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Plant Poisoning in Stock and the Development of Tolerance.

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INTRODUCTION.

A.—General.

As 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 decided to ascertain whether such a tolerance would also be developed in poisoning by 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* Linn.), modeccin (*Adenia digitata* Engl.), crotin (*Croton tiglium Linn.*), curcin (*Jatropha curcas* Linn.), ricin (*Ricinus communis* Linn.), and robin (*Robinia pseudacacia* Linn.).

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. This highly developed immunity is due not to an habituation of the tissues to the poison but to the development of specific antitoxins in the serum.

Much progress has lately been made in the immunisation of human beings against the pollens of some plants (hay fever), a problem to which many references are to be found in the literature.

B.—Historical.

Schamberg (1919) produced a tolerance to "*Rhus toxicodendron*" 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; 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, which the authors term "respiratory 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 to 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 expresses no definite opinion as to whether this condition is due to direct poisoning or is an anaphylactic phenomenon.

Bürgi (1931) states that a tolerence to *Taxus baccata* (Yew) can be produced in horses by feeding them small amounts of the plant.

Mackay (1931) was able to produce in rats a tolerance to morphine 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.

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, diarrhoea, 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 atropine, morphine, strychnine, paraldehyde, luminal and magnesium sulphate relieves 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* 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*).

ONDERSTEPOORT EXPERIMENTS.

ASCLEPIADACEAE.

Asclepias physocarpa Schltr.

Registered number: Onderstepoort Spec. No. 5333; 7/1/32.

Common name: Melkbos; wild cotton; milkweed.

Origin: Entembeni, Hluhluwe, Zululand.

State and stage of development of plant: Dry and in late flowering and seeding stage.

The results of experiments to determine the toxicity of this plant and to ascertain whether animals are liable to develop a tolerance when repeated and increased amounts of this plant are ingested are recorded in the following table :—

TABLE I.

EXPERIMENTS WITH *ASCLEPIAS PHYSOCARPUS* SCHLTR. ON SHEEP.

D.O.B. No.	Quantity of plant given and dates of dosage.	Total amount of plant given. gm.	Period of dosage.	Result.
28203	100 gm. on 13/1/32	100	1 dose only	Within two hours after dosage dyspnoea and an accelerated pulse setin. In the course of the next two days cyanosis, hoven, groaning, pronounced dyspnoea, a weak and accelerated pulse, fever, inappetence, apathy and a pronounced foetid diarrhoea were present. Improvement set in on the third day, the animal being in normal health again on 25/1/32.
26446	300 gm. on 12/1/32	300	1 dose only	Symptoms set in within one hour after dosage—apathy, inappetence, cyanosis, accelerated pulse, dyspnoea, fever, the animal dying with symptoms of asphyxia seven hours after dosage. *Post-mortem appearances:* General cyanosis, pronounced hyperaemia of the lungs and spleen, localised hyperaemia of abomasum, slight acute catarrhal duodenitis and caseous lymphadenitis (bronchial lymph glands).

TABLE I—(*continued*).

