OBSERVATIONS ON THE ACTION OF BOERRHAVIA DIFFUSA

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Natural Order Nyctagineæ, popularly known as Punarnava in Bengal and Gadha Purna (Hind.).

Distribution.—Widely through Bengal and Chota Nagpur, extensively found during the rainy season.

Description of the plant.—It is a large diffusely-branched herb, with opposite leaves which are faintly undulated at the margin, small and paniced, flowers capitate; stamens one or two to five; anther didymous; ovary oblique and slender; ovule erect; stigma peltate; fruit enclosed in the ovoid; seed adherent with testa.

There is another plant closely allied to this—it is a red variety, stronger and larger, more branched, lasting longer and bearing red flowers. It resembles the white variety in every particular. The roots of the red plant are bigger, thicker and longer than the white variety.

Popular uses.—It is extensively used for food purposes, specially by the Bengalee; the whole plant is used as fodder for cattle in the Central Provinces under the idea that it increases the quantity of milk. Illiterate persons use a decoction of the root regularly as a sedative to the urinary passages, specially if there is lessened urinary secretion.

Its antiquity as a drug.—From a very early period its medicinal value was recognised, as may be inferred from its mention in Raj Nirghanta and Bhabaprokash (two very old Sanskrit works on medicine).

Composition.—The whole root and half of the stem were first

turned into a pulpy mass with the help of pestle and mortar. This mass was then macerated with water (twenty times its volume) for about a week and then filtered through a fine rag. The filtered extract was then evaporated to dryness; the dried mass was treated with dilute sulphuric acid (equal parts of water and H_2SO_4) for a week. The acidulated extract was then filtered, and the filtrate was neutralised with ammonia until it gave a distinct alkaline reaction and until no more precipitate began to fall. The precipitate was allowed to settle, the upper liquid was decanted off and the contents evaporated to dryness. A portion of this was treated with petroleum ether, giving no change.

Another portion was treated with absolute alcohol, which dissolved it entirely in the course of three days; the alcoholic liquid was concentrated on a vapour heater until only a little of the fluid remained. On the surface of the fluid floated a very minute quantity of black scum, suet-like in appearance and sticking on the hand like gum on touching.

The black scum was removed by decanting and treated separately with ether, in which it was perfectly soluble; on evaporation of the ether, a greenish-black sticky substance was left. Under the microscope it looked like small oil globules with green colouring matter. This substance is, therefore, probably fatty in nature.

Finally the alcoholic extract was evaporated in an air chamber, when a dry brown powder was left. This powder was soluble in alcohol and satisfied all the tests of alkaloid except that ferric chloride gave only a slight brown precipitate. Under the microscope it appeared as dark amorphous granules. The brown powder was then treated with dilute sulphuric acid and water in equal parts and kept for twenty-four hours so that the whole of the granular mass was dissolved—the amount of dilute sulphuric acid added being about twenty times. This fluid was then evaporated to one-tenth of its volume and allowed to cool, when small needle-shaped crystals began to settle at the bottom; the whole was then kept in hot air chamber so that extra fluid evaporated and crystals only were left behind.

Physical character of these crystals.—They were small, needle-shaped, brownish-white in appearance when in mass; taste nearly bland or very faintly bitter; they were light and voluminous. Under the microscope they appear as long or short needle-shaped crystals, about one-fifth to one-tenth mm. in length. This is evidently the sulphate of the granular body obtained after evaporation of the alcoholic extract. It resembles impure quinine sulphate. The amount extracted was very small, so that the plants were very poor in the amount of the alkaloid. Thus 20 oz. of the original plant treated yielded only 300 mgrms. of the sulphate (about 5 grains) or about $\frac{1}{2000}$ th part of the original plant taken.

The ash of the dried plant yielded only about 15 per cent. of the solid matter; it was partially soluble in water, and the solution gave tests for chlorides and sulphates of the alkali metals (specially of sodium and potassium), and minute traces of nitrates, and a very faint trace of chlorate.

