THE TOXICITY OF SODIUM HYDNOCARPATE

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INTRODUCTION

Martindale and Westcott ([6]) experimented with rabbits and cats to determine the toxicity of selected sodium salts of chaulmoogra, called sodium chaulmoograte "C". A rabbit tolerated an intravenous injection of a 20 per cent solution in the amount of 0.1 gm. per kilo body weight, equivalent to 6.3 gm. for a 140-pound man. A dose (2 per cent solution) calculated for a man as 3.15 gm. caused marked dyspnoea and tremors, and one equal to 7.5 gm. for a man killed the animal in five minutes. In anesthetised cats there was survival after 0.1 gm. per kilo (20 per cent solution), but immediate death followed 0.184 gm.; subcutaneously 0.15 gm. per kilo had no obvious effect, and twice that amount only caused temporary dyspnoea and loss of appetite.

From these experiments they concluded that a man ought certainly to tolerate a dose of three grains (about 3 mgm. per kilogram) in either 2 or 20 per cent solution, even if given intravenously, though the subcutaneous method would be preferable. They say repeatedly that, in their opinion, chaulmoogra treatment probably necessitates a saturation of the patient's system with the active constituents of the oil. We would say that there is no reason apparent to justify such a procedure, and draw attention to the fact that this toxic drug in excessive amount may injure the kidneys and liver. In our earlier studies upon chaulmoogra ([10]) it was shown that excessive doses in dogs and rabbits led to emaciation, hemoglobinuria, albuminuria, fatty infiltration of the liver and glomerular nephritis.

The previous studies by both Martindale and myself dealt with the more extreme conditions prevailing after what, for the human, would be excessively large doses of the drug. Because of this, two series of experiments were initiated in this institution. One of them was carried out by Dr. C. N. Frazier, who undertook experiments

upon rabbits with sodium hydnocarpate in a dosage comparable to ordinary clinical usage; his results are reported elsewhere (2). Our own undertaking was to investigate the comparative toxicity of large and more variable doses of two particular commercial preparations of the sodium salts.[1] One of these, "alepol", is described by the makers as the sodium salts of the fatty acids of lower melting point from *Hydnocarpus* oil (1); it is referred to in this paper as "sodium hydnocarpate I." The other product was made from *Taraktogenos* oil free from the irritating palmitate and comprised the lower acids with relatively low melting points, the combined melting point being approximately 25°C. (6); it is referred to here as "sodium hydnocarpate II."

HISTORICAL

Up to the time that Power (9) isolated the specific fatty acids of the oil of *Taraktogenos kurzii* and named them chaulmoogric and hydnocarpic acids, the term "gynocardic acid" was commonly used in referring to the total fatty acids present in the oil. Moss (7) in 1879 gave the name to the lower melting point fatty acids of chaulmoogra oil. Unna (14) in 1900 recommended the use of "Gynokardseife" for leprosy as a preparation affecting the stomach and intestines less unpleasantly than the pure oil. This gynocardium soap was the sodium salt, for which he gave a detailed method of preparation. It is clear that Unna's sodium gynocardate was a mixture of the total fatty acids, though since the preparation was thoroughly washed it may have been deficient in part of the soluble hydnocarpates. It was given by mouth in keratin-coated pills, hence there were none of the problems concerning painful injections with this salt that arose later.

It is unnecessary to review all the literature to point out how the term gynocardic acid was erroneously applied, first to chaulmoogric acid, then to the hydnocarpic fraction. *Gynocardia* and chaulmoogra seeds are now clearly identified as being unrelated, and it is readily seen how inappropriate the name is for any preparation of chaulmoogra.

It should be understood that there is no official sodium salt of any of the fatty acids from chaulmoogra oil, nor has any firm yet prepared the pure salts on a cheap scale for commercial purposes.

[1] The samples of drugs used in these experiments were kindly supplied by Sir Leonard Rogers and Dr. Robert G. Cochrane.

Various workers have fractionated these acids. Moss in 1879 showed that those with the higher melting points formed sodium salts insoluble or only slightly soluble in water. These were about half of the total fatty acids, and are now known to be chiefly palmitic and chaulmoogric acids. Those with the lower melting points, the mixture melting at about 29°C, formed water-soluble sodium salts. Rogers (12) in 1916 tried out these and other fractional preparations made by Ghose. He eventually concluded that the mixed soluble fractions that he termed sodium gynocardate, which was a mixture of one fraction melting at 28°C. and another melting at 37° to 40°C., were the most effective in the treatment of leprosy.

