In the present state of the theory, no object is to be gained in pursuing these analogies further. They serve, however, to show directions in which further investigation is to be carried out.

It is clear that if a magnetic field is capable of orienting these aggregates, then a substance composed of them will rotate the plane of polarisation of light.

"The Pharmacology of Aconitine, Diacetylaconitine, Benzaconine and Aconine considered in Relation to their Chemical Constitution." By J. THEODORE CASH, M.D., F.R.S., and WYNDHAM R. DUNSTAN, M.A., F.R.S. Received January 13,—Read February 3, 1898.

(Abstract.)

The investigation which is described in the present paper has been carried out with pure specimens of the alkaloids aconitine, aconine, and benzaconine, the chemistry of which has been fully studied since 1891, by one of us in conjunction with his assistants and pupils, and forms the subject of numerous papers which have been communicated to the Chemical Society, and printed in the 'Journal of the Chemical Society.'* As these papers contain a full account of the chemical composition and properties of the various aconite alkaloids, it will not be necessary to do more now than summarise for reference the chief properties of the substances employed in this enquiry.

Aconitine is the poisonous alkaloid contained in *Aconitum napellus*.† Commercial specimens of aconitine vary considerably, many of them being mixtures.‡ Until quite recently the pure alkaloid was not an article of commerce. It is a crystalline base, very sparingly soluble in water, but readily dissolved by alcohol. Its alcoholic solution is dextro-rotatory, whilst solutions of its salts are lævo-rotatory.§ Even very dilute solutions produce a characteristic tingling and numbness on the tongue and lips. The alkaloid suffers decomposition when heated to its melting point; a molecular proportion of acetic acid is lost, and an alkaloid *pyraconitine* remains.‖ The hydrolysis of the alkaloid occurs in two stages. In the first, which is best effected by heating a salt of aconitine in a closed tube with water,¶ a molecular proportion of acetic acid is formed, and an

* 'Chem. Soc. Journ.,' 1891—1897.

† Dunstan and Ince, 'Chem. Soc. Journ.,' 1891, vol. 59, p. 271; Dunstan and Umney, *ibid.*, 1892, vol. 61, p. 385.

‡ Dunstan and Carr, 'Chem. Soc. Journ.,' 1893, vol. 63, p. 491.

§ Dunstan and Ince, *loc. cit.*

‖ Dunstan and Carr, *ibid.*, 1894, vol. 65, p. 176.

¶ Dunstan and Carr, *ibid.*, vol. 65, p. 290.

alkaloid produced which is named *benzaconine*, the chief constituent of the *picraconitine* and *napelline* of previous observers.* Further hydrolysis, by alkalis or acids, resolves benzaconine into aconine and a molecular proportion of benzoic acid, and these are the final products of hydrolysis.

A characteristic qualitative reaction of aconitine is the formation of a crystalline purple precipitate of aconitine permanganate when a faintly acidified solution of an aconitine salt is mixed with a solution of potassium permanganate.† Most aconitine salts crystallise well from a solution in water, and in experiments on the physiological action of this alkaloid an aqueous solution of the hydrobromide has been employed.

Neither the composition nor constitution of aconitine can be regarded as settled. In determining the exact formula by which the composition is best expressed, there is the difficulty of deciding between several formulæ which represent the composition of the alkaloid within the limits of experimental error. Alder Wright‡ adopted the formula $C_{33}H_{43}NO_{12}$ as best expressing the composition. Later observers, Jürgens,‡ Lübbe,‡ and ourselves have so far accepted a formula identical with or differing but slightly from that of Wright, as indicating the composition of aconitine and its derivatives. Recently Freund and Beck§ have proposed for aconitine the formula $C_{34}H_{47}NO_{11}$ instead of that employed by us $C_{33}H_{45}NO_{12}$, since they have obtained from the ultimate analysis of the pure alkaloid nearly 2 per cent. more carbon than was found by Alder Wright and his colleagues, by Jürgens, by Lübbe, or by ourselves. The question of composition is, therefore, still unsettled and can probably only be finally decided by the analysis of simpler derivatives of aconitine than have been hitherto dealt with. The constitution of aconitine cannot be considered until more is known of the simpler derivatives and decomposition products. For the purposes of the present discussion it may be regarded as *acetylbenzaconine*, but nothing is at present known of the constitution of aconine.