Thus we see the composition to be (1) a sulphate of a body, alkaloidal in nature; (2) an oily amorphous mass of the nature of fat (probably); (3) sulphates and chlorides and traces of nitrates and chlorates from the ash.

The amount of the alkaloidal body is very small.

PHYSIOLOGICAL EFFECTS

A guinea-pig, weighing about 500 grammes, was given 200 mgrs. of the sulphate with milk; it took the drug well and developed no poisonous symptoms. Only change noticed was that the animal passed a very large amount of urine for two days.

As the quantity of the alkaloid obtained was very small in amount, all the experiments were henceforth carried out with a liquid extract of the plant (1 in 10).

The same animal was injected with 4 drachms of the extract at 12 noon, the only symptom it developed was that there was a little excess of urine passed by 4 o'clock; now another injection of 2 drachms

was given, which was repeated at 6 o'clock ; poisonous symptoms began to appear late at night, about seven hours after the last injection ; the animal became stupid, took no food that was given to it at night, passed neither stool nor urine, had occasional convulsions and a difficulty in standing. Next day it became perfectly stupid although consciousness was retained ; later in the day it became more or less comatose, with frequent convulsions. All the time there was no urine nor any stool. In this state it remained till 5 o'clock in the evening, and died at 6 o'clock in deep coma.

The post mortem examination made next morning showed the following appearances :—

- (1) Stoppage of the heart in ventricular systole.
- (2) Acute inflammation of the glomeruli of the kidneys, which were acutely congested and almost flesh coloured—more so at the cortical region ; on section of the kidneys the glomerular portions stood out prominently as so many reddish dots.
- (3) Congestion of the portal area, possibly due to the engorgement of the auricles and right side of the heart.

Microscopical examination of kidney.—Section of kidney showed excessive cell infiltration in and around the glomeruli ; the glomeruli were large and standing out prominently amongst other tissues ; around the glomeruli there appeared to be a kind of thin fibrinous deposit. The tubules showed practically no change except a little hazy material occupying the lumen of the tubules. Other organs showed practically no change.

Death was probably due to uraemia caused by the stoppage of the excretions from the kidneys.

Effects on isolated heart.—Direct application of the drug on the heart increases the force and frequency of the heart beat ; the duration of the systole is increased along with the force of the beat so that all the blood is squeezed out of the ventricle during the contraction and the heart appears paler for a time. In its increasing the force and frequency of the heart beat the drug resembles strychnine ; while in increasing the force of systole it resembles digitalis. The following

is a tracing of the frog's heart before and after the application of the drug while it was beating forcibly :—

Cardiographic tracing of frog's heart before and after the application of the drug ; the upper one represents the normal tracing before the application of the drug ; the lower one represents the tracing after the application of the drug ; all the while the heart was strong and beating forcibly.

The upper tracing represents the normal beats, while the lower tracing is taken after the application of the drug. In this lower curve the systolic tracing is sharper and more prolonged, indicating the force of the systole, while the downstroke, representing the pause, is about the normal or very slightly longer.

The following tracing was taken while the heart was weak and beating slowly ; various doses of the drug were applied—first two drops, then four drops and then treble the dose. Here the upper curve represents the normal, while the lower curve after the application of the drug.

1st Dose

Double dose

Treble dose

Cardiographs of frog's heart after the slowing of the heart due to weakness.

Here, too, we find the systole more prolonged and sharper, systolic plateau being distinctly longer after the application of the drug. The tracing after the third dose is quite remarkable.

In both cases the tracing represented by the systole is more prolonged and sustained.

This action of the drug on the heart is probably muscular and not nervous, as may be deduced from the following experiments.

