Prothrombin Time and Hemorrhagic Death in Dicumarolized Rats Receiving Pituitary and Adrenal Hormones*)

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Previous studies in this laboratory have established that when rabbits and rats are given indirect anticoagulants and then are exposed to such stresses as frost-bite (1, 2) fifty per cent will die between 60 and 72 hours later. On post mortem, hemorrhage can be demonstrated in many animals — either subcutaneous, into the pleural or other cavities, externally or at other sites. This phenomenon has been termed hemorrhagic death and can be produced by various combinations of treatments. The present authors have recently shown (3) that combined treatment with dicumarol and ACTH leads to a significant number of hemorrhagic deaths in rabbits.

In the present investigations an attempt was made to determine in rats whether the hemorrhagic effect of stress is mediated by the pituitary, the adrenal, or by some other effect of stress not acting through the pituitary-adrenal axis. To test this, rats were given dicumarol or warfarin and then subjected to treatment with various corticosteroids, corticotrophin (ACTH), somatotrophin (STH), sodium salicylate, adrenaline, histamine, phenergan and dial. It was previously observed that adrenalectomized rats all die of hemorrhage when given dicumarol. The effect of various steroids have therefore been studied on this. Other investigations in this laboratory (4) have shown that

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reserpine causes hemorrhagic death in adrenalectomized rats and in rabbits subjected to stress, but not in dicumarolized rabbits. This drug was therefore included in the series.

Methods

White rats of the Wistar strain supplied by a local dealer were used. Body weight was between 100 and 250 gms. Animals were selected to have approximately the same weight in any single group of experiments. Dicumarol was administered in the food. 1.0 mg in 2.5 gm of food per 100 gm body weight was given daily for 6 days. Animals were checked to make sure that all this was ingested and then this was supplemented with further ration without added dicumarol. A single intraperitoneal dose of 2 mg/100 g was administered on the 3rd day for hydrocortisone, cortisone, desoxycorticosterone, ACTH, STH. Sodium salicylate was given intraperitoneally as a single injection of 30 mg/100 gm. Sodium chloride was injected intrapertoneally in a 10% solution, 1.75 ml/100 gm. Adrenaline was given intraperitoneally, 0.1 mg/100 gm, histamine and reserpine, 0.25 mg/100 g, dial (diallyl mallonyl urea), 0.005 gm/100 g and phenergan, 1.0 or 3.0 mg/100 gms. Vitamin K_1 was injected intravenously in emulsion in a dose of 0.4 mg/100 g initially and as 0.2 mg/100 g subcutaneously each day following. Control animals were treated with each of the agents alone. Prothrombin times were determined, using 0.05 ml of tail blood and 0.05 ml of thromboplastin, by the whole blood prothrombin time method of Schwager and Jaques (5) using a commercial rabbit brain thromboplastin.

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Results

The Effect of Hormones and Pharmacological Stress on Hemorrhage and Prothrombin Time in Dicumarolized Rats

The prothrombin time was first determined on the rats. Dicumarol was then fed daily and the prothrombin time again determined on the 3rd day of feeding. After this, the additional treatment (injection of hormone, stress, etc.) was given. The prothrombin time was determined on the following days. In each experiment, rats were taken in groups of 5 to give 40 rats (one control group and one group for each treatment). The experiment was repeated 4 times to give 20 rats in each combined treatment. Control groups without dicumarol were also included. Results with stress agents and with hormones are shown in tables 1 and 2. With the very wide spread in prothrombin times resulting after the administration of dicumarol, arithmetic means of the values themselves have not a great deal of meaning. It has been pointed out by Mogenson, Fisher and Jaques (6) that if logarithmic values of the prothrombin time are taken

this gives an approximately normal frequency distribution curve and therefore some meaning to the ordinary statistical procedures and values such as standard deviation. The prothrombin times were therefore transposed to corresponding logarithmic values, and the mean and standard deviation calculated for each set of data. The mean value for 185 rats without any treatment was 1.5003

Tab. 1: Effect of Stress and Reserpine on Mortality and Prothrombin Time of dicumarolized Rats