Diacetyl-aconitine is an alkaloid obtained from aconitine by acting upon it with acetyl chloride,‖ and differing from it in containing two acetyl groups in the place of two atoms of hydrogen. It is a crystalline base, very sparingly soluble in water, but readily in alco-

* Dunstan and Harrison, *ibid.*, 1893, vol. 63, p. 443; Dunstan and Carr, *ibid.*, 1893, vol. 63, p. 991; Dunstan and Harrison, *ibid.*, 1894, vol. 65, p. 174.

† Dunstan and Carr, 'Pharm. Journ.,' 1896, vol. 56, p. 122.

‡ Alder Wright and Luff, 'Chem. Soc. Journ.,' 1877, vol. 31, p. 143; Jürgens, 'Inaug. Dissert. Dorpat,' 1885; Lübbe, *ibid.*, 1891.

§ Freund and Beck, 'Berichte,' 1894, vol. 27, p. 720.

‖ Dunstan and Carr, 'Chem. Soc. Journ.,' 1895, vol. 67, p. 459.

hol. A solution of its hydrobromide in water was used for the determination of its physiological action. This solution, like that of an aconitine salt, produces a persistent tingling and numbness of the tongue and lips.

Benzaconine, the product of the partial hydrolysis of aconitine, occurs with aconitine in *Aconitum napellus*,* and is the principal constituent of the substances named napelline and picraconitine by previous observers. It was first named by us *isaconitine*, as its percentage composition was found to agree within the limits of experimental error with that of aconitine.† The base is amorphous and separates from a solution in alcohol and ether as a varnish; it dissolves sparingly in water. Solutions of the alkaloid and of its salts are very bitter, but do not produce the tingling of the tongue and lips which is so characteristic of aconitine. Like aconitine, solutions of benzaconine are dextro-rotatory, whilst those of its salts are lævo-rotatory. When hydrolysed benzaconine furnished aconine and benzoic acid. Although the base has not been crystallised, the salts of benzaconine crystallise easily. For the experiments on the physiological action an aqueous solution of the hydrobromide has been employed. Since benzaconine differs from aconitine only in the absence of an acetyl group, attempts have been made to re-form aconitine from benzaconine by replacing this group. These attempts have, however, failed. Benzaconine does not furnish, under the several conditions tried, a monacetyl derivative, and the compounds which have been prepared containing more than one of these groups do not exhibit any of the characteristic properties of aconitine, and would seem to be isomeric, not identical; thus the triacetylbenzaconine is isomeric with diacetylaconitine, and tetracetylbenzaconine isomeric not identical with triacetylaconitine.‡

Aconine is the final basic product of the hydrolysis of aconitine, with which it occurs in *Aconitum napellus*.§ It is an amorphous alkaloid readily soluble in water and in alcohol, though not in ether. Its solutions are sweet in taste, alkaline in reaction, and dextro-rotatory—like aconitine and benzaconine, aconine salts being also lævo-rotatory. The salts are crystalline; a solution of the hydrobromide has been used for the experiments described in this paper.

Adopting Wright's modified formula for aconitine, the following formulæ and names represent the alkaloids dealt with in the present paper.‖

* Dunstan and Umney, *loc. cit.*

† Dunstan and Harrison, *ibid.*, 1893, and Dunstan and Carr, *ibid.*, 1894.

‡ Dunstan and Carr, *ibid.*, 1895.

§ Dunstan and Umney, *ibid.*, 1893.

‖ See further, Dunstan, "The Nature of Aconitine" ('Pharm. Journ.,' March, 1894); and 'Collected Papers from the Research Laboratory of the Pharmaceutical Society,' vol. 2, 1896.

Aconine, $C_{24}H_{39}NO_{10}$.
Benzaconine, $C_{24}H_{38}(C_6H_5CO)NO_{10}$.
Acetylbenzaconine (*aconitine*), $C_{24}H_{37}(CH_3CO)(C_6H_5CO)NO_{10}$.
Diacetylaconitine, $C_{24}H_{35}(CH_3CO)_3(C_6H_5CO)NO_{10}$.

As aconitine has been so largely used by previous workers, its action will be treated of in greater detail than will be necessary when considering its derivatives or its allies obtained from other varieties of aconite.

The modes of action of aconitine, diacetylaconitine, benzaconine, and aconine, respectively, have been tested with regard to the following points:—

1. Their effect upon the blood pressure, pulse, and respiration of anæsthetised cats.

2. Their general effect, and especially their action upon temperature and respiration of rabbits, and (occasionally) of guinea-pigs.

3. Their general toxic action towards frogs with their effect in detail upon circulation, respiration, cord reflex, motility, and cutaneous sensation of these animals.

