidneys will ultimately lead to fibrosis of their tissues.

(*h*) *Poisons Affecting the Uterus.*

Poisons may exert their effects (inhibition or stimulation) on the uterus in the following ways: (1) through the uterus-centre situated in the lumbar region (strychnine); (2) through the uterus ganglia; and (3) by affecting the musculature itself. The uterus is much more susceptible to drug-action in the pregnant than in the non-pregnant state. Many plants containing severe gastro-intestinal irritants may cause abortion, probably in an indirect manner.

(*i*) *Poisons Affecting the Liver.*

All poisons passing through or retained by the liver probably exert, to a certain degree at least, harmful effects on this organ, resulting in regressive changes (e.g. atrophy, degeneration necrosis) or progressive changes (e.g. inflammation, cirrbosis) or both. An outstanding example of plants which mainly affect the liver is certain species of *Senecio*. With regard to the functional activity of the liver acted on by certain poisons, Whipple and Speed (1915) state: "It has been established that specific liver poisons (e.g. chloroform, phosphorus) causing histological changes in the liver cells, decrease the liver excretion of phenoltetrachlornaphthalein. Also vascular disturbances (Eck fistula, passive congestion) with or without histological evidence may cause a fall in the output of naphthalein through the liver. Sufficient evidence has been brought forward to show that the phenoltetrachlornaphthalein excretion is a valuable

index in respect of the functional activity of the liver. Ether anaesthesia for a period of two hours usually causes a depression in the naphthalein curve during the twenty-four hours following the anaesthesia.

Paraldehyde in doses sufficient to give anaesthesia and stupor for a few hours will give a definite fall in naphthalein excretion.

Chloral and urethane usually cause a decrease in naphthalein output when given in considerable amounts.

Alcohol causes a drop in the naphthalein curve when given in large doses sufficient to cause stupor for a few weeks. The drop in phenoltetrachlornaphthalein excretion is demonstrated in the twenty-four hours following administration of the drug. A drop in the naphthalein curve to two-thirds or one-half of normal indicates a definite liver injury and temporary impairment of function."

(*j*) *Poisons Affecting the Salivary Glands.*

Poisons may cause increased salivation by (1) stimulation of the salivary centre (pilocarpine); (2) stimulation of the peripheral endings of the salivary nerves (pilocarpine); (3) stimulation of the peripheral taste nerves; and (4) stimulation of the gland-cells themselves. Decrease in salivation will be caused by reverse processes, atropine, for example, inhibiting salivation by paralysing the nerves concerned.

(*k*) *Poisons Affecting Sweat Glands.*

The actions of poisons on the sweat glands are analogous to those described under " Poisons affecting the salivary glands ".

(*l*) *Poisons Affecting the Eye.*

Poisons may affect the muscles controlling the movements of the eye either directly or through their nerves. Myosis may be caused by (1) paralysis of the mydriatic centre in the brain (morphine in the dog); (2) peripheral stimulation of the oculomotor nerve; and (3) stimulation of the sphincter muscle in the iris (eserine). Mydriasis, on the other hand, may be effected by (1) paralysis of the oculomotor nerve (atropine); (2) stimulation of the mydriatic centre in the brain (morphine in the cat); and (3) peripheral stimulation of the mydriatic nerves.

(*m*) *Poisons Disturbing Processes of Metabolism.*

The means at our disposal of studying this most involved problem are very imperfect, and at present it can only be investigated to a certain extent by chemical examination of urine, faeces, and exhaled air. Many poisons cause a decrease in the oxidation processes in the body by (1) decreasing the oxygen carrying capacity of the blood (carbon monoxide, chlorates); (2) by preventing the red blood corpuscles from disposing of the oxygen they have conveyed to the tissues (prussic acid), or (3) inhibiting the intracellular processes of metabolism through partial or complete paralysis of the cells as in the case of protoplasm poisons (quinine). The processes of metabolism may, on the other hand, be increased by certain poisons acting on the centre of heat regulation.

Kahn and Goodridge (1926, p. 373) write: "Loevy, in 1907, demonstrated that hydrocyanic acid not only increased the protein catabolism, but also influenced the metabolism qualitatively. Wallace and Richards studied the effect of potassium cyanide upon metabolism and they observed that the total sulphur output was increased on the day of poisoning but, unlike the total nitrogen, it fell on the following day. The neutral sulphur fraction was increased, whereas the sulphate sulphur was diminished, showing that the oxidative processes in the body were lessened".

In strychnine poisoning there is an increase in the calcium content of the blood serum, which is due most probably to calcium being forced out of the muscles during attacks of spasms (Beznák, 1931).

Cutler (1932) found that within a few hours after the administration of carbon tetrachloride the guanidine content of the blood is increased and suggests that carbon tetrachloride poisoning is largely due to this guanidinaemia. There is a severe disturbance of carbohydrate metabolism, the blood sugar content, after a short preliminary rise, falling to a very low level. The quanidine present in the blood interferes with the oxidation processes in the tissues with a consequent rise of the lactic acid content of the blood and urine owing to the inability of the tissues to reconvert lactic acid into its precursors. The result is that the carbohydrate stores of the body are rapidly depleted and the hypoglycaemia appears to be the immediate cause of death. At the time of death the glycogen content of the liver is very low.

In animals poisoned with thallium the lipoid metabolism is disturbed, as is evidenced by the fact that there is a marked decrease in the lipoid content, or, even a complete disappearance of lipoids from the adrenal cortex, the skin and nervous system, (Buschke and Peiser, 1932).

Oxalic acid absorbed into the blood combines with the calcium present in the blood liberating potassium and sodium with the result that the ratio $\frac{Na+K}{Ca+Mg}$ is upset and an alkalosis produced.

(n) Poisons Affecting other Organs.

Stiffsickness ("stywesiekte") caused by the ingestion of *Crotalaria burkeana* Benth may be mentioned here, as it affects the hoofs of cattle. In connection with plants which affect the skin *Chrysocoma tenuifolia* Berg, the cause of alopecia in kids and lambs may be referred to here. It is not known whether loss of hair is due to the poison acting on the skin directly or whether it is caused indirectly through endocrine sympathetic disturbances. From preliminary investigations made it would, however, appear that the loss of hair is due to the latter disturbance, as is thought by some authorities to be the case in alopecia caused by thallium poisoning (Buschke and Peiser, 1932). Mackay (1931) produced a pronounced increase in the weight of the adrenal glands of white rats by repeatedly dosing them with morphine sulphate.

The fact that quite a number of hypothesis have been put forward to explain the action of poisons on the cells and tissue elements, is ample proof that very little is known about it. There are hypotheses which postulate that the reactions of cells to poisons are due to chemical changes induced in the cells affected, or changes in the interrelationship of the cell constituents, and that this modification is associated with a change in the electrical charge, which in turn causes the cell to react in certain ways. The similarity in the action of chemically closely related poisons and the fact that the action of such related poisons can, to a certain extent, be deducted from their structural formulae, have influenced some investigators to advance the hypothesis that the actions of poisons depend directly upon their chemical structure.

The discussions of Henderson (1930) and Henderson and Lucas (1932) in connection with the theories of narcosis are most interesting. They refer to the theory of Bibra and Harless, to the theories of precipitation, dehydration, water solubility, asphycia, absorption, permeability, and also to those postulated by Traub, Meyer-Overton (lipoid theory), Beutner, and Claude Bernard. The last-named authority advanced the theory that narcosis is due to the fact that narcotics cause a state of reversible semi-coagulation of the substance of the nerve cells.

There seems little doubt that the actions of the different poisons are exerted in different ways and that these actions depend on a large number of factors about which we know very little at the present time.

Acute and Chronic Poisoning.

Before concluding this chapter acute and chronic poisoning must be referred to. The quantity of a poison ingested and the time within which it is taken are the factors which determine the symptom complex in the affected subject. Highly lethal quantities of a poison taken in one dose may cause sudden death, whilst repeated small doses may cause symptoms of poisoning over prolonged periods. With regard to poisonous plant the course of poisoning (peracute, acute, subacute and chronic) is determined by the nature and amount of poison present in the plant and the time in which any quantity is taken.

Again, some plants may cause death very soon after ingestion (plants containing prussic acid), whilst others exert their actions only when a certain period has elapsed after ingestion (*Pachystigma pygmaea* Schltr. Robyns; *Crotalaria dura* Wood & Evans). This period that elapses between the discontinuation of feeding on a plant and the appearance of symptoms has in the past frequently been referred to as " incubation period ". The term " incubation period " should, however, be applied only to those cases where organisms (bacteria, protozoa) finding their way into the system, are capable of producing poisons (toxins) in the body. In plant poisoning, accumulation of poison in the body is only possible when the plant is eaten repeatedly within certain time limits. The term " period of latency " is suggested for the period of time which elapses between

the discontinuation of feeding with the plant and the appearance of symptoms, as the period of latency is quite different from that termed "incubation period" in infectious diseases.

It is indeed a difficult task to determine the toxic and lethal doses of plants which exert their effects after a certain period of latency only. In order to elucidate this point, it is necessary to consider why certain plants behave in this way. There are two possibilities for this behaviour, namely, (*a*) in the case of a certain number of these slow acting poisons it may be necessary for them to accumulate in the body of the animal before clinical symptoms appear; and (*b*) each small quantity of the poison taken in repeatedly may cause progressive processes of disease (degeneration, inflammation, etc.) in the organs. Do these processes continue after every trace of the poison had been eliminated from the body, or does the undamaged portion of this organ become affected when it is subjected to sudden increased function (resulting from sudden changes in diet, excessive exercise, etc.)? Such an affected animal may then die with symptoms of staggers resulting from further elimination of liver tissue.

Experience gained with plants like *Pachystigma pygmaea* (Schlt.) Robyns, *Crotalaria dura* Wood and Evans, *Crotalaria globifera* E. Mey., and various species of *Senecio*, support the latter view. It is well known that animals may still die from poisoning many months after having ingested these plants. Well marked lesions may be present in one or more organs without any clinical symptoms being discernible. The matter is further complicated by the fact that in *Crotalaria* poisoning in the majority of the horses there is a chronic pneumonia, whereas in Seneciosis the liver is severely damaged. It is obvious that such affected animals are much less resistant to diseases and poisons than normal animals.

These few remarks will suffice to point out the difficulty of determining the toxic and lethal doses of plants with a long period of latency.

VI. THE TOXIC PRINCIPLES OF PLANTS AND THEIR PHYSIOLOGICAL SIGNIFICANCE.

The toxicity of plants may be due to the presence of one or more of the following substances: alkaloids, glucosides, resins, picrotoxins, toxalbumins, volatile oils, alcohols (tremetol) and organic acids (oxalic acid and its acid salts). Although a number of investigators have interested themselves in this aspect of poisonous plants, our knowledge of the active principles of plants indigenous to South Africa is very limited indeed.

As a rule closely related plants have the same, or, chemically and pharmacologically closely related, active ingredients (solanin is present in a number of *Solanum* spp.), whilst in other cases such plants contain toxic principles different in their chemical nature and more of action (*Strychnos Nux-Vomica* L.) contains strychnine, which affects the spinal cord, whilst the amorphous alkaloid of *Strychnos Henningsii* Gilg. exerts its effects on the medullary centres

(Rindl, 1931). Again, the same, or similar active principles, may be found in plants belonging to different families as in the case of saponins and prussic acid.

Much has been written and said about the physiological significance of the toxic principles of plants and a number of theories have been advanced, but nothing definite is as yet known. Three main ideas are held in this connection, namely, that toxic substances contained in plants are (*a*) products of catabolism (excretory products), (*b*) produced in order to protect plants against being eaten by man and animal, (*c*) stages in the processes of anabolism in the plant. Various facts may be mentioned to prove and disprove each of these hypothesis and it seems quite feasible that one or more of the above-mentioned points may be responsible for the production of poisons in plants. The least acceptable suggestion is that a plant produces a poison in order to protect itself against being eaten by man and animal. Why should some plants and not others protect themselves? If this were the case it would appear likely that the plants most eaten by stock would be the most likely ones to produce poison in order to prevent them from being eradicated. If plants produced poisons in order to protect themselves they would most likely have concentrated these poisons in the parts growing above ground. This is not the case with many poisonous plants, as their roots or bulbs contain the largest proportion of the poison. Again, why should plants protect themselves only under certain climatic conditions, whilst at other times they are valuable stock-feeds? This is the case with *Tribulus terrestris* L. (duwweltjie), which in certain areas and under certain climatic conditions causes "geel-dikkop" ("yellow thick head"), whilst at other times it saves thousands of animals from starvation. This also is the case with a number of our most valuable veld grasses (see *Gramineae*), which when wilted and stunted often produce deadly amounts of prussic acid. Furthermore, it is inconceivable why plants growing in certain areas should protect themselves to a greater degree than those of the same species growing elsewhere. It is a well-known fact that members of the same species of plant growing in different areas may vary considerably in their toxicity, and striking variations in toxicity have been found even in members of the same species of plant growing beside each other.

The fact that many plants concentrate their toxic principles in the bark is held to be a proof of the hypothesis that these principles are excretory products of such plants. Such poisons are "eliminated" by the plant casting the bark.

The facts that many plants are more poisonous in the earlier than in the later stages of development (the development of prussic acid in *Sorghum vulgare* Pres. and *Linum usitatissimum* L.), and that poisons (prussic acid) disappear from certain plants when they are grown in darkness, are given as evidence to support the hypothesis that toxic ingredients of plants are normal products encountered in the processes of metabolism. These processes are more active in the growing than in the maturing plant, and in the plant kept in darkness photosynthetic processes are reduced to a minimum.