Stimulation of the vagus at the crescent after the application of the drug causes the heart to cease beating, while the removal of the stimulus and re-application of the drug restores the former action of the heart. First, Stannius's ligature after the application of the drug causes the inhibition of the heart, while removal of the ligature and re-application of the drug brings about the contraction of the heart after a little while. Again, application of the drug after double Stannius's ligature brings about one or two contractions of the apex. Thus we see that the nerve (vagus) is unaffected by the drug, and the action exerted by the drug on the heart is probably muscular.

The number of heart beats was markedly increased, and it rose from 76 to 90 in case of one frog; in another from 68 to 81; in a third from 70 to 80, and so on. These phenomena were more marked while the heart was in its wane, and then the frequency in the number of beats was well marked.

Effects on pulse beat in man.—These facts were also borne out by the condition of the pulse as experimented on human beings. The following tracings indicate the condition of the pulse before and after the application of the drug.

Sphygmographic tracing before the administration of the drug. Pulse beat = 83 per minute; sphygmographic pressure = 92.

Sphygmographic tracing after administration of the drug. Pulse beat = 92 per minute. sphygmographic pressure = 128. Here the upstroke is longer and sharper, while the downstroke is more prolonged and the dicrotic wave is well marked.

Sphygmographic tracing before the administration of the drug. Pulse beat = 82 per minute ; sphygmographic pressure = 95.

Sphygmographic tracing after the administration of the drug. Pulse beat = 108 per minute ; sphygmographic pressure = 140. Here, too, the dicrotic wave is very well marked, the upstroke longer and sharper.

Similarly, other pulse tracings were taken, and all gave similar results. In all the cases we see that the upstroke due to the expansion of the artery is sharp and long, consequent on the increased force and duration of the systole of the left ventricle. The dicrotic wave is more prominent in all the cases, and that is probably due to the larger amount of blood flowing into the aorta and thereby closing the semi-lunar valves more completely and tightly.

The pulse rate is also quickened—thus :—

	Before		After
Roghu	82	...	108
Gopu	78	...	82
Gokul	83	...	92

The blood pressure is also raised, as experimented by sphygmometer ; thus we have :—

	Before		After
Roghu	95	...	140
Gopu	70	...	120
Gokul	92	...	128
Beshua	85	...	122

This increase in blood pressure is purely cardiac and not peripheral; this was seen by the effect of the drug on the frog's mesentery; it neither dilated the blood vessels nor contracted them. Thus we see that this rise of blood pressure of the arteries is purely cardiac. Hence we conclude that the condition of the pulse exactly coincides with that of the heart and *vice versa*. Consequently from these experiments we draw the following conclusion :—

That the drug increases the force, strength and frequency of the heart beat, increasing at the same time peripheral blood pressure, which is purely cardiac.

The dose of drug used in these experiments in case of human beings was a single dose—4 drachms of the extract—and the results were recorded two hours after the administration.

Experiments on kidney secretion.—It has already been shown that 200 mgrs. of the alkaloidal sulphate caused increased secretion of urine in guinea-pigs. The effects on the urinary secretion in man were tested as follows :—The drug was given in 2-drachm doses of the extract every four hours ; altogether four doses being given during twenty-four hours.

Before the application of the drug.

Name	Quantity of urine in twenty-four hours	Urea	Chloride.	Total solid
Gokul	535 c.c.	13 grm.	7.7 grm.	32.6 gr.
Seria	1070	13.7	7.9	35.2
Seionandan.....	720	13.6	5.2	26.3
Bishua.....	855	14.2	9.9	28.2

After the application of the drug.

Gokul	1st day	600 c.c.	6.9 gr.	7.32 gr.	33 gr.
	2nd day	860	15.4	12.88	39.6
	3rd day	960	9.2	18.6	42.7
	4th day	1400	13.6	19	44.1
Seria	1st day	1110	12.2	10.6	39.4
	2nd day	1200	14.7	15.4	43.5
	3rd	1480	13.2	20.6	46
Seionandan...	1st day	1480	12.6	13.1	39.7
	2nd day	2000	14.7	14.28	46.01
	3rd day	2600	15	21.7	49.5
Bishua	1st day	1092	15.5	12.7	41.7
	2nd day	1209	13.6	15.2	42.1
	3rd day	1600	15.4	22.04	45.4

Now, if we compare the results, we find a general increase in the quantity of urine ; if we further analyse the results we find that the chlorides are proportionately increased as quantity of urine increases ; urea also increases in a few cases, but bears no proportion to the increase of urine. The quantity of total solids, although increased, only maintains the relation with the quantity of urine increased, and, as may be seen, the initial coefficients were not greater, or even in some cases less.