Treatment	Mortality	Prothrombin Time (in log secs.) Mean n s. e. p value			
		Day 3	Day 4	Day 5	Day 6
Control (Dicumarol alone)	8/95	1.8342 60 0.0374 <0.01	2.0716 50 0.0408 <0.01	1.7677 20 0.0328 <0.01	2.0231 46 0.0520 <0.01
10% Sod. chloride	47/96	1.9178 80 0.0307 0.1	2.1262 55 0.0408 <0.4	2.1896 8 0.1549 <0.05	2.1121 44 0.0863 0.4
Sod. salicylate	9/20	1.8717 15 0.0680 >0.5	2.4229 10 0.1232 <0.02	2.2442 8 0.1579 <0.02	2.3975 8 0.1196 0.02
Adrenaline	8/15	1.7315 5 0.0995 0.4	2.0833 15 0.0938 >0.5	—	2.3166 11 0.1224 <0.05
Histamine	6/10	1.9569 10 0.0662 <0.2	2.2353 10 0.0830 <0.1	—	2.3837 9 0.1188 0.02
Reserpine	7/15	1.8620 5 0.0468 >0.5	1.7746 15 0.0562 <0.01	—	2.0312 14 0.1087 >0.5
All treatments	77/156				

Mean prothrombin time without dicumarol for 25 rats — 1.4976 (= 31.4 secs.) with s. e. 0.0111. Mortality with stress alone (10% NaCl intrp.) — 2/35. *p values:* for dicumarol alone — for the 3rd day compared with value before dicumarol; for 4th, 5th und 6th day compared with value of the previous day. For all others, p value calculated comparing the reported value with the value obtained with dicumarol in the control series on the same day.

Tab. 2: Effect of Corticosteroids and pituitary Hormones on Mortality and Prothrombin Time of dicumarolized Rats

Treatment	Mortality	Prothrombin Time Values (logs of prothrombin times) { Mean n s. e. p			
		Day 3		Day 4	Day 5	Day 6
Cortisone	2/20	1.8941	T	2.0086		2.1108
		10		20		18
		0.0843	R	0.0585	—	0.0718
		<0.5	E	0.4		<0.4
Hydrocortisone	3/20	1.6692	A	2.2434	1.5368	1.5670
		20		10	9	10
		0.0503	T	0.1487	0.0222	0.0537
		<0.02		<0.2	<0.01	<0.01
			M			
Desoxycorticosterone	13/20	1.8675	E	2.2703	1.8197	2.4242
		15		10	10	5
		0.0560	N	0.0737	0.0800	0.1151
		>0.5		<0.05	>0.5	<0.05
			T			
ACTH	11/20	1.7442		2.2391	1.8758	2.5686
		15		10	10	7
		0.0435		0.0907	0.1139	0.1015
		<0.2		>0.1	<0.4	<0.01
STH	9/20	1.9107		1.9440		2.4555
		20		20	—	14
		0.0669		0.0882		0.1031
		<0.4		0.2		<0.01
Cortisone (repeated days 4, 5, 6)	4/15	2.0171		2.4275		2.0976
		10		15	—	11
		0.0875		0.0657		0.0520
		<0.2		<0.01		>0.5

Experiment conducted together with that reported in table 1. p values are calculated comparing values reported with those for rats with dicumarol alone (table 1).

(equivalent to a prothrombin time of 31.6 secs.) with standard error of 0.0038.

The results of injections of 10% NaCl, sodium salicylate, adrenaline, histamine and reserpine in dicumarolized rats are shown in table 1. A high mortality (50%) was observed in all these animals. The control group (dicumarol alone) shown in table 1 also serves as control for table 2 since the two series were run simultaneously. 35 rats received injections of 10% NaCl only. 2 of these died. No deaths were observed in control rats given sodium salicylate, adrenaline, histamine or reserpine at the same dose. Of the 77 rats which died, most died