VII. DETECTION OF POISONOUS PLANTS AND THEIR ACTIVE INGREDIENTS IN THE BODY.

A. In the Gastro-intestinal Tract.

The examination of the stomach (rumen in ruminants) contents is of great value in peracute and acute plant poisoning as in such cases it is quite likely that remains of the plants ingested will still be found in the stomach. It is, however, in most cases not an easy matter to identify with any amount of certainty the masticated and partly digested portions of plants present in the stomach. Leathery leaves and hard fruits (seeds) will retain their original appearance to a far greater extent than those more easily digested. In the case of poisonous plants which exert their effects comparatively long after ingestion (*Pachystigma pygmaea* Schltr. Robyns, *Crotalaria dura* Wood and Evans, *Crotalaria globifera* E. Mey., and species of *Senecio*), the examination of gastric contents is of relatively little value as the animals may die weeks and even months after the plant has been eaten. On the other hand, portions of the leaves of *Dichapetalum cymosum* Hook (gifblaar) and species of *Homeria* and *Moraea* (tulips) may be found in the stomach contents of animals which have succumbed within a short while after feeding on these plants.

During life the faeces, milk and urine may be examined for the presence of any poisonous substance that is suspected. A poison may find its way into the faeces through being incompletely absorbed from the gastro-intestinal tract, or/and through excretion by the bile and gastro-intestinal mucosa.

B. In the Blood and Organs.

The methods of detection of poisons in the blood and organs cannot be so extensively applied to plant poisons as in the case of mineral poisons owing to the fact that our knowledge of the poisonous ingredients of plants, especially those indigenous to South Africa, is very limited. Very little is known of the active principles of South African poisonous plants, their distribution in the body, their extraction from the blood and organs, and their identification by chemical and pharmacological means.

I need hardly stress the point that the utmost care should be exercised in drawing conclusions from toxic substances that have been isolated from the gastro-intestinal contents, as these contents may harbour poisonous substances (for example biogenic amines), which pharmacologically may have effects on animal organs very similar to those exerted by the active principles of certain plants. The longer the period between death and the examination of the gastro-intestinal contents the greater is this danger owing to processes of decomposition.

The mere presence of a poisonous substance in an organ or organs by no means warrants a diagnosis of poisoning by such a substance, this evidence being corroborative and not diagnostic. The amount of poison present in an organ, the nature of this organ, the amount of poison ingested and the time that has elapsed between ingestion and death, are of the utmost importance in the diagnosis of poisoning.

The amount of poison present in the gastro-intestinal tract is not of such great importance in the diagnosis as the quantity present in organs to which this poison has been conveyed by the blood. Fatal quantities of poisons may be present in the gastro-intestinal contents without causing symptoms of poisoning [that is, when they are present in an inabsorbable (insoluble) form] whilst the presence of any such poison in the organs is of great diagnostic value.

The amount of poison present in an organ depends on the quantity ingested and on the period of time that has elapsed since ingestion. It is quite possible that a poison, when taken in a small quantity over prolonged periods, may cause damage to an organ or organs, and that this damage progresses after all traces of the poison have been eliminated from the body. This probably is the case in poisoning by *Crotalaria dura* Wood and Evans and in *Pachystigma pygmaea* Schltr. Robyns, as animals which have partaken of fatal amounts of these plants may only die from " Jaagsiekte " or " Gousiekte " months after they have eaten the plants.

The knowledge of the distribution of a poison in the body is essential in the collection of specimens for analysis. A trace of prussic acid in the brain is of far greater significance than its detection in the gastric contents, and in carbon monoxide poisoning no co-haemoglobin is to be found in the blood of the spleen and bone-marrow. In chronic arsenical poisoning, which occurred months before the investigation, arsenic will be found in the hoofs, claws or nails and hair of the victims and not in the liver, kidneys and gastro-intestinal contents as in acute arsenical poisoning. As a rule the most essential organs to be collected in cases of suspected plant poisoning are liver, kidneys and gastro-intestinal wall, as well as gastro-intestinal contents and urine.

It should also be mentioned here that antibodies will be detectable in the blood of individuals who have partaken of plants containing toxalbumins provided such individuals live for such a period as to allow of the development of such antibodies.

VIII. DIAGNOSIS OF PLANT POISONING.

In addition to what has been said under " Detection of Poisonous Plants and of their active ingredients in the body ", the following remarks may be made here:—

It is in many cases a very difficult task to make a definite diagnosis of poisoning. The following method of procedure is adopted by the author in the investigation of suspected cases of poisoning.

A. Anamnesis.

The *anamnesis* is of the utmost importance in poisoning, especially information concerning the feeding or grazing of the animal or animals concerned prior to the development of symptoms of poisoning. The fact that animals may develop symptoms of poisoning months after they have eaten a particular plant (*Pachystigma pygmaea* Schltr. Robyns), must be borne in mind.

B. Symptomatology.

A sudden onset of symptoms of disease, especially when several animals are affected at the same time, is indicative of poisoning. Again, symptoms like profuse diarrhœa, skin lesions (photodermatitis), inappetence, icterus, disturbances of the heart action, respiration, urinary secretion and central nervous system (convulsions, staggering, shivering, pushing, wandering about aimlessly, delirium, hallucinations, chorea, tetany, hyperaesthesia, depression, blindness, paralysis and coma), may strengthen this suspicion. Some cases of plant poisoning may resemble the course taken by infectious diseases in that they have a period of latency (incubation period) and cause the development of fever. The point of greatest importance in distinguishing between infectious diseases and cases of plant poisoning, when they make their appearance in herds or flocks, is that, as a rule, in the former case one or only a few animals will be suddenly taken ill, whilst in the latter case a large percentage of a herd or flock will develop symptoms of disease at the same time. Sometimes symptoms characteristic of certain poisonous plants assist us in diagnosing such cases (tribulosis, vangueriosis, alopecia, seneciosis).

C. Post-mortem Appearances.

These are of great value in the differential diagnosis as the lesions found in many diseases and those causes by poisonous plants are known.

D. Histology.

Also histological lesions may be of diagnostic value, e.g. cirrhosis of the liver in seneciosis; fibrosis of the myocard in "gousiekte".

E. Examination of Gastro-intestinal Contents.

In many cases of peracute and acute plant poisoning the remains of masticated and partly digested portions of the responsible plants may be found in the stomach (rumen in ruminants).

F. Isolation of the Active Principles of Plants from the Gastro-intestinal Contents and Organs and their Chemical and Pharmacological Identification.

In this connection our knowledge of South African plant poisons is very limited indeed and hence of comparatively little value in the diagnosis of plant poisoning.

It should, however, be pointed out that the utmost care must be exercised in expressing an opinion as to the nature of poisons, especially when only traces are present, in corpses and carcases, because it should be remembered that poisons like ptomaines, markedly resemble some vegetable poisons. Aconite-like, coniine-like, codeine-like, colchicine-like, veratrine-like, and strychnine-like ptomaines are known (Autenrieth, 1928). It is, therefore, most essential that wherever possible chemical tests for poisons should be confirmed by biological tests. To my mind, a positive biological test for strychnine is absolutely essential before it can be definitely stated that strychnine is present in a corpse or carcass.

IX. PROGNOSIS OF PLANT POISONING.

The prognosis depends on a large number of factors, which are fully discussed under " Factors concerned in the Determination of the Toxicity of Plants ". Suffice it to say here that in most cases of poisoning it is very difficult to predict the result not only with regard to death, but also as far as complete recovery is concerned. Furthermore, some plants exert their effects in a two-fold manner as in the case of poisoning with *Adenia digitata* (Harv.) Harms, and improvement after exhibition of severe symptoms of poisoning is by no means an indication that the patient is well and on the way to recovery. The tuber of this plant contains two poisonous principles prussic acid and a toxalbumin, modeccin. Symptoms of prussic acid poisoning set in very soon after ingestion of the tuber. The victim may, however, survive, and may only succumb to the effects of the toxalbumin, modeccin, which exerts its actions on the system within a few days after ingestion.

In the case of plants which exert their effects only after a certain period of latency, it is an even more difficult task to express an opinion as to the future health of such an animal. The sooner after ingestion of poisonous plants the animals are treated, the more favourable the prognosis will be, as the sooner the bowels are emptied the smaller the quantity of poison absorbed.

X. GENERAL PRINCIPLES OF TREATMENT OF PLANT POISONING.

The general principles of treatment of all cases of poisoning are embodied in the following rules: (A) Prevention of further absorption of the ingested poison, (B) treatment of symptoms of poisoning, and (C) promotion of excretion of the poison. In addition, the animals should be prevented from further ingestion of the poison.

(A) Prevention of Further Absorption of Poison.

The most effective method of procedure as adopted by the author is (*a*) to prevent the animals from drinking water, and (*b*) to render the poison still present in the gastro-intestinal tract inabsorbable and to remove it by the administration of purgatives on emetics or by stomach lavage. The absorption of poison still present in the gastro-intestinal canal may be retarded or prevented by administering chemical and physical antidotes. Tannic acid will, for example, cause the precipitation of insoluble alkaloidal tannates, and will therefore be of great value in preventing the absorption of poisonous alkaloids. Potassium permanganate will cause the destruction of many plant poisons through oxidation; it is said to be the most effective when in acid solution. Furthermore, some poisons exert their toxic effects in an acid environment, whilst others require an alkaline medium. Animal and wood charcoal and liquid paraffin may be used as physical antidotes. Charcoal is an active absorber of many plant and mineral poisons, and liquid paraffin, being absorbable to only a very slight extent, will when passing through the gastro-intestinal canal, carry with it a certain amount of the

poison present. When the administration of these two substances is followed by purgatives, the amount of poison absorbed can be appreciably reduced. The absorption of poisons from the gastro-intestinal tract can be further retarted by the administration of astringents (tannic acid, lime water, bismuth subnitrate, alum). It goes without saying that the purgatives to be used in cases of poisoning must act quickly, and whenever possible purgatives which require water as a solvent must be avoided, as in many cases the introduction of water will facilitate absorption of the poison. In equines arecoline, pilocarpine and eserine, administered subcutaneously, are valuable purgatives, whilst in cattle, sheep, goats, pigs, dogs, cats and birds calomel, castor oil and croton oil must be resorted to in the first place. It is not advisable to use saline purgatives in cases of plant poisoning for the reasons mentioned above.

As emetics the following may be used: Apomorphine, veratrine rhizoma veratri albi, radix Ipecacuanhae, tartar emetic, zinc sulphate, common salt and mustard. Emetics are to be used only in those animals which vomit with ease.

In the irrigation of the stomach it is essential that substances, which are likely to form insoluble compounds with the poison, be used. When plants containing alkaloids as the active principle cause poisoning, then tannic acid should be used, as it forms insoluble alkaloidal tannates and at the same time is an astringent, thus retarding absorption. Furthermore, glucose should be administered to animals in all cases of poisoning, especially where liver damage occurs, as the detoxicating effect of this organ appears to be directly dependent on its carbohydrate content.

(B) Treatment of Symptoms of Poisoning.

In most cases we have to resort to the treatment of the symptoms as they arise (symptomatic treatment), as very few specific antidotes, which will inactivate the poison in the blood stream and in the organs, are known. Cramps and convulsions are traeted with sedatives and narcotics and symptoms of paralysis with stimulants (strychnine), whilst in prussic acid poisoning we have a specific antidote in some sulphur preparations forming the harmless sulphocyanides. The administration of heart and respiratory stimulants is essential in many cases of plant poisoning.

Gastro-intestinal irritation may in many cases be effectively treated with raw linseed oil or limewater, either alone or mixed in equal parts. The author found that the beneficial effect of this mixture in the treatment of obstinate diarrhœa may be appreciably increased by the addition of a small amount of tannic acid. Other substances that have an alleviating effect on gastro-intestinal irritation are linseed and barley gruel and the whites of eggs beaten up in milk.

Other essential points in the treatment of poisoned animals is to shade them and to allow them as much rest as possible. Driving, especially in cases of animals suffering from poisoning with plants which affect the central nervous system (cynanchosis, cotyledonosis,

equisetosis), in many instances causes death, while it left undisturbed the animals stand a better chance of recovering. It is also essential that poisoned animals should receive a suitable diet.

(C) Promotion of Excretion of the Poison.

Excretion of poisons may be facilitated by the administration of purgatives, diuretics, cholagogues, sialagogues, and diaphoretics. Many purgatives stimulate the secretion of the glands of the gastro-intestinal mucosa, which excretes many poisons, and, in addition, such drugs prevent, to a certain extent, the reabsorption of bile, which carries with it poisons excreted by the liver, by causing a quick passage of the intestinal contents. The kidneys are the most important organs concerned in the excretion of poisons, hence the effect of stimulating renal secretion by means of diuretics is clear. Also the liver, salivary glands and sweat glands are active excretors of many poisons. The fact that lactating mammary glands are very active excretors of poisons, should be borne in mind, as cases of poisoning in human beings may arise from drinking the milk of poisoned animals.

The bleeding of animals suffering from poisoning is considered by some authorities to be of no value, but it seems likely that much benefit will be derived from bleeding affected animals and replacing the volume of blood lost by physiological saline solution containing calcium gluconate or by blood transfusion. Through the bleeding a certain proportion of the poison contained in the blood is removed from the body, calcium in many cases of poisoning supports the fighting powers of the body against poisons, and it has been established that the higher the glycogen content of the liver the more effective it is as a detoxicator.

In many cases of poisoning, especially when poisons causing haemolysis and reduction in the oxygen carrying capacity of the blood are concerned, blood transfusions are of life-saving value.