Now these facts exactly coincide with the observations made above ; thus we saw that the injection of the drug in fatal dose caused a state in the kidney, affecting the blood vessels and the glomeruli and causing total cessation of the watery secretion of the kidney ; we also observed that there was increase in the force and strength of the heart beat as well as a rise of blood pressure, which is also evidenced in the arterioles of the kidney, and the result is that the watery part

is thrown out, relieving the blood pressure. Increased and proportional increase in the excretion of chlorides is also suggestive; for a chloride is a salt easily diffusible through the membranes, and hence it is that it shares the same fate as the water, or, in other words, it comes out with the water that is excreted out in excess.

Now increase in the secretion of urea may suggest some increased secretion from the tubules of the kidney ; but the experimental facts are not quite in favour of it. As we have seen in case of guinea-pigs that the tubules showed no sign of affection, it may be possible that they would have been affected had there been sufficient time, but as it is no definite opinion about it can be given ; moreover, the increased secretion of urea is merely comparative and not a real increase.

Such experiments were also conducted by Dr. Harris, of the Medical College Hospital, on clinical cases, in 1901 ; the drug was given indiscriminately to all cases having oedema and kidney affections or ascites, and in almost all cases the urinary secretion, specially the watery part, increased in a marked degree.

Recently the drug was tested in some of the cases in the Hospital ; and although the urine increased in every case, the results cannot be given here as the experiments were done so irregularly and perfunctorily. I had the fortune to try the drug in three cases having ascites and oedema, and they all showed increase in the urinary secretion.

Dr. Satis Ch. Banneryu, late House Surgeon and now Assistant Professor of Physiology, also testifies to the increase of urine by the administration of the drug.

Other practitioners of the town also recommend its use in urinary troubles, and testify to its value in increasing the secretion of the urine.

From these data we can infer that the urinary secretion, so far as the watery part is concerned, is invariably increased, that this increase occurs in healthy persons as well as in diseased ones, that the glomeruli are mainly if not solely responsible for the secretion and that the tubules, if affected, are only partially so ; the increase of chlorides is proportional to the increase of the watery part and that the increase of urea is possibly merely comparative.

The drug has been said to have some action on the respiratory system and digestive system, but the experiments on those organs brought about negative results.

CONCLUSIONS

1. The active principle is a diuretic chiefly acting on the glomeruli of the kidney through the heart, increasing the beat and strength, and raising the peripheral blood pressure in consequence ; on the cells of the tubules it exerts little or no action and, if any, it is only initial and comparative.

2. On respiration it has little or no action, and if it is anything, it is probably due to the fatty principle found in the weeds.

3. On liver the action is principally secondary and in chemical combination with other drugs.

4. On other organs the drug has practically no effect.

From what has been gone through it may be inferred that the drug may be given in any condition of the kidney where there is lessened secretion or where increased secretion of kidney is wanted. Thus it may be given in all renal affections stopping secretion of kidney, in ascites, either from cirrhosis of liver or heart or kidney. As it increases the systole of the heart it may be useful in all stenosed conditions of the valves, as by increasing the force and duration of the systole it can pump all the blood from the heart. Where there is dropsy and ascites due to weakness of the heart or to dilatation of the heart, this medicine, in my opinion, may do extreme good by relieving the circulation through the kidney. In pleurisy and some such affections where there is accumulation of fluid in the cavities, the drug may be useful by increasing the quantity of urine.