4. Their lethal dose towards some or all of the various animals employed.

Whilst the scope of this paper will be limited to these alkaloids, there are many other alkaloids and derivatives closely allied to aconitine which have been under examination, and it is intended to present a further communication concerning them with as little delay as possible. Among them may be named *pseudaconitine*, the alkaloid of *A. ferox*; *japaconitine*, the alkaloid of *A. japonicum* or *Fischeri*, as well as several derivatives of aconitine.

The following is a summary of the pharmacological action of the alkaloids.

Action on the Circulation.

Aconitine at first stimulates medullary centres slowing the heart, acceleration follows, auricles and ventricles taking up an irregular and (at one stage of toxic action) independent rhythm. Imperfect systole (especially in the ventricles) develops. Irritability of ventricular wall is much increased. Extensive variations of blood pressure accompany the preceding phenomena. After great ventricular acceleration with very imperfect systole, delirium of the ventricles supervenes. The vagus (stimulated) continues to restrain speed of contraction (especially acting upon the auricle), and may favour closer sequence of ventricular upon auricular systole, so as to cause a rise in blood pressure. For the same reason during a stage of sequence, it may cause the usual effect (fall of pressure). In slow poisoning the cardiac vagus on stimulation ceases to produce any effect. Atropine is unfavourable to the independent rhythm of auricles and ventricles

and also to the ultimate reduction of ventricular action to incoordinate contraction (delirium).

The vaso-motor centre is at first stimulated, but later depressed in function, but peripheral splanchnic stimulation is active to some degree throughout poisoning.

Diacetylaconitine, whilst producing effects in the main resembling those of aconitine, shows less tendency to cause independent rhythm of ventricles upon auricles. In half the experiments made a failure of systole occurred without asequence, in the remaining half an aconitine-like effect was witnessed.

The cardiac vagus is less affected than by aconitine, but the result of its stimulation depends much upon the sequence or non-sequence of ventricular upon auricular action present at the time.

The vaso-motor centre and peripheral vaso-constrictors respond to this alkaloid much as they do towards aconitine, but stimulation in the early stage of action is less marked.

Benzaconine.—After very brief pulse acceleration, slowing with reduction of blood pressure occurs, the latter being due mainly to the depression of the motor mechanism within the heart. After a stage of irregularity, during which full diastole of both auricles and ventricles is exceptional, a blocking of auricular impulses to the ventricle succeeds, so that a rhythm of 2 to 1 is produced. (After aconitine this state of affairs is largely reversed.) Complete though transitory failure in the production of a spontaneous beat (the ventricles being first involved, then the auricles) is seen in a large proportion of experiments. This is not due to stimulation of inhibitory apparatus, which is put out of action by atropine, for the phenomenon occurs after atropine. It is referable rather to depression of the motor apparatus. Contraction returns spontaneously, either from spontaneous revival in excitability of this apparatus, or from stimulation of the highly venous blood.

The vaso-motor centre, though depressed in function, retains some action, until the very low pressure is reached which invariably precedes death.

Vagus stimulation causes slowing, until in a late stage of poisoning, the blood pressure remaining very low, its action fails. After effective stimulation, pressure rises beyond the original level from acceleration of the heart and strengthening of the systole.

Digitaline is the most effective antagonist towards benzaconine.

Aconine is, relatively to the three compounds just considered, harmless towards the heart. At first it stimulates the vagal roots slightly, causing a slower beat. As, however, it strengthens the systole of the ventricle the blood-pressure rises, and is maintained at a high level throughout a long experiment. Asequence or disorder of rhythm is not produced, but an antagonistic effect is shown

towards aconitine and diacetylaconitine. In this action, aconine opposes independent rhythm of auricles and ventricles facilitating the transmission of the normal impulse, and it reduces the tendency to delirium of the ventricle. Only lethal doses reduce the activity of cardiac vagus terminations. The vaso-motor centre is practically unaffected.

The circulation remains active in frogs for days, in entire absence of reflex and respiratory movements.

Action on Respiration.

Aconitine at first stimulates the respiratory centre and the sensory vagal fibres in the lung. Depression rapidly follows, death in mammals being due to central respiratory failure. The peripheral innervation of respiratory muscles is not interfered with.

Diacetylaconitine produces a slighter initial stimulation than aconitine. Death results from central failure. Pulmonary œdema is commonly observed in rabbits. Respiratory spasm occurs at death.

Benzaconine does not appear to stimulate either respiratory centres or pulmonary vagus as do the two former. The centres are depressed from the first; respiratory failure induces death without spasm; to this the reduced action of motor nerve endings in respiratory muscles contributes.