XI. FACTORS CONCERNED IN THE DETERMINATION OF THE TOXICITY OF PLANTS.

A. The Plant.

The most important factor concerned in the determination of the effects of a poisonous plant on any subject is the rate at which such a plant is ingested. Most striking examples of how the toxic and lethal doses of poisonous plants can vary are found amongst those plants which contain gaseous or volatile poisons which are rapidly eliminated. An animal may, for example, eat with impunity within twenty-four hours a certain quantity of a plant containing prussic acid without suffering any ill-effects, while the same quantity, if eaten within six hours, would cause death. The degree of toxicity of a plant, therefore, depends on the time allowed to the body tissues and fluids to eliminate or to destroy the poisonous principle.

It is well known that individual plants of the same species growing in different localities vary to a considerable degree in their active principle content. At Onderstepoort, Steyn (1932) found that specimens of **Cotyledon leucophylla* C.A.Sm. in the same stage of development and growing beside one another varied considerably in toxicity. Soil and climatic conditions are to a very large extent responsible for the difference in toxicity, but this cannot account for the differences in toxicity of plants of the same species growing beside each other. The latter point is discussed under "Transmission of the Degree of Toxicity of Progeny".

In spite of the fact that much time has been spent in the investigation of factors thought to be concerned in the determination of the toxicity of plants, no definite results have as yet been achieved. It is impossible here to discuss at any great length, and the following factors, which may play a rôle in the production of poison in plants, will be briefly discussed.

(*a*) *Soil and cultivation.*—The composition, character, bacterial and protozoal content, moisture content and temperature of the soil probably, in some cases at least, influence the production of poison in plants. The results of experiments with fertilizers are so variable that no definite conclusions can be drawn, except in the case of nitrates, which increase the prussic acid content of plants (Burtt-Davy, 1912; Couch, 1932). It must be mentioned that fertilizers are extensively used in the growing of medicinal plants in order to stimulate growth and thus increase the amount of active principle per unit area of soil surface. This use of fertilizers has, however, no relation to the utilization of fertilizers as far as the increase of active principle content per unit weight of plant is concerned. Tne character of the soil may possibly have an influence on the toxicity of plants, as the more porous a soil the better the aeration, and consequently oxidation and other processes dependent upon a free oxygen supply will be more active than in less porous soils. The moisture content and temperature, as well as the oxygen content of the soil are bound to influence the microbiological processes in the soil to a considerable extent. These varying conditions in the soil may be, and probably are, responsible for the production of substances of a very variable nature in soils of a different character, and these substances may in turn affect the toxicity of plants. Many farmers hold that *Pachystigma pygmaea* (Schltr.) Robyns (gousiekte bossie) growing on black clay soil, is much less poisonous than when growing on red sandy soil. It is also maintained that *Geigeria passerinoides* Harv. is most toxic when growing on limestone. In experiments conducted at Onderstepoort with *Cotyledon orbiculata* L. the specimens grown on black clay soil were less toxic after one year than at the time the experiment was begun, whi lthe reverse was the case with those specimens grown on red sandy soil (Steyn, 1932).

Cultivation produces a decrease in the toxicity and even the complete disappearance of the toxic constituents of some plants, whilst it apparently has no effect on the toxicity of other plants.

* *C. orbiculata* Burtt-Davy, A. Trans. & Swaz., I, 142, 143 (1925); ext. ref. Bot. Mag. et Journ. Bot. et extra Tvl. cit.; non Linn. (1753).

The seeds of cultivated varieties of *Phaseolus lunatus* L. constitute a valuable foodstuff, whereas those of the wild varieties contain fatal amounts of prussic acid. In cultivation there are improved conditions in connection with irrigation, aeration of the soil, and fertilization, and these probably influence the degree of toxicity of some plants. On the other hand, cultivation appears to have no noticeable effect on the toxicity of *Nerium oleander* L. (Morrison, 1926).

(*b*) *Climatic conditions.*—Temperature and moisture content of the air will to a large extent influence, as explained in (*a*), the chemical and microbiological processes in the soil. The alkaloidal content of medicinal plants growing in the same locality was found to be at its lowest in years of low temperature and deficient sunshine. *Ephedra* spp. grown in areas with a high rainfall are less toxic than those grown in localities with a low rainfall. Furthermore, these plants were found less toxic in rainy than in dry years (Ghosh and Krisha, 1930).

(*c*) *Nature and intensity of light.*—The nature and intensity of light depend on the time of the day, the altitude and the degree of cloudiness. The alkaloidal content of *Atropa belladonna* L. could not be increased by means of fertilizers, but full exposure to sunlight appeared to increase its active principle content (Ransom and Henderson, 1912), and Burman (1911) states that the alkaloidal content of this plant is at its lowest in years of low temperature and deficient sunshine. It appears that certain species of *Cotyledon* (*Cotyledon ventricosa* Burm., *Cotyledon wallichii* Harv.) are not dependent on the direct rays of the sun for the production of poison as they are almost invariably found growing under bushes and shrubs. It is, however, quite possible that some plants are to a certain extent dependent upon photosynthetic processes for the production of poison and that they do require light in the elaboration of poison Treub (Robinson, 1930) found that the darkening of the plant "*Pangium edule*" causes a decrease in its prussic acid content. It was found that plants of *Datura Stramonium* L. kept on a balcony facing east, south-east had a higher active principle content than those kept on a balcony facing north-west. Possibly certain rays of the visible and invisible spectra are essential to stimulate the production of poison.

(*d*) *Season.*—The poisoning of stock grazing under natural conditions, is most prevalent during the spring months. This is due not only to the fact that many poisonous plants are very deeprooted (*Dichapetalum cymosum* Hook) or are of a bulbous nature and hence are not dependent on spring rains for the development of young leaves and shoots, but also to the fact that many plants are most poisonous in the young stage of development. The active principle content of many plants varies in amount not only at different times of the year, but also at different hours of the day. André (Czapek, 1921) found the oxalate content of *Mesembrianthemum crystallinum* L. to be about five times higher in May than it was in August, whilst the reverse was the case with the malic acid content of this plant. Baur (Hecht, 1931) found that the percentage of active principle contained in *Atropa belladonna* L. and *Datura stramonium* L. was at its highest in the early morning hours. The early development of the leaves

and flowers of deeprooted and bulbous plants constitutes a great temptation to animals when the remaining vegetation is still dry and unattractive. It is for the same reason that so many animals succumb to plant poisoning during periods of drought.

(*e*) *Stage of development.*—Many plants may contain fatal amounts of poison when immature, but when mature they constitute valuable foodstuffs for man and animal. The unripe seeds of *Linum usitatissimum* L. may contain fatal amounts of the cyanogenetic glucoside, linamarin, whilst the ripe seeds in the form of cakes form a valuable foodstuff for stock. The wilted and stunted plants of *Zea mays* L., various species of *Sorghum* and certain other grasses contain large amounts of prussic acid, the younger the stage of growth, the higher the prussic acid content. An outstanding example of plants that are most toxic in the early stages of development is *Dichapetalum cymosum* Hook (gifblaar), in which the young leaves are much more toxic than the older ones. On the other hand, the young and mature leaves of *Cotyledon orbiculata* L. are equally toxic. The ripe berries of *Melia azedarach* L. are more toxic than the immature ones, whilst the berries of *Solanum nigrum* L. and *Solanum incanum* L. are poisonous when green and harmless when ripe.

(*f*) *Toxic parts of plants.*—The distribution of poisonous substances in plants in the same stages of development varies with almost every species of plant. The following plants may be quoted as examples: the bark and wood of the roots of *Derris elliptica* Benth are very poisonous, whilst the stems are slightly poisonous and the leaves not at all; the leaves of *Taxus baccata* L. (the yew tree) are more toxic than the fruit and it is said that the male tree is slightly more toxic than the female; the drupes of *Melia azedarach* L. are much more poisonous than the leaves; while in the case of *Datura stramonium* L. the seed contains less active principle than the leaves, stems and roots. Not only may the different parts of a plant vary in the amount of active principle they contain but the various portions of the same part may also vary to a considerable extent. Some peach, apricot and prune kernels contain fatal amounts of prussic acid, whilst the outer portion of the fruits are extensively eaten. Some plants contain their active constituents in a form other than that which exerts its poisonous effects on the body. Cyanogenetic glucosides, as such, are non-poisonous and require enzyme- or acid-action in order to liberate the deadly prussic acid.

(*g*) *State of plants.*—Some plants when dried and stored rapidly decrease in toxicity whilst others retain their active principle content for very long periods. The former will be the case especially with those plants which have gaseous (pussic acid) or volatile (ethereal oils) active principles. The active principles of other plants may, however, be destroyed by chemical processes (dehydration, oxidation, hydrolysis, ferment action, etc.), which continue or may set in after the plants have been collected. It is self evident that plants which are to be tested for the presence of any poisonous constituents formed in them under natural conditions, should not be in a decomposed state or attacked by fungi as both the decomposed matter and the fungi may of themselves liberate poisonous substances.

(*h*) *Transmission of the degree of toxicity to progeny.*—Certain plants are capable of passing on their degree of toxicity to their progeny. This has been proved to be the case with *Atropa belladonna* L. and *Papaver somniferum* L. (Hecht, 1931). Steyn (1932) pointed out that reliable results in connection with the investigation of the factors concerned in the determination of the toxicity of plants can hardly be expected when any one experiment is conducted with a large number of plants at the same time. This point came to the author's notice while conducting experiments with *Cotyledon orbiculata* L. Specimens of this plant in the same stage of development and growing beside one another were found to differ in toxicity to a considerable degree; also one and the same plant varied considerably in toxicity within short periods. It is because of these two facts that it is essential to conduct experiments with one and the same plant. Unfortunately the size and nature of many poisonous and medicinal plants do not allow of this procedure. In such cases where fields of plants have to be used in any one experiment at the same time, it would be of great importance to use the progeny of one and the same plant as, according to experiments conducted with *Atropa belladonna* L. and *Papaver somniferum* L. the toxicity of such plants will be approximately the same as that of the parent plant. *Cotyledon orbiculata* L. is eminently suited for investigations as to the influence of various factors on its toxicity as the nature of this plant is such that it can be used in one and the same experiment over a period of years. The procedure adopted at Onderstepoort is to follow the course of the toxicity of individuals of this species for one year and then submit some individuals to various influences and again follow their course of toxicity. In addition control specimens are grown and the course of their toxicity followed. It is hoped that by following this procedure we will be able in the course of time to throw some light on the factors influencing the production of poison in plants.

(*i*) *Nature of toxic ingredients of plants and channel of introduction into the body.*—The factors determining the degree of toxicity of a poison are the following: (1) Its rate of absorption. Gaseous and volatile poisons are most easily absorbed owing to their high degree of diffusibility. Poisons in solution or in a state of very fine division will act on the body more markedly as they are more rapidly absorbed, thus leaving little time for elimination or inactivation. For the same reason the toxicity of any poison is directly also plays an important rôle in the rate of absorption. It is evident that the larger the surface of absorption, the more quickly will the poison be absorbed. (2) The rapidity of its inactivation in the body. (See " The Fate of Plant Poisons in the Body ".) Vomicin, an alkaloid contained in *Strychnos Nux Vomica* L., is not poisonous when taken per os or injected subcutaneously, but only when introduced directly into the blood stream, as it is very rapidly inactivated in the tissues. (3) The rate of elimination. The more rapid the elimination of a poison from the body the less likely will it be to cause severe damage to the tissues. The highest degree of damage will be caused by a poison which has a special affinity for, or, is retained by a certain organ as its elimination will be retarded, with the result that it may exert cumulative effects. Gaseous and

volatile poisons are amongst those which are most rapidly eliminated. (4) The mode of application. The channel of absorption is an important factor in determining the degree of toxicity of a poison (see "Absorption of Poisons"). Many poisons act most rapidly when introduced directly into the blood stream, whilst others are inactive when introduced by this channel and require to be acted upon by the gastro-intestinal juices. The latter is the case with cyanogenetic glucosides, which are non-poisonous when introduced parenterally and which, when subjected to ferment or acid action in the stomach, liberate prussic acid. The same applies to mustard oil compounds, which require to be acted upon by ferments in order to liberate the active mustard oil. Croton glycerine, contained in the seeds of *Croton tiglium* L., is non-poisonous when introduced parenterally, as the gastric juice is required for the liberation of the active crotonic acid. Curare, a South American arrow poison, is absorbed slowly when taken by the mouth and is rapidly eliminated after absorption, hence it is comparatively speaking, non-poisonous when introduced by this channel. (5) Some plants require the presence of yet another plant in the gastro-intestinal tract in order to liberate its active principle in an active form. Plants may contain cyanogenetic glucosides, which require ferments, which are present in other plants, for the liberation of prussic acid. This is probably the case with *Eremophila maculata* F.M., whose cyanogenetic glucoside requires for its decomposition a ferment contained in *Acacia Georgina* Bailey (Finnemore and Cox, 1927). It should also be mentioned here that a plant may contain the pharmacological antagonist of its active principle. *Digitalis purpurea* L. for example, contains digitonin, which when administered intravenously is a pharmacological antidote to digitoxin.

From the above it is clear that when discussing the toxicity or harmlessness of a plant the following points should be mentioned, (1) origin of the plant, (2) part of the plant tested, (3) state of plant (whether fresh, wilted or dry), (4) stage of growth, (5) experimental animal used, (6) method of administration of plant (eaten or administered), and (8) the period in which the plant was eaten or administered.

Fodder plants may be rendered poisonous when attacked by fungi or decomposed by bacteria or ferments (see Fungi in Relation to Health in Man and Animal). Certain processes to which foodstuffs are subjected in the course of their preparation may also be the cause of poisoning by such foodstuffs (see "Poisonous Foodstuffs").