Gardner (4) later gave a method which produced a water-soluble sodium salt from the fatty acids that melted at between 32° and 34°C., these having been fractionated out of alcohol and dried completely before the melting point was determined; the sodium salt was made in alcoholic solution and distilled from the solvent at 80°C. Martindale's sodium chaulmoograte "C" is composed of the lower acids with a combined melting point of approximately 25°C. Gelarie and Greenbaum (5) applied themselves to the question of solubility of the sodium salts, and found that the preparations obtained varied according to the medium in which saponification was made, alcoholic soda producing salts far more soluble than aqueous solutions of sodium hydroxide.

It is seen that the criteria heretofore used for considering the relative value of the sodium salts have been (a) the melting points of the mixed fatty acids, (b) the solubility of the salts, and (c) freedom from irritation and obliteration of the vein when injected (13). These factors have not yet been reduced to one standard. There are, however, other considerations to be kept in mind besides the clinician's desire to secure easy and repeated injection of this useful drug. The experiments herein reported show (1) that more attention should be given to maintaining the body weight, (2) that tests should be made for albuminuria and hematuria, and (3) that possibly the liver and kidney function should be tested.

EXPERIMENTS

Series 1.—The first experiments were made with rabbits to compare the effects of the two commercial sodium hydnocarpate preparations, using solutions of widely varying concentration both subcutaneously and intravenously. (a) *Subcutaneous* injections were

given of solutions varying in strength from 0.25 to 20 per cent. (b) The *intravenous* experiment was set up for a similar comparison. (c) A third set was given subcutaneous injections of the mixed ethyl esters, these being diluted in olive oil in concentrations ranging from 0.25 to 4 per cent.

Series 2.—Dogs were given injections of relatively small doses over a long time. This was done in view of the fact that regular leprosy treatment usually extends over many months. (a) *Subcutaneous* injection of the sodium salts was made twice weekly, the original dose being 1.5 cc. per kilogram of body weight of a 2 per cent solution. This showed so little effect that after the fourth injection the amount was doubled. (b) *Intravenous* injections were made weekly for 4 months, 1 cc. per kilogram of a 1 per cent solution being used. (c) One dog was started, for a comparative trial of the ethyl esters, using subcutaneously the same dose as of the salts.

Series 3.—Comparative trials were made in different animals of the effects of equal doses in two different concentrations. This was done because it is so often taken for granted that the factor of concentration is irrelevant, whereas it is a fact that soaps in particular exhibit very different physico-chemical behavior at low and high concentrations.

Solutions of the sodium salts were made in distilled water or in normal saline. After standing, solutions were obtained up to 20 per cent concentration, though prolonged standing (overnight) caused a flocculence, very pronounced in the sodium hydnocarpate II. This preparation was darker in color than sodium hydnocarpate I. Their solutions tested in a Lovibond colorimeter showed about ten times more yellowish-brown color in the former than in the latter.

In observing the injected animals special attention was given to (1) loss in body weight, and (2) effects of the drug upon the kidney. The urine was tested daily for albumen and hemoglobin, by the nitric acid and guaiacum tests respectively. After the animals were killed by bleeding, sections of the kidneys were made, both of frozen material for staining with sudan III, and of fixed tissue for eosin and methylene blue. Gross and microscopic examinations were also made of the tissues of the liver, lung, heart and spleen.

Hemolysis in vitro.—The hydnocarpate preparations were tested in vitro for their relative hemolytic effect upon sheep's blood. In 5 per cent solution the blood hemolysed to a dark cherry red jelly. Red cells which had been centrifuged to remove the serum were mixed with the drug diluted with normal saline to 0.3 per cent, and again centrifuged. Both of the salts gave a decided red tinge. At 0.25

per cent the hydnocarpate I gave no hemolysis, though No. II was still definitely hemolytic. With lesser concentrations there was no evident effect.