Aconine, whilst slowing the respiration from its action upon the centres, possesses a pronounced curare-like action upon motor nerve endings in respiratory muscles. No spasm attends death.

Action on the Nervous System.

Aconitine in large doses causes occasional loss of consciousness, with failure of conjunctival reflex and dilated pupil. This is not a directly narcotic effect, but is secondary to reduced oxidising power of the blood from circulatory and respiratory impairment. For a time there is evidence of stimulation of motor areas, and especially of the medulla with its contained centres; to this depression succeeds; reflex centres in the cord are stimulated, and then depressed by large doses. In frogs, voluntary movement outlasts reflex. Sensory nerves at the periphery are depressed in function after very transitory stimulation, whilst motor nerves are practically unaffected.

Diacetylaconitine produces a stimulation of the medulla, but less in degree than that caused by aconitine. The subsequent depression, especially of the respiratory centre, is well marked, the respiration being relatively more affected than the circulation. The general reflex function of the cord is depressed after preliminary excitement. The action with reference to sensory nerves is the same as that of

aconitine, but motor nerve terminations, though they are not powerfully affected, are reduced in activity by diacetylaconitine.

Benzaconine causes a lethargic and ultimately semi-narcotised condition, which is referable to low intracranial blood-pressure as well as to a direct action upon the cortex. Whilst the medullary centres are early depressed, both direct and cross cord reflexes are elicited in a limb excluded by vascular ligature from access of the alkaloid. Sensory nerves are unaffected except in deep poisoning. On the other hand, motor nerves and their terminations are reduced in function, a peculiar intermittency of response following stimulation.

Aconine produces in mammals loss of volition and impairment of conjunctival reflex only shortly before a large dose proves fatal. Motility is interfered with, but this is mainly due to a curare-like effect upon motor nerve endings. The respiratory centre is depressed, respiration failing when the heart still beats vigorously.

Action on Oxidation Processes.

All the four alkaloids here considered reduce the oxidising power of vegetable protoplasm; aconitine being most and aconine least active. Diacetylaconitine is more energetic than benzaconine.

Action on Internal Temperature.

Aconitine produces a fall (exceptionally preceded by a slight rise), which increases as respiratory slowing develops, but the minimum is reached (50—70′ in rabbits) after a partial recovery of respiration. Exposure to a cold atmosphere increases the fall and delays the recovery. Diminished oxidation produced directly and through impairment of circulation and respiration indirectly are causal to the fall.

A dose of aconitine less than half the lethal proportion will cause a fall of nearly 2° C. below the normal.

Diacetylaconitine occasions less effect than aconitine on the temperature when the dose bears an equal relationship to the respective lethal doses. This is due to a less vigorous action on heart and respiration. Like aconitine, it interferes both indirectly and directly with oxidation.

Benzaconine produces a trifling reduction of temperature until a dose is reached which greatly reduces the pulse and speed of respiration when a proportionate fall occurs. The reduction of muscular movement tends still further to limit heat production. Proportionately to its toxic dose the effect is not so active as in the case of diacetylaconitine.

Aconine is inoperative towards body temperature, except in very large doses, which enfeeble respiration and cause a curare-like action on motor nerve terminations. Even then the effect is relatively slight, as the heart remains active and the vaso-constrictor system is still in play (lethal dose causing death (guinea-pig) in 60′ reduced the temperature by 1·7° C.).

Action on Skeletal Muscle.

Aconitine does not in ordinary lethal doses materially affect irritability, capacity for work, or form of contraction of frog's muscle. Exposure to the direct action of aconitine solutions causes fibrillation and lengthening of the muscle curve (an effect resembling slight veratrine action has been described). Fibrillation is abolished by aconine and curare, and is therefore not attributable to the action of aconitine directly on muscular tissue, but to a stimulation of motor nerve endings.

Diacetylaconitine reduces the irritability of muscular tissue, the muscle (after poisoning *in situ*) is more readily fatigued, the curve of contraction therefore losing in altitude whilst increasing in length.

Benzaconine in large doses produces rapid fatigue with failure of contractility which is, however, restored by rest. Contact of strong solutions reduces excitability and capacity for work.

Aconine in doses sufficient to immobilise frogs is inoperative. Larger quantities slightly reduce excitability and capacity for work, but have not the action so characteristic of benzaconine.

Lethal Doses.

The results are stated in decimals of a gram per kilo. of the body weight, and where two figures are given the lethal dose lies between them.