B. The Animal.

It is well known that the toxic or minimum lethal dose of a poison may vary to a considerable extent in human beings, in animals belonging to different classes, and also in animals of the same class. In the course of experiments conducted at Onderstepoort it was found that the degree of resistance of the same rabbit to the same dose of potassium cyanide varied considerably from day to day (Steyn, 1932b). One or more of the following factors may be responsible for this variation in susceptibility.

(*a*) *Species of animal.*—The various species of animals as a rule vary in their susceptibility to poisons. This variation may in some cases be explained on physiological and anatomical grounds. There is for example, a great difference in the method of preparation of plants for digestion and absorption as well as in the anatomical structure of the gastro-intestinal tract of ruminants and non ruminants. As a rule poisonous plants after ingestion will act more quickly in non-ruminants than in ruminant as the latter poison is much more diluted in the stomach and the passage of the ingested plants from the stomachs into the small intestine is much slower than in non-ruminants. The active ferment and bacterial action to which poisonous plants are exposed in the rumen may to some extent destroy their active principles. Canines and fowls use very little or no saliva in swallowing their food, whilst cattle, sheep, and horses, during the process of mastication, secrete enormous amounts of alkaline saliva. This alkaline saliva may destroy the actions of such active principles of plants which require an acid medium in order to exert their actions. Such acidophilous active principles will, on the other hand, have pronounced effects on the dog, in which animals this protecting influence of the saliva is absent.

Many examples of the difference in the susceptibility of the different classes of animals to the same plant poison may be mentioned. The following are the most outstanding: Horses are much more susceptible than cattle to poisoning by ricin and *Ornithogalum thyrsoides* Jacq; sheep and goats are very resistant to the ripe drupes of *Melia azedarach* L. (syringa berry), whilst pigs are very susceptible; and the quantities of some species of *Senecio*, which will cause death in dogs, has no effect on rabbits. In addition to this difference in susceptibility of animals to the same poison, many poisons produce different symptoms in animals belonging to different classes of animals, as is illustrated by the following examples: *Crotalaria burkeana* Benth, which affects the hoofs in cattle, causes staggers in horses; *Crotalaria dura* Wood and Evans causes catarrhal gastro-enteritis and cirrhosis of the liver in cattle, whilst in horses and sheep it usually affects the lungs; several species of *Geigeria* usually cause vomiting and other gastro-intestinal disturbances in sheep and goats, while in cattle it frequently produces paralysis; and morphine has a sedative effect on dogs but is a powerful nervous stimulant in cattle.

This difference in susceptibility to poisons is sometimes met with in the same class of animal. Ducks and geese are for example, about ten times more resistant to prussic acid than fowls are (Forchheimer, 1931).

(*b*) *Breed of animal.*—Highly bred animals are, as a rule, more susceptible to poisons than mixed breeds. The general resistance of the former animals has been probably reduced by methods of breeding and by being kept under artificial conditions. A thoroughbred is known to be more susceptible than an ordinary cart horse to the actions of poisons. The same applies to purebred cattle and native cattle. Experiments conducted with potassium cyanide upon white Angora rabbits, ordinary short-haired white rabbits and grey rabbits,

proved the former more susceptible than the two latter breeds (Steyn, 1932b). This phenomenon is most probably due to the selective breeding of Angora rabbits.

(*c*) *Size of animal.*—The toxic or lethal dose of a poison is determined per unit body-weight of animals, as the size and weight of animals belonging to the same class may vary to a considerable extent, especially in the case of dogs and horses. Vollmer (1931) found that small mice are less susceptible to alcohol than larger mice. Care must be exercised in the choice of experimental animals used to determine the relative toxicity of poisons, as in the case of long woolled or pregnant animals we cannot calculate the minimum lethal dose per unit body-weight. Some poisons are more toxic to small than to larger sized animals of the same class. Colchicin and hydrochinon, whose oxidation products are poisonous, are more deadly to small than to large sized mice and rats, whilst in ethyl alcohol which is detoxicated by oxidation, the reverse is true. Vollmer (1932) holds these phenomena to be proof that the degree of oxidation is higher in small than in large animals. It therefore appears essential that in the determination of the minimum lethal dose animals of approximately the same size and condition should be used. Animals with a high percentage of body fat will, when the dose is calculated per unit body weight, receive relatively higher doses than animals in normal condition. This naturally will give rise to wrong calculations as to the minimum lethal dose per unit body weight. Body fat, which has very little or no value in the detoxication of poisons in the body, places such an animal at a disadvantage if it ingests an amount of poison calculated on the minimum lethal dose per unit body weight.

(*d*) *Age of animal.*—Generally speaking, the younger the animal the more susceptable it is to the actions of poisons. There are, however, exceptions. Young rabbits are more resistant to strychnine than full grown ones, and puppies in their first and second month require more apomorphine to produce vomiting than adult dogs (Schlossmann, 1931). Young dogs withstand bigger doses of calomel than full grown ones, whilst the former are much more susceptible to santonin than the latter. Animals in extreme age are more susceptible to poisons than animals in the prime of life. This phenomenon is due, partly at least, to the impaired functions of the organs of excretion and of those organs, tissues and fluids, which play a rôle in protecting the system against the action of poisons.

(*e*) *Condition of animal.*—Animals in a bad condition or suffering from some or other disease are more likely to be affected by poisons than animals in good condition and in good health. The general resistance of the former animals are lowered and in addition poisonous plants may attack organs which are already affected by disease. On the other hand, it was found that patients suffering from strychnine poisoning and from tetanus, stand three or four times the dose of chloral which will be tolerated by an ordinary human being (Smith, 1932).

Animals with diseased organs of excretion will naturally have an increased susceptibility to the action of poisons. Inflammatory conditions in the gastro-intestinal tract, which increases the permeability

of the mucosa, facilitate the absorption of poisons. Worms which damage the intestinal mucosa will also accelerate absorption of poison from the gastro-intestinal canal. The detoxicating effect of the liver, which is of great importance in rendering poisons inactive, is greatly reduced by cirrhosis caused by liver fluke. Non-parasitic and parasitic skin diseases which destroy the protecting effect of the epidermis will naturally facilitate the absorption of poisons from the skin. Such cases of poisoning with dipping fluids frequently occur. It is, however, interesting to note that Leischman patients, as a rule, tolerate doses of tartar emetic better than individuals in good health, as antimony has a greater affinity for the Leischman parasites than for the various body tissues.

(*f*) *Sex of animals.*—It is probable that pregnant animals (and the more advanced the state of pregnancy the greater the probability) will be more susceptible to poisons than non-pregnant ones. It is not an easy task to compare the relative susceptibility of pregnant and non-pregnant animals to poisons as it is impossible to know the weight of the contents of the uterus, which should be deducted from the weight of the pregnant animal in calculating the minimal lethal dose per unit body weight. Females are, generally speaking, more susceptible than males to poisons. It is, however, quite possible that females in the lactation period may tolerate poisons better than males, as the lactating udder is an active excretor of poisons. On the other hand, lactating animals may possess an increased susceptibility to some poisons. This is the case with poisons such as oxalic acid and oxalates, which decrease the diffusibility of the blood calcium; hence lactating animals, which excrete large amounts of calcium in the milk, will be more susceptible than others. The same applies to cases of lead poisoning, as calcium facilitates the fixation of lead in the tissues.

(*g*) *Colour of animal.*—The colour of an animal plays a most important rôle in skin diseases caused by photosensitization, the unpigmented skin exposed to the direct sunlight being the only part to suffer. Those portions of the skin which are pigmented or well protected by wool or hair, are not affected. Plants responsible for photosensitization are *Tribulus terrestris* L., *Trifolium* spp. and *Hypericum aethiopicum* Thunb. to mention but a few.

(*h*) *Temperature.*—Extremes of temperature lower the body resistance and antagonise the elimination of poison by decreasing secretion. In experiments on frogs and cats Hirschfelder and his collaborators (1920) found that the toxic action of digitalis increased with elevation of the body temperature. This phenomenon is of the utmost importance in the calculation of doses of drugs for patients. The higher the body temperature the quicker the heart action, with the result that more poison will be absorbed and pass through the organs and tissues per unit time. This fact, to some extent at least, is responsible for the phenomenon that poisons are more active on hot days or when the affected individuals exert themselves. For the above reason it is quite clear why the hot sun has a detrimental effect on poisoned animals.

(*i*) *Exertion.*—Exertion will effect increased heart action and temperature, hence will render subjects more susceptible to the action of poisons for reasons mentioned under (*h*). In addition, excitement will have a detrimental effect on the condition of poisoned subjects, especially those in which the central nervous system is affected. It is well known that driving animals suffering from *Equisetum ramosissimum* Desf. and *Cotyledon* poisoning will have fatal effects, whilst many animals will recover if left undisturbed.

(*j*) *Seasonal variation in susceptibility of animals.*—Armitage and his collaborators (1932) state that the blood pressure in cats is higher in spring than in winter, probably due to an increased activity of the sympathetic part of the autonomic nervous system. The nervous system is said to be more sensitive during spring. Hogden (1931) found a seasonal variation in the amount of calcium in the blood of the South African toad. It is quite conceivable that animals will be less susceptible to the actions of poisons and drugs in winter than in summer for reasons mentioned under (*h*). Hunt (1910) in his summary says: "Season has an important effect upon the resistance of animals to certain poisons; in some cases these effects seem to depend upon seasonable variations in the activity of the thyroid".

(*k*) "*Conditioned reflexes.*"—Pavlov and Krylow (Editorial, 1930) conducted some most interesting experiments upon dogs with apomorphine and morphine. Dogs were given small amounts of apomorphine subcutaneously and at the time of injection a note of a certain pitch was sounded. After having repeated these injections several times, salivation and vomiting could be produced by the sound of the note alone. After dogs had received morphine injections on several days, salivation, nausea, vomiting, followed by profound sleep, could be caused to develop by allowing them to watch only the preparation for the injection. Such morphine treated dogs sometimes exhibited symptoms of morphine poisoning when seeing the experimenter or after the injection of a harmless fluid.

(*l*) *Conditions which favour or impede dissolution and absorption of, or, which effect changes in poisons present in the gastro-intestinal tract.*—(1) *Water.*—One of the most essential points in the treatment of animals suffering from plant poisoning is to withhold water from such animals until all the ingested plant material is removed from the gastro-intestinal tract. It stands to reason that water will facilitate the dissolution and absorption of the active principles of the ingested plants, especially those very soluble in water. Animals poisoned by *Diacheptalum cymosum* Hook, whose active principle is very soluble in water, frequently drop down dead soon after drinking water.

(2) *Drugs.*—Certain drugs when present in the gastro-intestinal tract, organs or body fluids, will protect the system against certain poisons. This is the main principle upon which we base preventive and remedial treatment of cases of poisoning. In South Africa great success has been achieved in the prevention of prussic acid poisoning in sheep resulting from the ingestion of certain grasses in a wilted state by supplying these animals with licks containing sulphur (see Graminae). Acids introduced into the gastro-intestinal tract will

facilitate the liberation of prussic acid from cyanogenetic glucosides. Macht and Finesilver (1922) found that sodium sulphate and magnesium sulphate markedly retard the absorption of phenolsulphonphthalein, potassium cyanide, chloretone, apomorphine, morphine, pantopon, cocaine, hydrochloride, strychnine, quinidin, tincture of digitalis, sodium salicylate, salol, aspirin, antipyrin, potassium iodide, urotropine, corrosive sublimate and phenol. Calomel, cascara sagrada, and castor oil did not have this effect on the above-mentioned drugs. Under "General Principles of Treatment of Plant Poisoning" the author has not recommended the use of saline purgatives on account of the relatively large quantities of water that are used to dissolve these purgatives. It is advisable to uphold this recommendation in the treatment of animals poisoned by South African plants as the active principles of most of these plants are unknown with the result that it is not definitely known whether saline purgatives will retard their absorption. Kohn and Costopanagiotis (1932) found that a 10 per cent. solution of urea injected intravenously decreased the toxicity of digitalis by 30-40 per cent.

(3) *Substances normally present in the gastro-intestinal juices.*—Acid, bacterial, ferment and enzyme action in the gastro-intestinal tract may facilitate or retard the liberation, dissolution or absorption of poisons. With regard to the rôle played by bile in the absorption of poisons, Langenecker (1930) says, that it facilitates absorption by increasing solubility, by decreasing absorption to charcoal and by rendering the cell wall more permeable.