on the 5th and 6th day or between 40 and 72 hours after receiving the second treatment or drug. The most common finding post mortem was hemorrhage in the intestine and congestion with possible hemorrhage in the lungs. Hemorrhage was also observed in some animals in the peritoneum or kidney or adrenals or under surface of the brain. While rats died after receiving dicumarol and reserpine with the typical picture of hemorrhage, 3 rats survived until the 12th to 14th day when they succumbed to pulmonary infection. As judged by the general behaviour of the rats, the dose of reserpine had a much greater tranquillizing effect in the dicumarolized rats than in the controls receiving reserpine alone. They ate much more slowly and were very much less active than the controls on reserpine or dicumarol alone. It is evident that in contrast to the results previously obtained with rabbits, hemorrhagic death is observed in rats when treated simultaneously with dicumarol and reserpine.

The mean prothrombin time on the 3rd day for the rats receiving dicumarol only was, of course, very much higher than the value for animals not receiving dicumarol. Again there was a further increase on the 4th day. On the 5th day, the mean value was significantly shorter but not on the 6th day. As judged by the prothrombin times on day 3, there was no significant difference between the groups of rats as regards their response to dicumarol. However, significantly higher mean values for the prothrombin time were observed in the rats receiving sodium salicylate. This was also observed with histamine on day 6 and possibly with sodium chloride, on day 5 and adrenaline on day 6. An increase in prothrombin time in rats with stress such as 10% NaCl has been reported from these laboratories (6). As discussed previously (7), the change in prothrombin time depends to a considerable extent on the exact phase of stress in the individual animal at the time of taking the blood sample, and with the further considerable variability in response to dicumarol, this is not readily seen in dicumarolized animals. Hence, only with sodium salicylate was there a significant increase in the mean value. On the other hand, the mean value of the prothrombin time 24 hours after reserpine was significantly smaller than the value for the control animals.

The same mortality (50%) is observed with all. These treatments (10% sodium chloride, sodium salicylate, adrenaline, histamine) in the doses used deplete adrenal ascorbic acid and cholesterol, increase steroid levels in blood, and decrease the circulating eosinophils (8, 9). Sodium salicylate caused 9 deaths out of 20, and caused an increase in the prothrombin time compared to the controls. Adrenaline gave 8 deaths out of 15. This dose of adrenaline causes an increase in level of steroids in blood. Histamine given together with the dicumarol resulted in 6 of 10 animals dying of hemorrhage and again gave an increased prothrombin time with the dicumarol. When reserpine was given to

dicumarolized rats 7 of 15 died of hemorrhage. However, death occurred much later with these rats. Deaths with reserpine were much delayed occurring on the 9-12th day or a week after the reserpine. This is in contrast to all the other agents causing death, in which the death occurred chiefly on the 5th and 6th day, that is 48—72 hours after the second treatment. The mean with dicumarol was significantly shorter on the day following reserpine. This effect of reserpine on the prothrombin time of the dicumarolized rats could be due to the tranquillizing effect, an effect on the liver or an effect on platelets. As described above, the reserpine was much more effective in the dicumarolized rats. These ate the food much more slowly so that the absorption of dicumarol was not the same in these rats. As the rate of metabolism of reserpine in the liver was affected by dicumarol, it is also possible that the reserpine also interferes with the uptake of dicumarol by the liver. It is also possible that reserpine in its effect on platelets will affect activity of factors involved in the prothrombin time.

Results of treatment with corticosteroids and pituitary hormones are shown in table 2. Rats receiving dicumarol or with added cortisone or hydrocortisone showed a low mortality (c. 10%). On the other hand when desoxycorticosterone, ACTH or STH were given to dicumarolized rats, half the rats died of hemorrhage. The most frequent lesions observed were hemorrhage in intestines and congestion in the lungs. Less frequently were observed peritoneal hemorrhages, petechiae on the kidneys. In 1 case, hemorrhage was observed on the undersurface of the brain. Death commonly occurred on the 6th day on dicumarol. Death does not occur in rats with these hormones in the dosages used, when given alone. Cortisone did not significantly affect the prothrombin time resulting from administration of dicumarol. On the other hand, the dicumarolized rats receiving hydrocortisone gave prothrombin times on the 5th and 6th day, not significantly different from that of normal rats. Animals receiving desoxycorticosterone, ACTH or STH, showed significantly higher mean prothrombin time values than the dicumarol controls on the 6th day. While death removed a certain number of rats, this did not appear to explain the difference in prothrombin time. It would appear unlikely that the differences in prothrombin time with dicumarol could explain the marked mortality with desoxycorticosterone, ACTH and STH.