RESULTS OF EXPERIMENTS

EFFECT ON BODY WEIGHT

Previous experience showed that after extremely toxic doses emaciation is marked, and may be associated with anorexia and diarrhoea caused by the drug. In the present experiments with graded doses there was no such effect; the changes in weight were more gradual and less marked. In Table 1 are given the principal figures for the rabbits injected subcutaneously with the two sodium salts and with the ethyl esters in olive oil.

TABLE 1.—*Effects on weight of rabbits of subcutaneous injections of the sodium salts and the ethyl esters.*

Drug and amount per kilo of body weight	Number of injections	Weight of animals, in grams		
		Original weight	Lowest or highest	Final Weight
Sodium hydnocarpate I				
5.0 cc. of 10 per cent	4	1,200		1,070 (—130)
5.0 cc. of 2 per cent	6	1,650	1,570 (— 80)	1,850 (+200)
2.5 cc. of 2 per cent	4	1,720		1,600 (—120)
2.5 cc. of 1 per cent	2	1,310		1,220 (— 90)
2.5 cc. of ½ per cent	3	1,440		1,530 (+ 90)
2.5 cc. of ¼ per cent	3	1,120	1,230 (+110)	1,200 (+ 80)
Sodium hydnocarpate II				
5.0 cc. of 10 per cent	4	1,020	1,040 (+ 20)	980 (— 40)
5.0 cc. of 2 per cent	6	1,920	1,740 (—180)	1,860 (— 60)
2.5 cc. of 2 per cent	4	1,870		1,520 (—260)
2.5 cc. of 1 per cent	2	1,250		1,200 (— 50)
2.5 cc. of ½ per cent	3	1,460	1,540 (—120)	1,600 (+140)
2.5 cc. of ¼ per cent	3	1,400		1,420 (+ 20)
Ethyl Esters				
2.5 cc. of 4 per cent	2	1,360		1,330 (— 30)
2.5 cc. of 2 per cent	3	1,440	1,650 (+210)	1,530 (+ 90)
2.5 cc. of 1 per cent	3	1,340	1,450 (+110)	1,430 (+ 90)
2.5 cc. of ½ per cent	3	1,350		1,400 (+ 50)
2.5 cc. of ¼ per cent	12	1,500	1,540 (+ 40)	1,520 (+ 20)

There was a definite loss in weight with all drugs after subcutaneous injection of concentrations stronger than 2 per cent in doses of 2.5 cc. per kilogram of body weight. In lesser concentrations the sodium salts appeared to be more harmful than the ethyl esters. When 5 cc. of the 2 per cent solution was used the sodium salts caused a primary decrease in weight followed by a progressive increase, implying the development of some kind of a tolerance. This perhaps can be correlated with the nitrogen, sulphur and calcium excretion, which have been shown to undergo marked changes but with an es-

pecially great output taking place only after the first dose of the drug (11).