(*m*) *Diet.*—The diet of an animal may have a pronounced effect on its susceptibility to the effects of poisons as is illustrated by the following examples: Hunt (1910) in his summary writes: "(1) A restricted diet markedly increases the resistance of certain animals to acetonitrile. (3) Diet has a marked effect upon the resistance of animals to certain poisons; the resistance of some animals may be increased forty-fold by changes in diet. (4) Certain diets, notably dextrose, oatmeal, liver and kidney, greatly increase the resistance of mice to acetonitrile; their effect is similar in this respect to the administration of thyroid. (5) The effect of an oatmeal diet in increasing the resistance of certain animals to acetonitrile is probably due in part to a specific effect of the diet upon the thyroid gland; this is an illustration of how an internal secretion may be modified in a definite manner by diet. (7) Certain diets (notably eggs, milk, cheese, and various fats) greatly lower the resistance of certain animals to acetonitrile; their effect is the opposite of that of thyroid. (10) Diet causes distinct but not very marked differences in the resistance to morphine". Graham (1915) states that "the feeding of carbohydrates to adult animals lessens their susceptibility to the production of liver necrosis by chloroform". He also concludes that "the relative difficulty with which the characteristic central lobular liver necrosis can be produced in young pups after chloroform administration is in some way referable to the high glycogen contents of their livers". Opie and Alford (1915) working on white rats found that a diet rich in carbohydrates protects the parenchymatous cells of the liver and of the kidneys from necrosis caused by chloroform, phosphorus, potassium chromate and uranium nitrate. Fat and meat

diets do not protect to the same extent as a carbohydrate diet. Opie and Alford refer to experiments conducted by Foster, who found that a protein poor diet inclines to protect dogs against ricin poisoning. Eisner (1931) found that rabbits, which when poisoned with small amounts of uranyl nitrate on an oats-water diet almost invariably survived when the diet contained beetroot, fresh green feed and the stems of cauliflower. Similar results were obtained both with the fresh and the boiled juice of cauliflower stems. Scholl (1932) increased the resistance of rats to phosphorus poisoning by feeding them on meal or dahlia bulbs. On discontinuing the feeding of meal the resistance decreased. On the other hand, a meal and dahlia diet had no effect on the susceptibility of rats to sodium cacodulate, atoxyl, and neosalvarsan. Couch (1932) states that lucerne hay, linseed cake and glucose retard the production of prussic acid in the gastro-intestinal tract, and also that cattle on a corn ration (starchy feeds) are more resistant to prussic acid poisoning. Cutler (1932) found that (1) a meat diet rendered dogs more susceptible to carbon tetrachloride poisoning as it tends to increase the production of guanidine, and (2) a calcium-rich diet and a carbohydrate diet is a preventive against carbon tetrachloride as the former diet antagonises guanidine and the latter relieves the hypoglycaemia. A calcium-rich diet to a certain extent is a protection against poisoning with oxalic acid and oxalates as these poisons cause the formation of insoluble calcium oxalate and decrease the diffusible calcium content of the blood. A diet rich in calcium also has a protective action in lead poisoning as calcium facilitates the fixation of lead in the tissues. Hence blood rich in calcium renders the system less susceptible to acute lead poisoning. Acid feeds facilitate the liberation of prussic acid from cyanogenetic glucosides, whilst alkaline foodstuffs have the opposite effect. Poisoning with iodides are counteracted by starchy feeds. The water content of the diet naturally plays an important rôle in the rate of dissolution and absorption of poisons. As a rule diets with a high carbohydrate content have a protective action against poisons as the liver is freely supplied with carbohydrates Hoekstra (1931) states that saponin not only increases the toxicity, but also favours the cumulative effects of the digitalis glucosides. Feeds which have an irritating effect on the gastro-intestinal mucosa, will be inclined to facilitate the absorption of poisons, hence increasing their toxicity. This effect is exerted by feeds with a high saponin content. Ewart (1931) states that the presence of small amounts of saponins facilitate the absorption of poisons as they increase the permeability of the epithelial layer of the alimentary canal without causing any injury to it. Plants containing tannin precipitate saponins to a certain extent, and hence protect against the effects of the latter. Plants rich in chlorophyl have a protective action against saponin poisoning as chlorophyl reduces the saponifying and haemolytic powers of saponins.

(*n*) *Tolerance and immunity in relation to plant poisoning.*— Tolerance and immunity must be distinguished from each other as they are used to describe two completely different phenomena as far as desensitization to plant poisons is concerned. Tolerance means an increase in resistance to plant poisons of a non-albuminoid nature, whilst immunity is not due to an habituation of the tissues to a

poison but to the development of specific antitoxins in the serum against plants whose active principles are of an albuminoid nature, for example, *Ricinus communis* L., *Adenia digitata* (Harv.) Harms. We must distinguish between a natural tolerance and an acquired tolerance.

(1) *Natural tolerance.*—With regard to natural tolerance we have to distinguish between the tolerance of the individual and the tolerance of the species. It is a well-known fact that animals belonging to the same class and even the same animal at different times, may vary considerably in susceptibility to poisons. On the other hand, there is a striking difference in the tolerance of different species of animals to poisons. Natural tolerance may be due to (i) diet, (ii) conditions which impede dissolution and absorption, or which effect changes in poisons present in the gastro-intestinal tract, (iii) the tissue cells being more active in the destruction (oxidation, reduction, decomposition), fixation, modification and elimination of poisons, and (iv) slow absorption from the point of application. These points have already been referred to.

(2) *Acquired tolerance.*—It was found (Steyn, 1932) that it was possible to cause the development of tolerance to *Chrysocoma tenuifolia* Berg poisoning in goats by repeatedly drenching these animals with small amounts of this plant; it was therefore decided to ascertain whether such a tolerance will also be developed in poisoning with other plants. It is a well-known fact that an active and specific immunity can be produced against those plants containing toxalbumins as active principles. These toxalbumins are abrin (*Abrus precatorius* L.), modeccin (*Adenia digitata* Engl.), crotin (*Croton tiglium* L.), crucin (*Jatropha curcas* L.), ricin (*Ricinus communis* L.), and robin (*Robinia pseudacacia* L.). This immunity, which must be distinguished from tolerance, may be developed to such an extent that an animal repeatedly treated with non-toxic amounts of the above toxalbumins may tolerate without any apparent ill-effects up to eight hundred times the minimum lethal dose. Jacoby (1924) states that according to Ehrlich (Zeitschr. f. Hyg. u. Infektionkrankh. 12 Bd. 1892) experimental abrin-immunity of mice is transmissible to the young. This transmission of immunity to abrin occurs through the milk, as the young of immunized mice show no immunity to this poison when suckled by mice susceptible to abrin, and the young of susceptible mice become immune when suckled by immune mice. Much progress has lately been made in the immunization of human beings against hay fever caused by the pollen of plants (hay fever), a problem to which many references will be found in the literature. Schamberg (1919) produced a tolerance to *Rhus toxicodendron* L. in human beings by giving *per os* small and increasing doses of the tincture to susceptible persons. Strickler, Schamberg's assistant, succeeded in preventing attacks of dermatitis in human beings caused by this plant by injecting them subcutaneously with an alcoholic extract of the plant. Schamberg has found that the "immunity" set up by his method generally does not persist longer than one month after the discontinuation of the administration of the tincture.

Sutton (1919) discusses the relation between anaphylaxis and immunity and, quoting Cooke, says that when few antibodies or none are present, the non-sensitive state exists, whereas when antibodies are numerous and attached to the body cells, the sensitive or anaphylactic state prevails; and when antibodies are in excess, with many unattached to body cells the immune state prevails. He states that " anaphylaxis and immunity are the same in principle differing only quantitatively ".

Ratner and Gruehl (1927-1928) demonstrated that normal guinea-pigs when exposed to an organic dust (horse dander) could become sensitised through inhalation. Guinea-pigs thus sensitised and subsequently exposed to the same dust after a suitable incubation period, exhibited unmistakable signs of anaphylaxis. Further experiments proved that typical respiratory anaphylaxis (bronchial asthma) can be produced in guinea-pigs by allowing them to inhale castor bean dust and again exposing them to this dust after an incubation period of two or three weeks.

Figley and Elrod (1928) refer to the occurrence of a large number of cases of asthma caused by the inhalation of castor bean dust liberated in the air from the pipes of a castor oil factory.

Petri (1930) mentions that a condition known as " fabismus " arises when the fruit of " *Vicia faba* " is eaten or when its pollen is inhaled. This condition, which is characterised by a rapid development of anaemia, icterus with urobilinuria, and swelling of the spleen and liver is supposed to be an " intolerance " to *Vicia faba*. Petri expressed no definite opinion as to whether this condition is due to direct poisoning or is an anaphylactic phenomenon.

Bürgi (1931) states that a tolerance to *Taxus baccata* L. (Yew) can be produced in horses by feeding them small amounts of the plant, and according to Kobert (1902) pigs, sheep and rodents acquire a tolerance to *Agrostemma Githago* L. after eating non-toxic amounts over certain periods.

Mackay (1931) was able to produce a tolerance to morphine in rats by administering this drug per os and found an increase of 70 per cent. in the weight of the adrenal glands in such morphine treated rats. Most of this increase had occurred in the cortex of the adrenals.

Tatum and Seevers (1931) made a valuable contribution to the study of drug addiction. They define addiction, tolerance and habituation as follows: " Addiction is a condition developed through the effects of repeated actions of a drug such that its use becomes necessary and cessation of its action causes mental or physical disturbances ".

" Tolerance is a condition developed by certain drugs such that progressively larger and larger quantities are required to produce the effects desired."

" Habituation is a condition in which the habitue desires a drug but suffers no ill-effects on its discontinuance."

Some drugs produce addiction and no tolerance (cocaine) and *vice versa* (organic nitrites) while others produce both (morphine).

With regard to strychnine and cocaine Tatum and Seevers state that experiments on animals point to increased sensitivity rather than tolerance. They state furthermore that tolerance appears to be developed only to that class of drugs which produce a reduction in the activity of cells and increased sensitivity to those drugs which increase the activity of cells.

Biggam, Arara and Ragab (1932) refer to drug-addiction in Egypt in which heroin, opium, morphine, hashish, manzoul, cocaine and mixtures of these drugs are concerned. The withdrawal symptoms exhibited by these addicts are restlessness, sleeplessness, excitability, irritability, sneezing, yawning, lachrymation, colic, diarrhœa, headaches, vomiting, and pains in the limbs. These symptoms persist for about four days and then subside. They have found that a substitution therapy with atrophine, morphine, strychnine, paraldehyde, luminal and magnesium sulphate relieve the withdrawal symptoms very markedly.

Santesson (1932) succeeded in producing a tolerance in rabbits to copper sulphate by injecting them subcutaneously with small and increasing quantities of this salt.

Simpson and Banerjee (1932) state that horses develop a tolerance to *Abrus precatorius* L. when the seeds are given in small and gradually increasing doses.

Speight (1932) states that ill-health and insanity are inevitable results of the excessive and continued use of dagga (*Cannabis sativa* Lam.).

It is a most interesting phenomenon that a tolerance is developed to one poison whilst another will cause a hypersensitivity when taken in repeated small amounts. Of still greater interest is the fact that a certain organ may develop a tolerance to a certain poison, whereas another organ will become sensitised to the same poison. As an example of the latter type of poison Caffeine, which causes desensitization of the kidney and sensitization of the central nervous system, may be quoted.

Animals, which have developed a tolerance to some or other poison (acquired tolerance) can hardly be regarded as normal as some or other physiological or (and) histological change is bound to have occurred in their system. In experiments at Onderstepoort sheep developed tolerance to *Centaurea picris* D.C. whilst they became more sensitive to *Asclepias physocarpa* Schltr. (Steyn, 1932). Rabbits after having received a preliminary treatment with increasing doses of potassium cyanide appear to develop a tolerance to this poison (Steyn, 1932b).

The nature of acquired tolerance is still an unsettled problem. This acquired state of desensitization is probably due to a mobilization of the defensive powers of the system and the following suggestions are advanced by the author with regard to the development of acquired tolerance to poisons:—

(i) *Cellular tolerance.*—When living cells are brought into contact with low but increasing concentrations of poisons, it is possible that these cells will in the course of time adapt themselves to their new environment and perform their functions in a normal way in spite of the fact that they are bathed in a fluid which under normal circumstances would have seriously interfered with their activities. To further elucidate this point I might mention drug fast bacteria and protozoa. This cellular immunity may be intracellular or extracellular or both. That is, the cells may allow the poison to enter into their interior and they may in some or other way inactivate or destroy the poison within their structure; or, they may develop their defensive powers to such an extent as not to allow the poison to enter into their protoplasm. The latter process may be termed " selective osmosis ", and is probably responsible to a large extent for decreased absorption.

(ii) *The production of antibodies (immunity).* No proof has as yet been brought forward to support the hypothesis that acquired tolerance to non-albuminoid poisons is due to the production of antibodies.

(iii) *Increased rate of inactivation, elimination and destruction of the poison.*—It would appear possible that the activities of the body tissues and the liver, as detoxicators, and of the organs of excretion (liver, kidneys, skin, gastro-intestinal mucosa, lungs, lactating glands) may be increased when sufficient time is available in order to allow of the development of such an increase in activity by gradually introducing into the system non-toxic and increasing amounts of a poison. Mackay (1931) found that the weight of the adrenals of rats increased by about 70 per cent. when these animals receive gradually increasing doses of morphine sulphate. This may be an attempt of the body to combat the effects of the poison. Tolerance to alcohol and increased susceptibility to hydrochinon are due to an increase in the oxidising capacity of the system which is brought about by repeated administrations of these substances (Vollmer, 1932 a). The oxidation products of alcohol are relatively non-toxic, whilst those of hydrochinon are more toxic than hydrochinon itself.

(iv) *Decreased rate of absorption of the poison.*—It is clear that the efficiency of the organs of absorption and elimination will to a large extent determine the susceptibility of such an animal to poisons.

(*o*) *Idiosyncrasy (hypersusceptibility).*—Again we must distinguish between natural and acquired idiosyncrasy to poisons. The author considers that natural idiosyncrasy may be due to (1) the organ already weakened by disease is attacked by a certain poison, (2) decreased rate of inactivation, elimination and destruction of the poison by the tissues, (3) increased rate of absorption of the poison, and (4) certain tissues being extremely sensitive to the action of some poisons. On the other hand, acquired idiosyncrasy may be due to (1) sensitization due to ingestion of small amounts of plants containing toxalbumins, (2) the cumulative action of poisons, and (3) to the fact that the harmful effects of a substance is increased by another poison being already present in the body.

The above points have already been referred to in previous discussions. With regard to idiosyncrasy being due to the synergistic effects of poisons, metaldehyde and menthol could be mentioned. Leibbrandt and Mayer (1929) found that these two substances, when administered at the same time, increased in their toxicity to human beings and rabbits. It is furthermore a well-known fact that drugs with synergistic effects, when administered at the same time or within short periods of each other, increase each others actions to a degree much higher than the sum of the actions of the individual drugs.