Reduction of Hemorrhagic Death caused by Dicumarol and Stress

Attempts were made to modify the incidence of hemorrhagic deaths by dicumarol and sodium chloride stress using dial, cortisone, phenergan, vitamin K_1 (table 3). Dial was used as an anesthetic to depress the hypothalamus and thus

Tab. 3 : Reduction of Incidence in hemorrhagic Death caused by Stress in dicumarolized Rats

Additional Treatment	Stress	Mortality	Prothrombin Time (in log secs.) mean n s. e. p value		Day 4	Day 6
			Day 3			
Dial	—	5/15	1.9757 15 0.0715 <0.1	T R E	2.1177 12 0.0792 >0.5	1.9388 11 0.1502 >0.5
Dial	+	11/15	2.0640 15 0.0613 0.05	A T	2.3739 14 0.1003 <0.05	2.3111 10 0.1401 <0.3
Cortisone	+	9/10	2.0980 10 0.0987 <0.2	M E N	2.3984 10 0.1107 <0.05	
Phenergan — 1 mg	—	0/5	1.6885 5 0.0794 <0.2	T &	1.8699 5 0.1581 <0.3	1.7635 5 0.0833 <0.05
Phenergan — 1 mg	+	3/10	2.0238 10 0.0947 0.3	S T	2.2310 10 0.0981 <0.5	1.9034 8 1.1070 <0.2
Phenergan — 3 mg	—	0/5	1.9182 5 0.0308 <0.2	R E	2.2927 5 0.1135 <0.2	1.8467 5 0.1696 <0.4
Phenergan — 3 mg	+	6/10	2.1327 9 1.1070 <0.1	S S	2.3497 9 0.1088 <0.1	1.7064 5 0.0594 <0.02
Vitamin K1	+	2/19	1.9299 20 0.0553 >0.5 ↓ K1 90'			
			1.6053 20 0.0253 <0.01	S T → R E S S	1.6845 19 0.0261 <0.01	1.6316 18 0.0509 <0.01

Stress was administered 30 minutes after dial or phenergan, 2 hours after vitamin K1, and 4 hours after cortisone.

p values are for comparing the prothrombin time values recorded with these values reported without the additional treatment. Control values for dicumarol alone, and dicumarol + NaCl are given in table 1.

interfere with the possible pathway of stress. The dial was given intraperitoneally 1/2 hour before injecting 10% sodium chloride intraperitoneally. Good anesthesia was obtained. No death occurred in control animals receiving dial alone. 4 rats on dicumarol died before recovering from the anesthesia with dial. This suggested that the dicumarolized animals were less resistant to the anesthetic. Those animals which received injections of sodium chloride following dial gave no motor responses or any other movement on the injection of sodium chloride, indicating anesthesia was complete in this regard. Many hemorrhagic deaths were observed in rats treated with dicumarol — sodium chloride — dial. Evidently then the dial did not block the action of the 10% sodium chloride as a stress.

The administration of cortisone will depress the pituitary and thus interfere with liberation of ACTH. The cortisone was administered 4 hours before the injection of 10% sodium chloride. However, far from the cortisone protecting from the effects of stress, 9 of 10 rats receiving cortisone followed by 10% sodium chloride died of hemorrhage within 48—72 hrs. Similarly phenergan failed to protect against the hemorrhagic death due to sodium chloride administered to dicumarolized animals. The 1 mg dose was used as an antihistaminic. With 3 mgs there was definite sedation. 5 rats received dicumarol — 1 mg of phenergan — 0.1 mg of adrenaline 100 g and 2 rats died of hemorrhage, the same as in a control group without phenergan.