	Cat.	Rabbit.	Guinea pig.	Frog (R. Temp.).
Aconitine	0·000134	0·000139	0·00012	0·000586 (March) 0·0014 (July)
Diacetyl-aconitine	0·004—0·00515	0·0042	0·0042	0·039
Benzaconine ..	0·0245	0·0272	0·0238—0·0293	0·284
Aconine	0·166—0·4	—	0·275	1·055—1·75

General Conclusions.

It would therefore appear from our study of the pharmacology of these alkaloids, that the introduction of two additional acetyl groups into the molecule of aconitine does not create any pronounced varia-

tion in the pharmacological action, but results merely in a general weakening of the characteristic action of the parent alkaloid.

Considering next the effect of removing the acetyl group from aconitine, which is seen in the behaviour of benzaconine, we find that the characteristic features of aconitine action are almost entirely annulled. The great toxic power of aconitine has been greatly reduced, so that the lethal dose of benzaconine for both cold- and warm-blooded animals is relatively so considerable as to remove it from the class of poisons in the ordinary acceptation of the term.

In the action of benzaconine on the heart and circulation very little trace of the effects of aconitine can be observed; whilst after the administration of aconitine the ventricles ultimately beat more rapidly than, and often independently of, the auricles, the opposite is the case in the action of benzaconine. On the heart, indeed, it acts to some extent as the antagonist of aconitine, causing slowing, especially of the ventricles, in opposition to the great acceleration produced by aconitine, so that in a certain measure it is observed that benzaconine behaves as an antidote to aconitine poisoning, though not so effectively as atropine. This is a point of considerable practical importance when it is remembered that benzaconine occurs to a variable extent with aconine in *A. napellus*, from which plant the ordinary medicinal preparations are made.

The removal of the acetyl group has also abolished the stimulating effect of aconitine on the respiratory centres and the pulmonary vagus. On the other hand, in its general action on the respiration and on temperature a certain resemblance is traceable between the depressant action of benzaconine and aconitine. Peripherally benzaconine depresses the activity of motor nerve endings and, in a lesser degree, of skeletal muscular tissue, whilst aconitine acts principally upon sensory nerve terminations.

In contrasting the action of aconine with that of benzaconine we are studying the effect of withdrawing a benzoyl group. It has been seen that in removing the acetyl group from aconitine we produce an alkaloid which is no longer a virulent heart poison; the removal of the benzoyl or benzoic group from benzaconine furnishes aconine which is so far from being a heart poison that it may be ranked as a general cardiac tonic, and in virtue of this action as the antagonist of aconitine. In a much greater degree than benzaconine it is an antidote to aconitine, so much so that we have found that the administration of aconine is successful in averting in small animals the effect of a lethal dose of aconitine. Amongst the distinctive features in the pharmacological action of aconine is to be noticed a curare-like effect on the motor nerve endings of the muscles which is not observed with either aconitine or diacetyl-aconitine. No fault of sequence between ventricles and auricles, such as is

observed (though in an opposite direction), after the administration of aconitine and benzaconine can be observed in the action of aconine. Aconine cannot be classed as a poisonous alkaloid, very large doses being necessary to produce death even in frogs.

The results of this inquiry, which has occupied the authors for the greater part of four years, brings out in a most striking manner the almost complete dependence of the extraordinary toxic power and pharmacological action of the aconitine molecule on the presence of the radical (acetyl) of acetic acid, whilst, in a lesser degree, the action of benzaconine is seen to depend on the existence in the molecule of this alkaloid of the radical (benzoyl) of benzoic acid. The inertness of the alkaloid, aconine, denuded of both the acetyl and benzoyl groups of aconitine seems to the authors to be one of the most interesting facts in chemical pharmacology. From the practical point of view the authors regard the demonstration of the antagonism of aconine and benzaconine towards aconitine as an important result of this investigation, which, taken as a whole, it is believed will throw into clearer light the mode of action of the alkaloids of *Aconitum napellus*.

The chemical part of this inquiry, for which one of us (D.) is responsible, has been conducted at first in the Research Laboratories of the Pharmaceutical Society, and afterwards in the Scientific Department of the Imperial Institute. The pharmacological experiments have been made in the Department of Pharmacology, in the University of Aberdeen.

In conclusion, we desire to acknowledge the assistance which has been rendered to our work by the Royal Society, which has made several grants from the Government Fund, and we wish to express our indebtedness on the chemical side to those whose names have been referred to, and especially to Mr. Francis H. Carr, Salters Research Fellow in the Laboratories of the Imperial Institute. In the conduct of the pharmacological experiments Dr. Robb, Dr. Findlay, and Dr. Arthur Lister have rendered valuable service.