(*p*) *Direction of passage of poisons through organs.*—Kahlson (1932) drew attention to the fact that the action of a drug depends on the direction in which it passes through a cell-group. Substances of the muscarine group are much more active when passed into the heart by means of a canula, than when the whole heart with sinuses and atria is submerged in solutions of these poisons. It was established that in both cases the heart contained equal amounts of the poison. Acetylcholin causes a much more marked increase in peristalsis when it passes through the intestinal wall in the direction mucosa-serosa, than when it passes in the opposite direction (serosa-mucosa).

(*q*) *Other conditions, which may bring about a change in susceptibility to poisons.*—Vollmer (1930) found that preliminary treatment with caseosan increased the resistance of white mice to alcohol. This phenomenon is ascribed to an increase in the oxidation processes caused by the caseosan. This increased tolerance lasts from four to five days. Treatment of white mice with caseosan had no effect on their susceptibility to morphine, colchicine and hydrochinon. Similar results were obtained in white mice treated with caseosan and subsequently subjected to the effects of sufrogel. Vollmer and Buchholz (1930) reduced the susceptibility of white mice to alcohol by preliminary treatment with thyrocin, sodium lactate, glucose and methylene blue. This treatment, however, increased susceptibility to colchicin and hydrochinon. Preliminary treatment with thyroxin caused no change in susceptibility to morphine. The changes in susceptibility to the above drugs are held by Vollmer and Buchholz to be due to an activation of the oxidation processes in the body. Vollmer and Behr (1930) confirmed the results of experiments conducted by Riesser and Hadrossek in that they found that the irradiation of white mice with the Osram-Vitalux lamp (white glass) increases the tolerance of these animals to alcohol. One irradiation has the same protecting effect against alcohol as repeated irradiations. This protecting effect is present only half to one and a half hours after the last irradiation. Similar results were obtained by irradiations with the Heraeus-Mercury-Quartz lamp. Irradiation with these two lamps increased the susceptibility of white mice to hydrochinon and colchicin and had no effect on their susceptibility to morphine. These changes in susceptibility brought about by irradiation are attributed to an increase in the oxidation processes in the body. Vollmer (1931 a) experimenting upon white mice and rates found that (*a*) a single injection of glucose does not affect the narcotic action of ethylalcohol; (*b*) a too intensive irradiation of the

animal especially with the Heraeus-Quartz lamp, does not detoxicate ethylalcohol and aniline or increase the toxicity of hydrochinon. This effect is due most probably to an inhibition of the process of oxidation; (*c*) preliminary treatment with thyrocin, glucose, methylene blue, or sodium lactate increases the action of anilin; irradiation of the animal or preliminary treatment with caseosan has no effect on the action of anilin; (*d*) the actions of strychnine could in no way be influenced; (*e*) animals subjected to a preliminary treatment with caseosan or glucose showed a slightly increased susceptibility towards salvarsan; and (*f*) preliminary treatment of the animals with thyroxin, glucose, caseosan or irradiation with the Osram-Vitalux or the Heraeus-Quartz lamp had no effect on the action of methylalcohol, iso-propylalcohol, n-propylalcohol, iso-butylalcohol and n-butylalcohol.

Not only mature tissues but also embryonic cells are capable of developing a tolerance to poisons. Wilson (1922) draws the following conclusions from his experiments: " Embryonic mesemchyme cells, cultivated in weak solutions of copper sulphate and sodium arsenite, develop in the course of two days on acquired intracellular tolerance for strong doses of these two poisons ".

XII. CONDITIONS GIVING RISE TO ACCIDENTAL INGESTION OF POISONOUS PLANTS.

The following conditions are considered by the author to give rise to accidental plant poisoning in stock:—

A. Under drought conditions animals, in the absence of edible vegetation, or when such vegetation is scanty, are forced to feed on poisonous plants. As an outstanding example *Geigeria passerinoides* Harv. may be mentioned. Veld burning should also be mentioned as it frequently is the cause of plant poisoning, when stock are allowed to graze on recently burnt veld. On such grazing deeprooted poisonous plants (*Dichapetalum cymosum* Hook, *Pachystigma pygmaea* Robyns) and bulbous plants (*Urginea Burkei* Baker) sprout more quickly than grass and hence constitute a great temptation and danger to stock.

B. In winter and in early spring before the summer rains have fallen when there is no or hardly any edible green herbage, animals are attracted by the green leaves and flowers of poisonous non-deciduous trees and shrubs (*Acokanthera venenata* G. Don) and by other poisonous plants, which having deep roots or bulbs are not dependent upon spring rains for the production of leaves and flowers (*Dichapetalum cymosum* Hook, *Urginea Burkei* Baker). Allowing stock to graze on old mealie lands in winter and early spring, a general practice in South Africa, should also be mentioned here. The edible vegetation on such lands is mostly dry with the result that the animals are very much tempted to eat poisonous plants which are fresh and green [*Dimorphotheca spp.* (bietou)] or succulent (*Cucumis myriocarpus* Naud). It is obvious that thirsty animals will eat any green plants appearing in an otherwise dry veld and in this way poisonous plants become particularly dangerous.

C. It frequently happens that through the intergrowth of normal veld vegetation and poisonous plants, animals are unable to avoid the ingestion of poisonous plants when these grow in close association with grass. Striking examples of this intergrowth can be seen in grass veld infested with *Moraea* and *Homeria* spp. (tulips) and *Geigeria* spp. (specially *Geigeria aspera* Harv.).

D. Plant poisoning is of very frequent occurrence in transport and draught animals, as these hungry animals, when outspanned, partake greedily of practically any plant. In earlier days " transport riders " suffered severe losses among their oxen as they usually outspanned in valleys (vleis) near water where there frequently was abundant growth of *Homeria*, *Moraea* spp. (tulips) and *Dimorphotheca* spp. (bietou).

E. Animals imported from overseas or animals introduced into new areas often fall easy victims to poisonous plants, not being familiar with the vegetation they are unable to exercise their sense of discrimination. Acclimatization, therefore, not only implies the immunization of animals, against infectious diseases, but also a development of a sense of discrimination between edible and poisonous plants. Stable-fed animals and animals brought up under unnatural conditions also lose this sense of discrimination. Again we have to consider the possibility and probability of animals which have been reared in areas infested with poisonous plants, having developed a tolerance to these plants after the ingestion of non-toxic amounts over prolonged periods.

F. Poisonous plants may be accidentally ingested with hay, and in this way *Moraea spp. Homeria spp.* (tulips), *Ornithogalum thyrsoides* Jacq., and *Crotalaria dura* Wood and Evans, have caused heavy losses.

G. Aphosphorosis causes a craving for substances which animals in normal circumstances would not ingest. This condition may prompt animals to partake of poisonous plants.

H. Animals may acquire a craving for certain poisonous plants and other animals may follow their example. Animals are said to develop a craving for the loco weed (*Astragalus sp.*) in Western United States and for *Swainsonia spp.*, "*Cucumis myriocarpus*" and other plants (Seddon, 1930). This phenomenon may to a certain extent be responsible for sudden outbreaks of plant poisoning. In this respect sudden changes in the toxicity of plants, a fact which has been well established, must also be considered.

I. Certain plants may need certain constituents of other plants in order to liberate their active principles. This may be the case with plants containing cyanogenetic glucosides, from which prussic acid can be liberated by the action of a ferment contained in another plant or plants. In Australia it was found that the cyanogenetic glucoside contained in *Eremophila maculata* Fv. M. required an enzyme present in *Acacia Georgina* Bailey for its decomposition into prussic acid (Finnemore and Cox, 1927).

J. The evil of overstocking, which is practised in South Africa to an alarming extent, is responsible for the death of thousands of animals from plant poisoning yearly. The veld is denuded of valuable edible vegetation and the stock are left the choice of either dying from starvation or from poisonous plants. Overstocking in many cases is the cause of the repid spread of poisonous plants as they are left to grow and seed, whilst the valuable edible plants are continuously eaten and may eventually completely disappear. A fact worthy of mentioning is that plants which constitute the sole diet of animals may cause severe losses but when eaten together with other vegetation they may be harmless or even valuable in times of drought. This is the case with *Geigeria passerinoides* Harv. and *Chrysocoma tenuifolia* Berg. (Steyn 1932 a).

XIII. PREVENTION OF PLANT POISONING.

The author considers that losses from poisonous plants can be combated very successfully by (*a*) keeping animals away from dangerous areas; (*b*) allowing stock access to dangerous areas when the plants concerned are least toxic; (*c*) exercising special care during drought periods; (*d*) paying special attention to stable-fed animals, *trek* animals and stock newly introduced into areas where poisonous plants occur; (*e*) fighting the evil of overstocking; (*f*) allowing animals access to water before they are allowed to graze on reaped lands where the edible herbage is dry and on which green and succulent poisonous plants occur; (*g*) allotting grazing on which poisonous plants occur to those classes of stock which are less susceptible to the effects of the plants concerned; (*h*) using the rotation camp system; and (*i*) preventive treatment.

A. Keeping Animals away from Dangerous Areas.

This seems so self-evident that it would be a waste of time to remark on it. In areas where poisonous plants abound those portions of the farms infested with such plants could be used, if suitable, for the cultivation of crops. This has, for example, been successfully done on farms where *Dichapetalum cymosum* Hook (gifblaar) and *Melianthus comosus* Vahl abounded.

B. Allowing Stock Access to Pastures containing Poisonous Plants, but at a Time when they ar not Toxic or only slightly so.

Many plants are most poisonous in the pre-flowering and flowering stages, hence grazing where such plants occur should be used when these plants are in their last stages of development. The fact that deeprooted and bulbous poisonous plants sprout before the spring or summer rains, which are essential for the growth of grass and many other kinds of edible herbage, should also be considered here. It is obvious that animals will be tempted by any green vegetation when the rest of the herbage is dry. It is for this reason that in spring and early summer such severe losses among stock are sustained from *Dichapetalum cymosum* Hook and *Urginea burkei* Baker poisoning. In addition, the young leaves of the former plant are much more toxic than the mature ones. Veld abounding

with *Dichapetalum cymosum* Hook could, therefore, be used at very little risk when this plant has very few young leaves or mature leaves only (see *Dichapetalum cymosum* Hook). At times when prussic acid poisoning is likely to occur through the ingestion of wilted grasses, it would be of some value to allow animals to graze in the early morning as the hot afternoon sun will cause an increased production of prussic acid in the grasses concerned.

C. Exercising Special Care during Periods of Drought.

It is obvious that during periods of drought and scarcity of grazing animals will be more likely to partake of poisonous plants. In many cases they are left with the choice of dying from starvation or the effects of poisonous plants. Valleys (vleis), although they may constitute valuable grazing in times of drought, may on the other hand be dangerous owing to the prevalence of poisonous plants.

D. Paying Special Attention to Stable-fed Animals, Trek Animals and Stock Newly Introduced into Areas where Poisonous Plants Abound.

Stable-fed, trek and transport animals and animals newly introduced into areas are, when turned out to graze, much more likely to ingest poisonous plants than animals accustomed to the areas concerned and running under natural conditions owing to a decreased sense of discrimination between edible and poisonous plants. This decreased sense of discrimination in these animals is due to artificial conditions, hunger and unfamiliarity with new environments.

E. Fighting the Evil of Overstocking.

It is not intended here to go into details as this point is elucidated under " Conditions giving rise to the accidental ingestion of poisonous plants ".

F. Allowing Animals Access to Water before they are allowed to Graze on Reaped Lands where the Edible Herbage is Dry and on which Green and Succulent Poisonous Plants Occur.

The grazing of harvested lands, especially mealie lands, is practised very extensively in South Africa. In many cases most of the edible vegetation on such lands is dry hence any harmful and poisonous plants which are green (tulp) or succulent (*Cucumis myriocarpus* Naud.) will constitute a great temptation to animals grazing on such lands. This temptation will be greater when these animals are thirsty, hence the necessity of allowing the animals access to water before they are allowed on to the lands.

G. Allotting Grazing on which Poisonous Plants Occur to those Classes of Stock which are Less Susceptible to the Effects of the Plants Concerned.

The fact that some classes of stock when grazing on areas where poisonous plants occur, do not develop symptoms of poisoning may be due to the animals not eating the plant or plants, or to their being persistant to the poison contained in the plant or plants

concerned. On farms where *Matricaria nigellaefolia* D.C. poisoning occurs in cattle, the grazing could be utilized for sheep and horses as these animals were found by Andrews (1923) to be resistant to the poison.

H. Using the Rotation Camp System.

The removal of poisoned animals from one camp to another often decreases the morbidity and mortality although the poisonous plants which are the cause of the trouble are also present in the new camp. The reason for the decrease in mortality is probably due to the fact that the animals being in a new environment eat plants other than the poisonous ones for the first few days at least. The rotation camp system is of the greatest value in areas overgrown with plants which are poisonous in large amounts only (*Geigeria passerinoides* Harv.).

I. Preventive Treatment.

As a rule preventive treatment in plant poisoning is of little value. Great success has, however, been achieved in some cases by (*a*) additional feeding, and (*b*) preventive treatment with drugs.

(*a*) *Additional Feeding.*—This can be done only on farms with an adequate supply of water for the growing of crops or by those farmers who can afford to buy the necessary foodstuffs. It stands to reason that animals when allowed some substantial feed in the morning before being turned out to graze, will exercise more discrimination in feeding than when turned out hungry. In addition, some plants (*Geigeria* spp., *Chrysocoma tenuifolia* Berg) when eaten alone, will cause poisoning whilst when taken together with edible plants will not be harmful or may even be of good feeding value.