Vitamin K_1 was given to the rats on the 3rd day after dicumarol in a dose of 0.4 mg/100 g i.v. After 1 1/2 hours, the prothrombin times were determined and were almost normal (mean = 40 secs.). 10% sodium chloride was then injected intraperitoneally. Dicumarol administration was continued and also 0.2 mg/kg of vitamin K_1 was given intraperitoneally each day following. All the animals survived and prothrombin times in all cases were found to be normal. This demonstrates the significance of dicumarol in the hemorrhagic death and also indicates that this presumably is not due to a separate toxic effect of dicumarol but due to the direct effect on the prothrombin time.

Hemorrhagic Death in Adrenalectomized Rats receiving Dicumarol

It has been shown previously (6) that adrenalectomized rats maintained on sodium chloride quickly die when given dicumarol. An experiment has therefore been carried out in which various steroids have been tested for their ability to increase survival of adrenalectomized rats on dicumarol (table 4). Steroids were given for 8 days before starting dicumarol treatment. Dicumarol was then fed (10 mg/100 gm) daily for 6 days. Some of the animals received hormone during this period and on the 2 days following. Others received no hormone while receiving dicumarol.

Tab. 4: Mortality of adrenalectomized Rats on Dicumarol when treated with Corticosteroids

Treatment			
Before Dicumarol	During Dicumarol	Mortality	Remarks
Desoxycorticosterone 0.25 mg	Desoxycorticosterone 1 mg	15/15	All dead in 6 days
Desoxycorticosterone 0.25 mg	Desoxycorticosterone 0.25 mg	7/7	All dead in 6 days
Desoxycorticosterone 1 mg	Saline	17/17	All dead in 6 days
Desoxycorticosterone 1 mg	Desoxycorticosterone 1 mg	8/8	All dead in 9 days
Desoxycorticosterone 1 mg	Saline	8/8	All dead in 8 days
Extract — 0.25 mg	Extract — 0.5 mg	6/8	
Extract — 0.25 mg	Saline	8/8	
Cortisone 1 mg	Cortisone 1 mg	0/7	
Cortisone 1 mg	Saline	5/6	Died by 7th day
Hydrocortisone 1 mg	Hydrocortisone 3 mg	1/8	Died on 6th day
Hydrocortisone 1 mg	Hydrocortisone 1 mg	6/9	Died on 13th day
Hydrocortisone 1 mg	Saline	5/7	Died by 7th day

All rats maintained on 0.9% saline. Extract = Adrenal cortex extract (Upjohn). Doses given in mgs per 100 g body weight.

Desoxycorticosterone in doses of 0.25 mg and 1 mg/100 gm rat had no effect on the mortality from dicumarol in any group. All animals were dead within 6 days as reported previously for adrenalectomized rats receiving dicumarol. While hemorrhage was observed in 20 of the 23 rats treated continuously with a low dose of desoxycorticosterone, it was only observed in 7 of the 17 rats which received saline while on dicumarol. The other 10 rats showed more the appearance of death from adrenal insufficiency. This difference was not marked for the rats receiving the higher dose of desoxycorticosterone or adrenal extract or hydrocortisone.

7 rats received cortisone 1 mg/100 gm daily for 6 days before receiving dicumarol and then were continued on this dose of cortisone for the 8 days following. All 7 rats survived treatment with dicumarol. Corresponding controls all died during the period of treatment with dicumarol. 6 rats received 1 mg cortisone per 100 gm daily for 6 days. Then they were given dicumarol and the

cortisone replaced by saline. 5 of these rats died in the period on the dicumarol, 2 dying on the 3rd day and 3 dying on the 7th day following the initiation of dicumarol treatment. It is evident that pretreatment with this dose of cortisone delays death of adrenalectomized animals on dicumarol compared to controls and compared to similar rats receiving desoxycorticosterone. However, it is evident that with prolonged treatment in the absence of further supplies of cortisone the animals will die of hemorrhage.