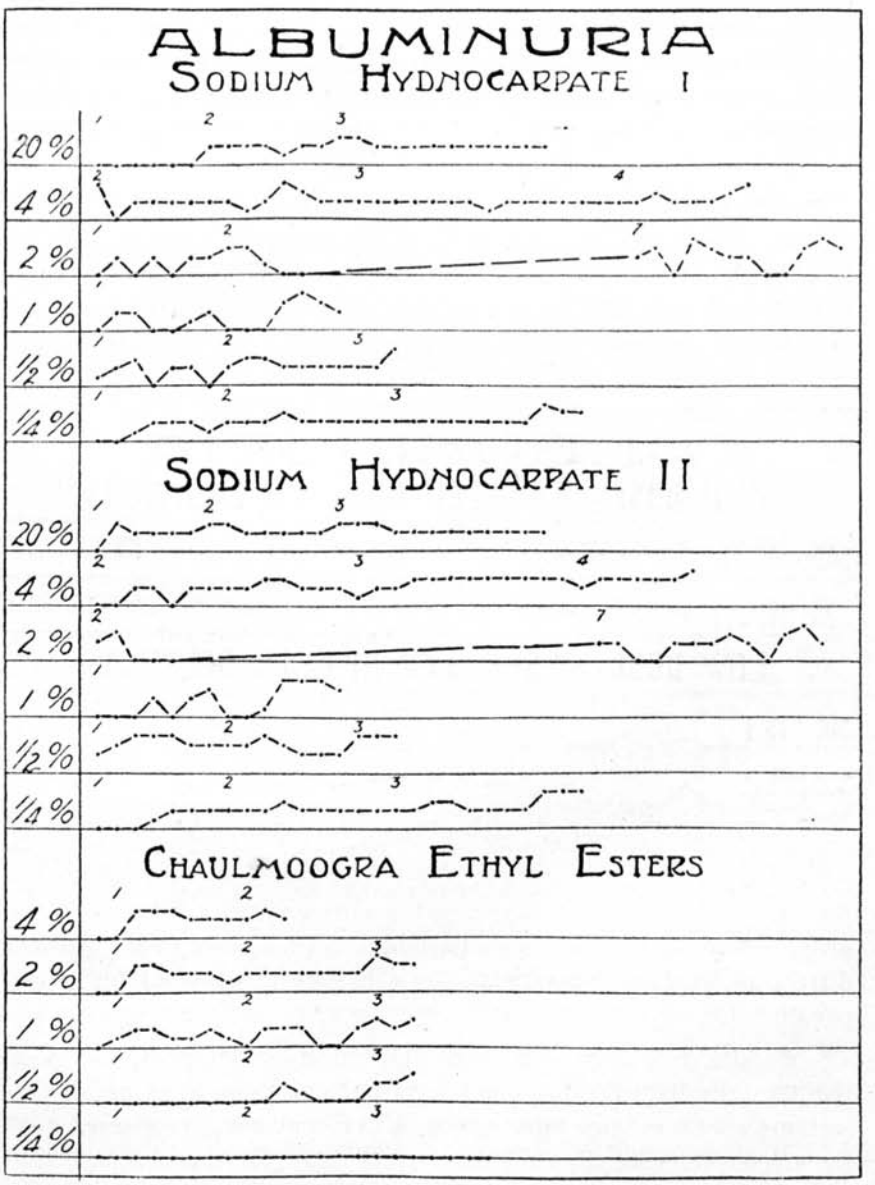
The intravenous injections in rabbits of the two sodium preparations caused little change. It is striking that the large doses (5 cc. per kilogram, 2 per cent solution) caused no decrease in either animal. With one-tenth the amount (0.5 cc.) both rabbits decreased somewhat at first, but after five weeks they had actually gained in weight. On the other hand, those given the same dose of half the concentration (i. e., 5 cc. of 1 per cent) both lost a little, the No. I animal about 3.5 per cent and the No. II animal 6 per cent.

In dogs treated subcutaneously with 1.5 cc. per kilogram of a 4 per cent solution for nine weeks there was some loss of weight for three weeks or so, but the No. I animal more than recovered this. The ethyl esters dog, given the same dose, also lost some for a time but recovered it. Both dogs given intravenous injections of 1 cc. per kilogram of a 1 per cent solution had gained weight at the end of the observation, thirteen weeks.

ALBUMINURIA

Results with rabbits.—Of the rabbits injected subcutaneously, those given the 0.5 per cent solution in a dose of 2.5 cc. per kilogram gave the most pronounced albuminuria (Text-fig. 1). The hydnocarpate II gave more immediate and intense change than hydnocarpate I. With both, the effects of the dose mentioned were more pronounced than with either higher or lower concentrations; weaker solutions were less active, while stronger ones were apparently not so well or so rapidly absorbed. This was clearly so with the 20 per cent preparations. In 10 per cent solution the injection formed a pocket of fluid which took about ten days to disappear. This accounts for the seeming lack of activity of solutions of greater strength than 0.5 per cent. Local necrosis with the formation of sterile abscesses has been long known, and is regarded by some as characteristic of rancid chaulmoogra oil.