(*b*) *Preventive Treatment with Drugs.*—Great success has attended the preventive treatment of poisoning with plants containing prussic acid or cyanogenetic glucosides by means of sulphur. As a rule the addition of 5 to 10 per cent. of sulphur to licks suffices to prevent losses, but at times when conditions are favourable for heavy outbreaks of prussic acid poisoning (see *Gramineae*), it is recommended to dose the animals with sulphur in addition to allowing them access to licks containing sulphur.

In areas where there is danger of oxalic acid or oxalate poisoning (*Mesembrianthemum* spp., *Psilocaulon* spp.) it would certainly be of value to supply stock with licks containing slaked lime as it will to a certain extent form the practically insoluble calcium oxalate, which will be passed out with the faeces.

XIV. ERADICATION OF POISONOUS PLANTS.

The adage "prevention is better than cure" is very appropriately applicable to the problem of plant poisoning. Once animals have developed symptoms of poisoning very little can be achieved with treatment, as the poison has already found its way into the blood circulation. In addition it frequently happens that when symptoms are noticeable irreparable harm has been done in some or other vital organ. This is almost invariably the case in poisoning with *Pachystigma pygmaea* Robyns and *Senecio* spp. The

sooner it is realised that with a few exceptions the treatment of large herds or flocks of stock for plant poisoning is useless, the better it will be for stock breeding in South Africa. In cases where the veld is overgrown with poisonous plants (*Tribulus terristris*, *Geigeria-passerinoides*) on which the stock are dependent to a large extent for their food supply, treatment is of no value at all, as animals will, as soon as they are released after treatment, again ingest such plants. This is the case in areas where severe outbreaks of disease caused by *Geigeria passerinoides* Harv. occur. It is for the above reasons that every attempt to eradicate poisonous plants should be made. It is realised that it is almost an impossibility to eradicate those plants, which do not grow in patches and whose underground portions penetrate the soil very deeply. This is the case with some species of *Homeria* and *Moraea* (tulips), which occur so extensively in valleys and whose corms are deeply rooted, and the eradication of which will entail an enormous amount of labour and capital. Many poisonous plants can, however, be eradicated at a comparatively low cost. The methods of eradication depend on the nature of the growth and propagation of the plants concerned. Annuals produce flowers and seeds in one season and can be effectively eradicated by hand pulling or digging up. Biennials take two years to produce seeds and they may be eradicated in the same way as the annuals; they will also succumb to continued cutting down. Perennials are propagated both by seed and underground rootstocks, bulbs, corms and tubers. They may be dug up when not too deeply rooted, or sprayed. The following methods may be used in attempts to eradicate poisonous plants.

A. Spraying.

In discussing weed killers the most important point that arises is the possibility of their causing poisoning in stock. It is obvious that weed killers which are to be extensively used on pastures should not be so toxic as to cause poisoning in such amounts as are likely to be ingested with the vegetation. The toxicity of arsenical compounds precludes their use as weed killers except in special cases, for example, in localised spots.

Another point of the utmost importance in the extensive application of weed killers to pastures is the degree of damage they will cause to the edible and valuable vegetation in such solutions as will destroy the weeds. This relative destructive value of weed killers both to weeds and edible vegetation is perhaps of more importance than the degree of toxicity of the weed killers to stock, as the poisoning of stock could be prevented by not allowing them access to treated pastures until after heavy rains have fallen.

From the results of experiments conducted by Fröhner (1919), Seddon and McGrath (1930) and by the writer at Onderstepoort, it would appear that sodium chlorate is relatively speaking, not very toxic to stock. As reports from New Zealand [Editorial 1930 (a) and Lyons, 1930] and the United States of America (Editorial 1931) record it to be an efficient weed killer, sodium chlorate would best seem to satisfy the requirements for a suitable weed killer to be utilised on pastures.

However, before its use as a general weed killer on pastures can be advocated, it is essential to conduct experiments in order to determine its relative destructive capacity for the weed or weeds to be killed and for the pasture plants. It is on this property that the suitability of sodium chlorate as a weed killer on pastures depends.

Leaves with uneven, rough and hairy surfaces retain more spraying material than leaves with smooth and hairless surfaces, hence weed killers will have a more pronounced effect on the former leaves. Plants should be sprayed on a clear day and when in their early stages of development, as in these stages they are less resistant and also less spraying material is needed. The following weed killers may be found useful: (*a*) Common salt. It is used in a 20-30 per cent. solution, and is a cheap and safe spray. It is very destructive when applied in hot and dry weather as it kills plants by absorbing moisture. (*b*) Caustic soda. Used as a spray in 5 per cent. solution it will kill practically all vegetation until washed out of the soil by rain. (*c*) Blue stone (Copper sulphate). It can be used in a 2-3 per cent. solution. (*d*) Sodium chlorate and calcium chlorate. Sodium chlorate is the cheaper of the two salts and is also more effective. It is very effective for destroying thistles and many graminaceous weeds. It is recommended in 2·5-10 per cent. solutions. (*e*) Arsenical preparations: on account of their toxicity these preparations can only be used in localised spots to which stock should have no access until after heavy rains have fallen. The eradication of *Dichapetalum cymosum* Hook (gifblaar) with arsenical preparations proved a failure. Investigations into methods of eradicating the plant are being continued by the Division of Plant Industry, Pretoria.

Favourable reports were received from farmers who have attempted the eradication of *Pachystigma pygmaea* Robyns by means of spraying it with locust poison. (*f*) Copperas (iron sulphate). It is recommended in a 25 per cent. solution.

Before apply ing the above weed killers to extensive areas of grazing it would be advisable to conduct preliminary experiments on a small scale in order to determine an effective strength of the weed killer and also to what extent it will destroy valuable pasture plants.

B. Crowding Out of Edible Plants.

Overstocking and veld burning are two factors which greatly assist in the spread of poisonous plants and weeds. Areas abounding with poisonous plants may be reseeded with desirable grasses or other edible vegetation (salt bush). As many poisonous plants are more resistant than edible herbage it is doubtful whether this method of eradicating undesirable plants will be of much value.

C. Close Grazing.

If we accept as true that a herd or flock of animals grazing over the same area ingest approximately the same plants we can conclude that the more animals there are to a unit of area the less of the poisonous plant or plants present in such an area will each animal ingest. The less toxic the plant or plants are the smaller will be

the risk of the animals becoming poisoned. Many farmers temporarily overstock camps infested with *Pachystigma pygmaea* Robyns without the animals developing *gousiekte*. It stands to reason that the abundance of poisonous plants on the areas concerned is of the greatest importance in the determination of the degree of safety of such areas as grazing.

D. Digging Up.

The most effective method of eradicating plants is to uproot them, but unfortunately this method is for various reasons not always practicable. By this method many farms have been rid of *Urginea burkei* Baker, *Urginea macrocentra* Baker, and various species of *Cotyledon*. The most economical method of keeping farms free from weeds and poisonous plants is to hire somebody especially for the purpose of digging up such plants. It is astonishing the size of the area which can be cleared of undesirable plants by one man in a month's time.

E. Veld Burning.

Some farmers maintain that persistant burning of veld where *Pachystigma pygmaea* Robyns occurs renders this plant non-toxic. Even if this statement were true it would seem advisable to attempt the eradication of this plant rather than practice veld burning with all its attendant detrimental effects on the grazing.

The eradication of poisonous plants, especially annuals from cultivated lands is a comparatively easy task and is practised by many farmers by allowing lands to lie fallow and then ploughing them again before the weeds reach the seeding stage.

XV. LEGAL ASPECT OF PLANT POISONING.

Owners of property may be held responsible for losses among stock due to poisonous plants growing over or through fences, or when cuttings from such plants are disposed of in such a way as to be accessible to stock. Also sellers of foodstuffs containing poisonous plants may be called upon to pay the damage done among animals by such plants.

With regard to the presence of portions of poisonous plants in wheat (bread poisoning) the following regulation [12 (7)] of the Food, Drugs and Disinfectants Act (No. 13 of 1929) has been enacted: "Every mill in which grain is milled for human consumption shall be provided with efficient sieving and winnowing appliances so as completely to remove the seeds of Senecio (Springkaanbos) and every other poisonous or unwholesome seeds or matter. Any person selling any flour or meal containing such seeds or matter shall be guilty of an offence".

XVI. INVESTIGATION OF PLANT POISONING IN THE FIELD.

In order to conduct a satisfactory investigation of outbreaks of plant poisoning, it is not only necessary to possess a good knowledge of the symptomatology, pathology and botanical aspect of plant poisoning, but it is also essential to have a good knowledge of

psychology in general and in particular of those people with whom one has to deal in the course of such investigations. A reliable diagnosis is often to a very large extent dependent upon the information supplied by the stock-owners concerned or by the managers of their property. It frequently happens that by the time an officer arrives at a farm where cases of plant poisoning occur the owner has already made a diagnosis and supplies information which gives support to his diagnosis and does not state facts as they are. This misleading information, which is not always given intentionally, sometimes makes a definite diagnosis impossible. For example, in different camps on a farm different poisonous plants, which causes similar symptoms in stock, may abound and if the stock owner does not supply the true history of the case, it would be a difficult task to trace the plant that caused the trouble unless definite information is obtained from the examination of the gastro-intestinal contents.

Another problem which is encountered among land and stock owners is their reluctance to acknowledge the presence of poisonous plants on their farms. Most farmers want to protect the "good names" of their property and simply will not believe that there are poisonous plants on their farms. It is obvious that the information supplied by such farmers to investigating officers is misleading in every respect. This matter is further complicated when cases of plant poisoning occur on farms that are in the market. Many farmers who know or suspect poisonous plants to occur on their property are desirous of disposing of such properties. It is "business" to advertise such farms as well as possible and for this reason no mention will be made about the prevalence of poisonous plants. Many farmers who have bought farms in areas with which they are not practically acquainted, have discovered to their cost that the farm they bought is badly infested with poisonous plants.

XVII. METHODS OF ASCERTAINING WHETHER PLANTS ARE TOXIC OR NOT.

The following method of procedure is adopted by the author in the investigation of suspected poisonous plants.

If a plant not known to be poisonous is suspected of having caused poisoning in stock, there is only one way of ascertaining whether the suspected plant is the cause of the trouble or not, and that is to cause a member or members of the class or classes of stock concerned to take such a plant or to force feed such animals with the plant in question. It is hardly necessary to state that the whole plant, or parts, of the plant concerned should be fed to or introduced into the experimental animals, as very unreliable results will be obtained by using the expressed juice of the plant or extracts prepared from it. Other points of the utmost importance in the investigation of the toxicity of plants are:—

A. The use of experimental animals which belong to the same class or classes of animals which are suspected of having been poisoned by the plant or plants concerned. This is obvious as there is a great difference in the susceptibility of the different classes of

animals to poisons. The fact that some plants may cause the development of tolerance in animals running on farms where such plants occur must be considered in the choice of experimental animals.

B. The use of the same parts of the plant, which must, if possible, also be in the same state and stage of development as the plant suspected of having caused the poisoning. The plants or extracts (if extracts of plants are concerned) must be administered in the same way in which they were taken by the victim.

C. The keeping of the experimental animals, if possible, under the same conditions as those animals in which the poisoning occurred (for example in plants causing photosensitization). It is unnecessary to go into details as the above points have already been fully referred to under "Factors concerned in the Determination of the Toxicity of Plants".

With regard to the investigation of suspected cases of poisoning in human beings it is a more difficult task to draw definite conclusions as we have to apply results obtained from experiments conducted upon animals to human beings. It goes without saying that the identical material (extracts, parts of the plant, etc.), suspected to have caused the poisoning in the human beings must, wherever possible, be used in the experiments to determine their toxicity, or when these are unobtainable, similar preparations should be made.

Once a plant is suspected of having caused poisoning in stock, the following methods of investigating the problem may be followed:

A. Grazing and Tethering Experiments.

This is the most natural way of ascertaining whether a plant is toxic or harmless. Unfortunately it is not always practicable, especially in a country like South Africa with such vast dimensions, it would entail too much time and expense to conduct such experiments in a reliable manner. It must, however, be realised that those cases of plant poisoning, in which soil and climatic conditions play a rôle, must be investigated on the spot where and at the time when they occur, as the forwarding of the suspected plants to a laboratory for investigation is of no value. This is the case especially with plants suspected of causing photosensitization (*geeldikkop* and *dikoor*) and also with plants which are poisonous when wilted (prussic acid). Patches where the suspected plant occurs must be cleared of all other vegetation and the experimental animal or animals confined to these patches by means of movable enclosures or by tethering. The disadvantages of this method are that the amount of plant taken in cannot be accurately controlled and that some animals may refuse to take the plant.

B. Feeding Experiments.

Although it is of great value that the experiments with suspected poisonous plants be conducted on the spot where such cases of poisoning have occurred it is for various reasons not practicable in most cases. The large majority of suspected plants are, therefore,

forwarded to the laboratories for investigation. Although the feeding of suspected plants to animals must be resorted to when such amounts as cannot be force-fed are required to produce poisoning, this method has disadvantages, which will be shortly discussed. In most cases of feeding experiments under laboratory conditions it is a most difficult task to induce the experimental animals, even after days of starvation, to take the plants offered to them, as they are accustomed to the ordinary routine foodstuffs. The animals may take small amounts of the plant fed and may develop a tolerance to that particular plant with the result that wrong conclusions are drawn: Again definite amounts of some poisonous plants must be eaten within a certain time in order that they may exert their toxic effects. Certain quantities of plants containing prussic acid may, for example, cause death when ingested within one hour, whilst equal amounts will have no effect when eaten within three hours. Feeding experiments do not allow of the accurate calculation of the amounts of plants eaten owing to wastage and, also loss in weight of fresh and green (succulent) plants due to loss of moisture. Very frequently suspected plants are mixed with foodstuffs and then presented to the experimental animals. Some plants are poisonous only when fed alone or in large amounts (*Geigeria passerinoides* Harv., *Chrysocoma tenuifolia* Berg). Furthermore, it may be essential that the suspected plant must be ingested very soon after collection as it may decrease in or lose its toxicity. This is the case with plants containing prussic acid or volatile active ingredients. Another important factor is that in feeding experiments the animals have to be isolated. As many as twenty-seven different plants have been received at Onderstepoort on one day. The amounts of space taken up by animals fed and the amount of time spent on weighing the material before and after feeding, can easily be appreciated.