D.O.B. No.	Quantity of plant given and dates of dosage.	Total amount of plant given. gm.	Period of dosage.	Result.
32313	20 gm. daily * from 16/1/32–19/1/32	80	4 days....	Diarrhoea with its accompanying symptoms set in on 19/1/32. 20/1/32—profuse diarrhoa; animal appears very ill. Dosing discontinued. Treated with a mixture of carron oil ... 1·0 gm. of tannic acid. 25/1/32—appears to be in normal health.
31578	20 gm. daily from 14/1/32–17/1/32 10 gm. daily from 18/1/32–1/2/32 20 gm. daily from 2/2/32–7/2/32 30 gm. daily from 8/2/32–15/2/32 40 gm. daily from 16/2/32–28/2/32 70 gm. daily from 29/2/32–6/3/32 80 gm. on 7/3/32.	1510	54 days...	17/1/32—inappetence and dyspnoea; hence daily dose reduced to 10 gm. 7/3/32—within four hours after dosing, diarrhoea and symptoms similar to those described above appeared; death occurring at 4 p.m. *Post-mortem appearances:* Pronounced general cyanosis, pronounced hyperaemia of lungs; slight hyperaemia of abomasum; slight acute catarrhal duodenitis and jejunitis; pronounced acute catarrhal colitis with haemorrhages in the mucosa; oesophagostomiasis (nodular form).
31485	5 gm. daily* from 20/1/32–1/2/32 10 gm. daily from 2/2/32–7/2/32 20 gm. daily from 8/2/32–14/2/32 30 gm. daily from 15/2/32–21/2/32 50 gm. daily from 22/2/32–24/2/32 Not dosed from 25/2/32–6/3/32 50 gm. daily from 7/3/32–13/3/32 60 gm. daily from 14/3/32–17/3/32	1105	58 days...	25/2/32—pronounced diarrhoea accompanied by inappetence, apathy, dyspnoea and an accelerated and weak pulse. Treated with carron oil + 1·0 gm. of tannic acid. 7/3/32—apparently healthy. 18/3/32—animal appears very ill—pronounced foetid diarrhoea and fever. 28/3/32—apparently healthy.

* Except Sundays.

From the above table it would appear that *Asclepias physocarpa* Schltr. is a severe gastro-intestinal irritant and that sheep are not likely to develop a tolerance when this plant is taken repeatedly in small amounts. On the contrary, it appears that there is a tendency for the development of cumulative effects when non-toxic amounts of the plant are taken continuously.

COMPOSITAE.

Centaurea picris DC.

Registered number: Onderstepoort Spec. No. 4594; 8/12/31.

Common name:

Origin: On cultivated lands, Carolspoort, De Aar.

State and stage of development of plant: Dry and in flowering and early fruiting stage.

This plant is referred to in the article titled "Poisoning of Human Beings by Weeds contained in Cereals (bread poisoning)" appearing elsewhere in this report.

The following table reflects the results obtained in an attempt to produce a tolerance to this plant in sheep:—

TABLE II.

EXPERIMENTS WITH *CENTAUREA PICRIS*, DC. ON SHEEP.

D.O.B. No.	Quantity of plant given and dates of dosage.	Total amount of plant given. gm.	Period of dosage.	Result.
Merino Sheep 31943 (full mouth)	8/12/31—600 gm. (in two doses of 300 gm. each)	600	One day...	8/12/31. Symptoms appeared within two hours after the second dose. Pronounced dyspnoea, hoven, groaning, weak and accelerated pulse, apathetic and fever. Died within twenty hours after first dose. *Post-mortem appearances:* General cyanosis; heart in systole; marked hyperaemia of lungs; nodular oesophagostomiasis.
Merino Sheep 31825 (full mouth)	9/12/31 — 300 gm., 10/12/31—300 gm., at 8.30 a.m., 300 gm. at 2 p.m.	900	Two days.	Symptoms appeared at 3 p.m. on 10/12/31 and were similar to those described in sheep 31943. Death occurred within thirty-six hours after the first dose. *Post-mortem appearance:* Intense general cyanosis; hydroperitoneum; hydrothorax; hydropericardium; pronounced hyperaemia and slight oedema of the lungs; acute catarrhal gastro-enteritis with numerous haemorrhages in mucosa of of small intestine; oesophagostomiasis.

TABLE II—(*continued*).