The rabbits which were given the ethyl esters mixed with olive oil, subcutaneously, showed more definite indication of a gradual increase in the effect of the drug as the concentration increased (Text-fig. 1). Three weekly injections of 0.25 per cent showed no effect; with 0.5 per cent the first sign of albumin appeared on the third day after the second injection; with 1.0 per cent albumen was present on the second day after the first injection. Greater concentrations

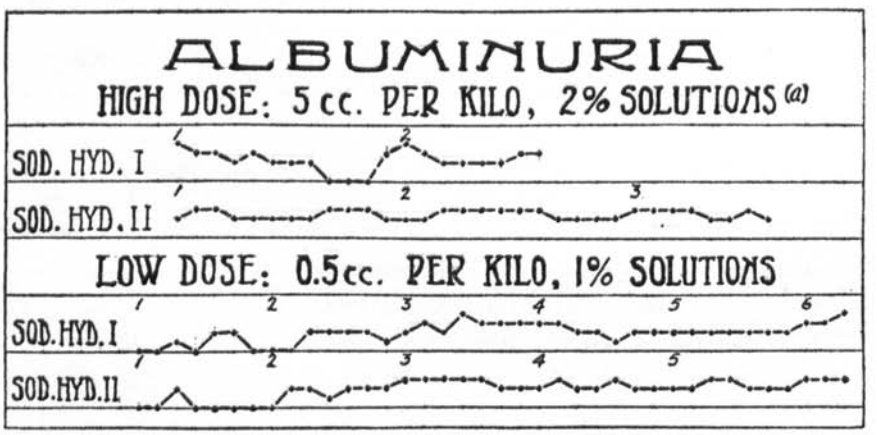


TEXT-FIG. 1.—*Albuminuria in rabbits after weekly subcutaneous injections of chaulmoogra-group preparations.*

The small figures refer in each case to the number of the injection. The degree of rise of the broken line corresponds to the degree of albuminuria (i. e., ±, +, ++, or +++).

caused more albumen, but in practically all cases it did not show till the second day after injection. But it is to be noted that albumin would often appear sooner or later, even when rabbits were given minute therapeutic doses. The urine would remain clear for weeks or months, but frequently with the cumulative effect of the drug albumen would eventually appear.

Rabbits injected intravenously with the hydnocarpates, like those treated subcutaneously, showed more irritation by hydnocarpate II than by No. I. With the latter, after the first injection, the albumen cleared upon the ninth day, but with the former the excretion of albumen was continuous (Text-fig. 2). With the smaller doses



TEXT-FIG. 2.—*Albuminuria in rabbits after intravenous injection of sodium hydnocarpates. (Explanation of chart as for Figure 1.)*

given intravenously the two preparations did not show such a marked difference, but the comparison was still somewhat favorable to preparation I.

Results with dogs.—In dogs injected subcutaneously, the comparative results with the three preparations from semi-weekly injections of 1.5 cc. per kilogram in 4 per cent solution showed that the ethyl esters in olive oil were apparently far more rapidly absorbed and reactive on the kidneys. Sodium hydnocarpate I was slightly more so than hydnocarpate II, which showed no effect for the first 24 days. Small doses given intravenously showed an entirely different picture. Though the hydnocarpate II was the less soluble and the less readily absorbed when given subcutaneously, it caused

greater kidney trouble when placed directly into the blood stream. It should be emphasized again that repeated injections showed cumulative effects, and that no albumen was found in the urine in the first day or two after the first injection, though it was present later.