C. Force Feeding Experiments.

Animals which refuse to take suspected plants may be forced to do so by balling with the hand or balling-gun or by drenching them. The disadvantages of this method are that the normal processes of mastication and deglutition are excluded. In addition in drenching plants a large amount of water has to be added to most of them in order to render the plant drenchable. The errors that may arise from this method are firstly that mastication may decrease the toxicity or prevent, to a certain extent, the liberation of the active principles of some plants. The large amount of alkaline saliva secreted by sheep, horses and cattle during the act of feeding will reduce the action of those plants, which exert their effects most markedly in an acid environment, and will also retard the liberation of prussic acid from cyanogenetic glucosides which are dependent upon an acid environment for their decomposition. Secondly, the water added to the plant material to be drenched may, and probably will in many cases, increase the rate of absorption of the active principle, thus rendering the toxic and lethal doses smaller than they actually will be when the plant is eaten. The author has attempted, time and again, to determine the relative toxicity of *Dichapetalum cymosum* Hook when fed alone, fed mixed with foodstuffs, balled alone, balled mixed with foodstuffs, and when drenched

by stomach tube. No definite results were achieved as the animals when fed refused to take the plants. It was, however, found that the plant was slightly more toxic when drenched than when balled, especially when water was added to the plant a long time before drenching. This result is quite conceivable as the active principle of this plant is water soluble.

Another disadvantage of the method of drenching is that a large amount of plant material is introduced into the stomach (rumen in ruminants) within a very short time. This naturally allows of and leaves little time for excretion of the active principles, quick absorption of the plants concerned, with the result that these plants will be more toxic when drenched than when eaten.

It has been stated by some critics that the drenching of plant material will cause some of the drenched material to flow right through the stomach (fore-stomachs in ruminants) into the small intestine, with the result that the undigested plant material will cause intestinal irritation with consequent diarrhœa. If the drenching is executed with any amount of discretion, this will not happen. Drenching experiments conducted by the author upon unstarved animals showed that amounts of plant material measuring up to five litres very rarely, and amounts up to three litres never found their way into the omasum and abomasum.

In addition large numbers of ruminants and non-ruminants are repeatedly drenched yearly at Onderstepoort with plants, and none of the experimental animals have developed diarrhœa after having been drenched with a non-poisonous plant.

Another disadvantage of the drenching method is that plants containing gaseous (prussic acid) or volatile active ingredients, lose a large percentage of these ingredients in the course of preparing the plants for drenching. Such plants when drenched will, therefore, be less toxic than when eaten.

The advantages of this method, however, are that (*a*) the plant finds its way into the animal very soon after collection; (*b*) the dosage is accurate; (*c*) a minimum of time for the completion of the experiments is required, and (*d*) all animals used in different experiments can be placed in one stable or enclosure and need not be isolated as in the case of feeding experiments.

The method of balling is only of value when small amounts of plant material are to be dosed, as otherwise it would entail an enormous amount of time especially if a number of plants are for investigation received at the same time.

If we consider the foregoing discussion, it appears that the method of drenching by stomach tube is the most reliable and most time-saving method, except in cases where animals have to take in large amounts of plant material daily, in which case it would be impossible to drench such amounts. It is for the above reasons that the method of drenching experimental animals by stomach tube has been adopted at Onderstepoort as a routine method, except in those cases where animals will take the plant material voluntarily without excessive starvation.

The following technique is employed by the author in the preparation of the plant material and drenching of the animals.

D. Preparation of the Plant Material for Drenching.

It is impossible to put on paper the many details in the methods of preparation of plant materials for drenching; these can be acquired through personal experience only.

As already stated, plants should be administered in the stage of development and state in which they are suspected of having caused poisoning and also by the route through which they have entered the system. Very serious mistakes have been made by expressing the juice of plants and drenching these to animals, or by preparing extracts of plants and drenching these, or even injecting them into animals. If reliable results are to be obtained the plant as such, and not its juice or extracts prepared from it, should be administered by stomach tube, unless of course the juice or extract is suspected of having caused poisoning. It is also essential that the prepared plant material should not be left mixed with water for a long time before drenching, as non-poisonous plants may in this way be rendered poisonous. Nitrates may be reduced to the more poisonous nitrates and plants containing mustard oil compounds (mustard seed cakes) and Cyanogenetic glucosides (linseed cakes) are liable to liberate, when moistened and left standing, toxic or lethal amounts of mustard oil and prussic acid respectively.

E. Drenching of Animals.

Poultry, Rabbits and Cats.

The plant material is minced when fresh, and ground, when dry, and in order to render it fit for easy passage through thin stomach tubes, it is then forced through a finely meshed sieve by means of a spatula. After this procedure there is very little likelihood of the plant material causing stoppage of the stomach tube. The beaks of birds are easily opened by hand for the introduction of the stomach tube. A safe and easy way of keeping the mouth of a rabbit and cat open is to place a piece of rubber tubing (the same thickness as that used for the stomach tube) behind or over the teeth in the upper and lower jaw, thus pulling the jaws apart. If pieces of string are used instead of rubber tubing, necrosis of the gums will set in when the same animal has to be dosed repeatedly within short periods. Another point of importance is that the material drenched should be continuously shaken during drenching, otherwise the plant material is liable to settle at the bottom of the funnel and block the tube. It is therefore essential that the stomach tube be fixed not to an ordinary glass funnel but to a bulbous container after the fashion of a separating funnel (without the cork used in the separation of the fluids). The stomach tube used in fowls is about 0·5 cm. by 60 cm., whilst that used in rabbits and cats is about 0·75 cm. by 80 cm. The volume of material drenched at a time should not exceed 100 c.c. in poultry and 150 c.c. in cats and rabbits. The volume of material drenched that will be tolerated naturally depends on the size of the animal and on the amount of food present in the stomach (crop).

Dogs and Pigs.

These animals are also drenched when they refuse to take the material fed to them. As dogs and pigs vomit very easily the volume of material drenched, the results of the experiments, especially with irritant substances, should be carefully considered before drawing any conclusions. The plant material is minced or ground and administered through a stomach tube about 1·25 cm. to 1·5 cm. in diameter and about 150 cm. long. An ordinary funnel could be attached to the stomach tube and the material shaken in the flask and poured slowly into the funnel so as to prevent the settling of the plant material at the bottom of the funnel. The pouring of a small quantity of water into the funnel (or bulb) attached to the stomach tube, and allowing this water to run down the tube just as the material to be drenched is poured into the funnel is of great value in preventing blockage of the tube. The volume of material to be drenched again depends on the size of the animal and the amount of ingesta present in the stomach. The mouths of young dogs and pigs can be opened by hand, whilst a piece of rubber covered wood with a central hole (for the passage of the tube) must be introduced cross-wise into the mouths of fullgrown dogs and pigs. Pigs will sometimes drink fluids from horns or old boots from which the points have been removed.

Sheep and Goats.

The procedure is the same as that described in dogs and pigs. Sheep and goats tolerate large volumes of material and can be drenched more than once on the same day without any apparent ill-effects. The stomach tube should measure 17·5 cm. to 2·0 cm. in diameter and 150 cm. in length. Three litres of material are easily tolerated by unstarved fullgrown sheep and goats. The mouths of these animals are easily opened by hand.

Bovines.

The stomach tube should be 2·25 cm. in diameter and 200 cm. long. Full-grown bovines may receive five litres of fluid without showing any ill-effects. The tongue must be held, and a rubber-covered piece of wood with a central hole must be placed cross-wise in the mouth and the tube passed through the hole.

Equines.

In equines the stomach tube can be passed either through the mouth or through the nose. The latter method is by far the best as the animals often resent the introduction of the gag, which frequently causes damage to the gums. As a rule the introduction of a tube through the nose can be done with very little trouble. Full-grown horses easily tolerate three litres of fluid.

For years the method of drenching animals has been extensively used in all classes of stock, dogs, rabbits and poultry at Onderstepoort. In many cases the same animal has been drenched daily (except Sundays) for months, the stomach tube at times being introduced as often as four times daily and in no case were any deleterious effects noticed both during the period of experimentation and at autopsy.

XVIII. REASONS FOR NEGATIVE RESULTS IN EXPERIMENTS WITH SUSPECTED PLANTS.

From previous discussions some of the reasons for negative results obtained in experiments with suspected poisonous plants are quite obvious, but it seems advisable to mention them again for the sake of completeness. Negative results may have been obtained because A. the plant was non-poisonous; B. non-toxic amounts had been fed or drenched; C. non-toxic parts of the plant had been given; D. the plant had lost its toxicity owing to a change in climatic conditions or after collection; E. the plant was in a non-toxic stage; F. the plant had been fed with too much additional food; G. the experimental animals were not kept under the condition necessary for the production of symptoms (photosensitization, *cynachosis*, *equisetosis*); H. animals which possess a natural or acquired tolerance or immunity to the plant were used in the experiments; I. animals were not kept under observation long enough (plants which cause symptoms of poisoning after a long period of latency); and J. it may have been necessary for the animal to have ingested some other plant along with the poisonous plant before the latter was able to liberate its active principle (for example, a plant may contain a cyanogenetic glucoside, whilst the enzyme necessary for its decomposition may be lacking in the plant concerned but contained in another plant (Finnemore and Cox, 1927).

XIX. REASONS FOR POSITIVE RESULTS IN EXPERIMENTS WITH SUSPECTED PLANTS.

These may be A. the plant is poisonous; B. too large amounts of the plant were introduced into the animal within a certain time; and C. the plant constituents may have changed during the process of preparation for drenching.

A point of importance is that animals fed on one plant only over long periods may develop symptoms of disease which are not due to the presence of poisonous substances in the plant concerned, but which are caused by the absence in the plant of some or other ingredient or ingredients essential for the maintenance of health and life. This is the case with plants deficient in minerals, vitamins, proteins, fats, etc. In addition plants may cause death by virtue of mechanical injury.

XX. LOSSES DUE TO PLANT POISONING.

It is very difficult to obtain reliable figures with regard to losses in stock sustained through plant poisoning as only those cases in which a large number of animals are involved are reported. The state of affairs is not exaggerated when it is stated that in South Africa more stock are lost annually from plant poisoning than from any other disease. The Senior Stock Inspector of Griqualand West reported to the author that *Geigeria passerinoides* Harv. (vermeersiekte) has taken toll of over a million sheep in Griqualand West and the south eastern portions of South-west Africa in the years 1929-1930. In the years 1926-1927 the losses from Tribulosis (geeldikkop) in the north-western Cape Province were calculated to be

between six and seven hundred thousand small stock. In the Uniondale-Willowmore area *Chrysocoma tenuifolia* Berg causes the loss annually of thousands of kids and lambs from *kaalsiekte*. In addition *Dichapetalum cymosum* Hook (gifblaar) and *Urginea burkei* Baker causes heavy losses yearly in stock in the Transvaal, whilst *Senecio spp.* (dunsiekte) have made the breeding of horses impossible in certain parts of the Union of South Africa and Basutoland. In some years wilted grasses (*geilsiekte*, prussic acid poisoning) cause very high mortaily in small stock in the semi-arid regions of South Africa. Tulip (tulp) and *Cotelydon* poisoning is so common that it need hardly be mentioned. Not only in South Africa, but also in America, New Zealand, Australia, Central Africa and India stock poisoning is very common. In Montana and Colorado over two hundred million dollars damage is done to the stock industry by plant poisoning every year.

XXI. ACTION OF POISONS ON FOETUSES.

It is possible for a poison to exert its harmful effects on the wall directly or indirectly through the nervous system of the pregnant uterus or on the foetus or on both. The expulsion of the foetus may be caused by the poison inducing contraction of the uterus or by bringing about the death of the foetus, which is then expelled by the uterus or in both these ways. It is a well-known fact that drastic purgatives very frequently cause abortion.

XXII. INDIRECT POISONING OF HUMAN BEINGS.

Human beings may become poisoned by A. eating the carcases of animals that have died from poisoning, B. drinking, or using in their diet, the milk of poisoned animals; and C. eating honey prepared from the flowers of poisonous plants.

A. Carcases of Poisoned Animals.

The edibility of the carcase, or a part thereof, of an animal which has died from poisoning depends on the channel by which the poison found entrance into the body. If the animals received the poison per os, the flesh can be safely eaten as has been proved repeatedly by a number of investigators. Fröhner (1919, p. 23) states that according to results obtained by his experiments and those of other investigators the flesh (including heart, liver and kidneys) of sheep, rabbits, geese, ducks, fowls, doves and a bovine poisoned with strychnine, eserine, pilocarpine, veratrine, apomorphine, arsenic, oleandrine and lead can be eaten with impunity. Some authors ate the flesh themselves, others fed dogs or examined the flesh for the presence of the poison. Ostertag (1922) also refers at length to the fact that the flesh of poisoned animals could be consumed with safety. It is advisable, as a rule to discard the organs of excretion as here the poison may be found in dangerous amounts. It is for this reason that the liver, kidneys, udder and milk, stomach and intestines should be discarded. If the poison was introduced subcutaneously and intromuscularly as is the case when animals are killed by poisoned arrows, all the flesh, except that part immediately surrounding the point where the arrow struck the animal, is edible.