D.O.B. No.	Quantity of plant given and dates of dosage.	Total amount of plant given. gm.	Period of dosage.	Results.
Merino Sheep 31578 full mouth)	300 gm. daily* from 1 1/1 2/3 1 to 17/12/31. 300 gm. daily from 18/12/31 to 22/12/31. (23/12/31—300 gm. 9 a.m. and 300 gm. 2 p.m. 24/12/31—300 gm. at 9 a.m. 300 gm. at 2 p.m.)—Tolerance test.	3700	14 days...	15/12/31. Apathetic; inappetence, fever, dyspnoea, strong and accelerated pulse. Not dosed. 16/12/31.—Appeared healthy. 23/12/31–24/12/31 : Tolerance test. No ill-effects were noticeable.
Merino Sheep 28895 (full mouth)	28/12/31—300 gm. at 8.30 a.m., 300 gm. at 2 p.m.	600	One day...	Died within twenty hours after the first dose with symptoms similar to the above. *Post-mortem appearances :* General cyanosis; congestion of subcutaneous tissues; hydroperitoneum; hydrothorax; dilatation of both heart ventricles; pronounced hyperaemia and slight oedema of lungs; pronounced hyperaemia of and haemorrhage in the bronchial, mediastinal and retrophyrangeal lymph glands; marked acute catarrhal gastro-enteritis.
Merino Sheep 31485 (full mouth)	100 gm. daily from 29/12/31–2/1/32. 200 gm. daily from 4/1/32 to 9/1/32. (11/1/32–300 gm. at 8.30 a.m., and 300 gm. at 2 p.m. 12/1/32–300 gm. at 8.30 a.m., 300 gm. at 2 p.m.)—Tolerance test.	2900	15 days...	This animal developed no symptoms of poisoning.

* Except Sundays.

The above results tend to show that small and increased amounts of *Centaurea picris* DC. are liable to produce a tolerance in sheep, in as much as a dose of 600 grams of the dry plant caused death in susceptible sheep, whilst it produced no ill-effects in sheep which had been subjected to a preliminary treatment with non-toxic amounts of the plant.

The fact that 600 grams of the dry plant caused death in sheep 28895 on 28/12/31 is proof that the plant has not decreased in toxicity on storage.

Muir (1928) found *Centaurea melitensis* on wheatlands in the Riversdale area. No records of its toxicity could be found in the available literature.

DISCUSSION.

Tolerance and immunity must be distinguished from each other as they are used to describe two completely different phenomena as far as desensitisation to plant poisons is concerned.

Tolerance means an increase in resistance to plant poisons of a non-albuminoid nature. The nature of this resistance is still an unsettled problem. This state of desensitisation is due probably to a mobilisation of the defensive powers of the system and the following hypotheses may be advanced with regard to the development of acquired tolerance to poisons :—

(a) *Cellular immunity.*—When living cells are brought into contact with low but increasing concentration 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 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."

(b) *Increased inactivation and (or) augmented rate of 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.

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 desensitisation of the kidney and sensitisation of the central nervous system, may be quoted.

According to Tatum and Seevers (1931) those drugs, which decrease the activity of cells, tend to cause the development of tolerance, whilst those which stimulate the activity of cells, tend to produce an increased sensitivity.

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. Desensitisation may in many cases be explained by a cumulative action of that particular poison, as is, for example, the case in repeated doses of strychnine and digitalis.

Contrary to tolerance, immunity to certain plant poisons (toxalbumins) is a definitely conceived phenomenon, in that, by reason of their albuminoid nature, they cause the production of antibodies in the body tissues.

Tolerance was produced in sheep to *Centaurea picris* DC. whilst *Asclepias physocarpa* Schltr. appeared to cause the development of an increased sensitivity.

SUMMARY.

(1) It is possible to cause the development of tolerance in animals, to certain poisonous plants, by drenching them with small and increasing quantities, whilst others do not produce this phenomenon and may even cause sensitisation, or have cumulative effects.

(2) The well known fact that animals, newly introduced to farms infested with poisonous plants, are much more liable to succumb to plant poisoning than animals born and reared on such farms, is most probably partly due to an acquired tolerance developed in the course of time by repeatedly partaking of small quantities of these plants. It is fully realised that discriminate feeding, which is a characteristic of stock reared in areas infested with poisonous plants, plays a very important rôle in the prevention of plant poisoning in these animals.

(3) Theories of tolerance and desensitisation are discussed.

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