HEMOGLOBINURIA

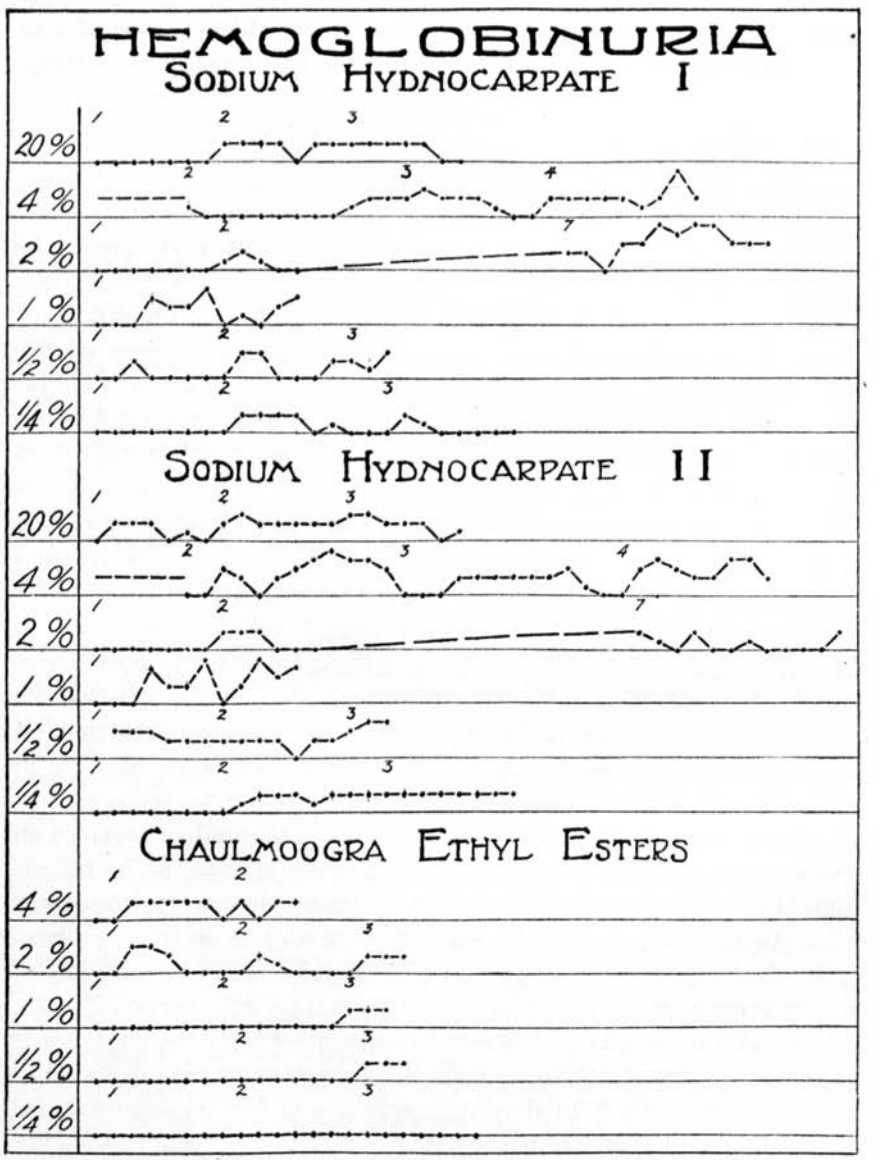
Results in rabbits.—Hemoglobinuria is a characteristic result of injection of rabbits with hydnocarpates, a statement which also applies to dogs though to a less degree. As stated in discussing albuminuria, it is clear that after subcutaneous injection of these substances the most immediate effect is seen with 0.5 per cent solutions, which are apparently well absorbed (Text-fig. 3). With the ethyl esters no hemoglobinuria was seen till after the third dose of 0.5 per cent solution; the 0.25 per cent solution was free from effect. The results with the higher concentrations were not remarkable except that the clearcut severity of their effects is a further indication that the esters are well absorbed.

Results in dogs.—In dogs given 1.5 cc. per kilogram of 2 per cent solutions subcutaneously for sixteen days, the effect was negative. Doubling the dose (4 per cent concentration) caused slight hematuria in a few days; though not severe, it was quite definite. As with the other effects noted, sodium hydnocarpate I was apparently better absorbed than sodium hydnocarpate II, and so showed its toxic effect on the kidney earlier. With intravenous treatment it was not until after the fourth injection that hemoglobin appeared in the urine of dogs.

From the standpoint of hemoglobinuria, the hydnocarpate I in 1 per cent concentration is tolerated moderately well, but hydnocarpate II is clearly more injurious. The damage may be to the blood, or to the kidney or both. The in vitro experiments to test the hemolytic effects of the two salts showed that 0.25 per cent solutions of the hydnocarpate II in saline caused hemolysis of sheep's red cells, but the hydnocarpate I did not. Under all conditions the former caused more hematuria in rabbits than the latter, especially when given intravenously. In dogs hydnocarpate II intravenously caused more hematuria than hydnocarpate I.

EQUIVALENT DOSES IN DIFFERENT CONCENTRATIONS

Two rabbits were given twelve injections of the ethyl esters in olive oil, the dose being the same for each—6.25 mgm. per kilogram



TEXT-FIG. 3.—*Hemoglobinuria in rabbits after subcutaneous injections of chaulmoogra-group preparations. (Explanation of chart as for Figure 1.)*

of body weight—but the concentration of the esters varying; one was 0.5 per cent and the other 0.25 per cent. The resulting albuminuria (Table 2) shows an effect of dilution; the stronger solution was apparently absorbed in greater concentration and reached the kidney in more concentrated form. These results are of the same order as those reported by Rogers (12) working with pigeons.

TABLE 2.—*Comparing the effects as regards albuminuria in rabbits of twelve subcutaneous injections of chaulmoogra ethyl esters, in equal doses (6.25 mgm. per kilogram of body weight) but in different concentrations in olive oil.*

Day after each injection	Solution 0.5 per cent Injections as numbered below												Solution 0.25 per cent Injections as numbered below											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
1st	—	—	—	+	—	++	—	+	±	—	—	—	—	—	—	±	—	+	—	—	—	—	—	—
2nd	—	—	—	+	+	+	+	±	+	—	—	—	—	—	—	+	+	+	+	+	+	—	—	—
3rd	—	—	—	—	+	+	+	—	—	—	—	—	—	—	—	—	+	—	+	—	—	—	—	—
4th	—	—	—	—	+	+	—	—	—	—	—	—	—	—	—	—	—	+	+	—	—	—	—	—
5th	—	—	—	—	+	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6th	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7th	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Note.—In both animals there was a trace of hemoglobin, more pronounced in the 0.5 per cent, on the first day after the fourth injection.

It has already been pointed out that the sodium salts in high concentrations are poorly absorbed. In rabbits, 0.5 per cent solutions showed the most rapid and intense effects. In dogs, hydnocarpate II in 2 per cent solution given hypodermically was not well absorbed; it took about five days for the subcutaneous pocket of the drug to be absorbed. In 4 per cent solution both products caused abscesses.

EFFECTS UPON THE KIDNEY

In all the animals, both rabbits and dogs, there was degeneration of the epithelium of the convoluted tubules. These showed fraying of the edges, breaking down of the cell substance, and filling of the lumen with granular material. Frazier (2) has described the effect of therapeutic dosage in the following words:

> Degenerative tubular lesions of the kidney closely similar morphologically to those of nephrosis in men have been produced by the action of dilute solutions of a soap consisting of the more soluble sodium salts of the unsaturated fatty acids of hydnocarpus oil.

We found with larger doses of the drug that the tubules are first affected, but that later the glomeruli are involved. They are either broken down entirely or show signs of hemorrhage into the capsule. Frozen sections showed numerous fat droplets, chifly in the convoluted tubules.

Extremely large doses of the hydnocarpate salts produce a lasting damage. After five weekly doses of 10 per cent solutions had been given subcutaneously the kidney sections showed blood corpuscles in the tubules. The sodium hydnocarpate II animal suffered more damage to the renal epithelium in general, and some glomeruli were involved. Intravenous injection showed more glomerular degeneration, with tubular nephritis.

EFFECTS UPON THE LIVER

In view of the fact that in our earlier experiments with lethal doses of chaulmoogra we observed fatty infiltration of the liver with central necrosis resembling phosphorus poisoning, it was with considerable interest that we examined sections of the livers of animals treated with smaller doses. That of a dog which was treated twice a week for 10 weeks with 2 per cent sodium hydnocarpate II in a dose of 1.5 cc. per kilogram, the injections being given subcutaneously, showed definite signs of fatty infiltration in the central areas. While in none of the animals was there definite necrosis of the liver cells, in some there were numerous fat droplets and marked congestion of certain areas. Frozen sections showed the fat particularly in the Kupfer cells.

Rabbits given sodium hydnocarpate I intravenously in large doses (2.5 cc. per kilo of a 4 per cent solution) showed in the blood vessels of the liver not only many red blood cells but much fine material, doubtless the result of the hemolytic action of the drug. One animal killed five days after injection showed much fat in the liver sinuses, and the lungs had much fat in the large vessels and all through the tissues. This was particularly marked in animals treated with the hydnocarpate II.

Even the rabbits treated with very small amounts of hydnocarpate I showed, after a year's injections, much the same picture in the liver, lung and kidney; there were vacuolated cells, congestion and blood debris in the vessels. The fatty degeneration of the liver was apparent in some slides, and in the kidney many fat droplets

were seen both in the convoluted tubules where there was a marked desquamation of the cells and also down the collecting tubules.

EFFECTS OF PROLONGED TREATMENT

The results suggest that while a few injections of the ethyl esters may not have any noticeable effect upon the urine, continued treatment does bring out some apparent cumulative action (Table 2). The animals that had been given prolonged treatment of one year's duration, with a therapeutic dosage of about 0.2 mgm. per kilogram bodyweight, showed at the end of the period both blood and albumen in the urine. Two other animals which had started with the same dosage were gradually increased till nearly 1 mgm. was reached; at the end of the treatment one showed slight albuminuria. These animals were not examined for albumen daily, but it is probable that if this had been done they would have shown periods of transient albuminuria and hematuria, as was seen in the dogs that were treated for several months.

DISCUSSION

The results reported in this paper, together with our previous findings (10), add to our knowledge of the cumulative action of chaulmoogra preparations and the tolerance which it is possible to demonstrate with them.

There is an undoubted cumulative action. This is clearly seen in the slowly developing toxic action on the kidneys of rabbits and dogs, small doses eventually producing albuminuria and possibly hemogolobinuria. In a former study of nausea and vomiting in dogs it was seen that prolonged subcutaneous treatment, instead of lessening these effects, gradually increased them until the animals eventually vomited their meals and showed blood in the urine. The emesis we assumed to be of central nervous origin, but we have since learned from clinicians (3) that patients claim to be able to taste the drug almost immediately after it has been injected, in which case it is possible that the hydnocarpates, like morphine, are excreted in the saliva. In any case there are indications that with continued treatment there is a gradual saturation of the organism with this foreign oil, which is gradually excreted in small dosage through the kidney and is not burnt up in the body like ordinary fats.

The inherently irritant character of this drug is apparently unchanged in the organism. Excessive or improper dosage may intensify the toxic effects. However, it seems probable that the or-

ganism adapts itself to a certain dosage, but that this does not render it immune to the effects of increased dosage. This was seen in the dogs treated subcutaneously, and in our earlier metabolism studies.

The tolerance to an appropriate dosage that is possibly developed seems to have two phases. In our metabolism studies (11) we showed that a second or third large dose will not produce the same dramatic changes in calcium, nitrogen and sulphur excretion that the first dose causes, unless the amount of the drug be increased. These changes, we assume, indicate the gradual development of a tolerance to the kidney effects after several doses of the drug have been given. Small doses of a 1 per cent solution given intravenously in rabbits caused much less hematuria after the fifth dose than after the third. A larger amount of the same concentration given subcutaneously showed less albumen after the second dose than after the first. The albuminuria after very small doses of the esters is a transient picture of a slowly developing tolerance, which a sudden change to larger dosage makes chaotic (Table 2). In clinical work such kidney effects possibly are to be correlated with the febrile reactions studied by Muir (8).

On account of its hemolytic action there is good reason for opposing the use of sodium hydnocarpate preparations in high concentrations, either intravenously or subcutaneously.

SUMMARY

1. High concentrations and large doses of commercial preparations of sodium hydnocarpate administered to rabbits and dogs intravenously and subcutaneously produce albuminuria, hematuria, and emaciation.

2. There is loss of weight when either the sodium salts or the ethyl esters are given subcutaneously in amounts more than 50 milligrams per kilogram of body weight. A certain degree of tolerance can be developed with suitable dosage.

3. Pronounced albuminuria is observed in rabbits after subcutaneous injection of 12.5 milligrams of the salts. With larger or smaller doses it is not so pronounced. In dogs, a 4 per cent solution of esters in olive oil is apparently most rapidly absorbed and gives the earliest traces of albumen.

4. The less readily absorbed and less reactive concentrations also produce albuminuria, but only after an interval of several days.

5. Hemoglobinuria is characteristic of treatment of rabbits with hydnocarpates; also of dogs in less degree. The hemolytic effects of the salts in 0.25 per cent solution upon red cells in vitro is apparently carried through in vivo, in the rabbit. In dogs, 2 per cent solution shows no immediate effect, but 4 per cent causes hemogloburia. There is a marked cumulative action in this respect.

6. The pronounced kidney effects shown in rabbits and dogs by excessive dosage with these chaulmoogra preparations suggest that care is needed in selecting suitable concentrations and dosage in treating human patients. The cumulative action casts doubt on the idea that treatment should be by large doses of high concentrations with a view to saturating the system.

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