Further groups of adrenalectomized rats were treated with hydrocortisone. These animals received 1 mg hydrocortisone daily/100 gm until dicumarol therapy was started. 8 animals received each day thereafter 3 mg hydrocortisone/100 gm. One of these rats died on the last day on dicumarol. The others all survived, although the hydrocortisone treatment was also stopped 2 days later. 9 continued to receive 1 mg hydrocortisone/100 gm/day during the period of dicumarol treatment and 2 days following. 2 of these rats died on the 5th day of dicumarol treatment, 1 on the 6th, 1 the day after stopping dicumarol treatment and 1 six days and 1 seven days later. Finally 8 rats which had received 1 mg hydrocortisone daily up until the time of receiving dicumarol were then given saline in place of the hydrocortisone. 1 animal died on the 5th day, 2 animals on the 6th day, 2 on the 7th day after starting dicumarol, and 2 animals were still alive a week later.

3 days after discontinuing dicumarol administration, hydrocortisone was also discontinued for those groups receiving it. 10 days later the dicumarol and hydrocortisone were given again. The 2 surviving animals in the group receiving saline only died of hemorrhage on the 6th day. 1 of the second group (receiving 1 mg hydrocortisone) died and 2 of the first group (receiving 3 mg hydrocortisone) also died of hemorrhage. It is evident then that protection can be given by pretreatment with hydrocortisone as well as by continuing treatment with steroids. It was observed that all the adrenalectomized animals lost weight while receiving dicumarol. The weight loss was greater with those who died.

Discussion

These results demonstrate that the high mortality previously observed when dicumarol treatment is added to treatment with frost-bite and similar stress procedures, can be obtained by injection of 10% sodium chloride, sodium salicylate, adrenaline, histamine. Further the picture can be reproduced by combining dicumarol with ACTH or STH or desoxycorticosterone. Cortisone and hydrocortisone did not give any marked mortality. The effects of stress observed might be explained by the liberation of ACTH but cannot be explained as due to this, causing the liberation of cortisone and hydrocortisone. Unfortunately

corticosterone was not available for use in this experiment. The latter is the chief normal steroid in the blood in the rat. However, the fact that desoxycorticosterone gave results closely comparable to ACTH strongly supports the view that the hemorrhagic death due to stress is effected through ACTH acting on the adrenals. However, ACTH does have some direct effects. E. G. Menkin has observed an effect on the inflammation process, and Li has observed a direct effect of ACTH on metabolism of protein. Those agents which caused hemorrhage in animals receiving dicumarol also tended to make the animals more sensitive to the dicumarol as judged by the prothrombin time on the 4th, 5th and 6th days. The differences are not very great and are hardly sufficient to explain the high mortality with a dose of dicumarol which has very little mortality by itself. The results with reserpine are interesting in that they demonstrate that the increase in mortality can be obtained in spite of decreased response to the dicumarol. In general the results illustrate the point discussed in previous communications that hemorrhagic death is not due to an increased effect on coagulation but due to the fact that the procedure is interfering with other hemostatic mechanisms. In the case of reserpine this is the effect on platelets causing the depletion of platelet serotonin. In the case of stress, ACTH, etc. it is due to the effect on blood vessels. ACTH and stress also depress adhesiveness of platelets (10). One must not overlook the possibility that in this situation some of the drugs, such as salicylate and histamine, may be having direct effects of their own separate from the general stress action. It is interesting that the direct actions of adrenaline as a vasoconstrictor and as a source of adrenochrome failed to provide any protective action against the stress effect. Presumably such protective action wears off too quickly to provide real protection.

The results on attempted protection of animals from hemorrhagic death are in some ways difficult to explain. The experiment with vitamin K_1 demonstrates that protection can be achieved. If the effects of stress are simply due to the liberation of ACTH and its effects on the adrenal, then is should be possible to prevent this by either depressing the hypothalamus as with dial or depressing the pituitary directly as with cortisone. Phenergan will have the double action of interfering with the mid-brain and of preventing the action of histamine in the periphery. However, these attempts were not successful.

When the protection of the adrenalectomized animal from hemorrhage in the presence of dicumarol was studied, no protection was observed with desoxycorticosterone, but effective protection was found with cortisone and with hydrocortisone. The best results were obtained with cortisone. This appeared to be at least three times more active than hydrocortisone. These results are in agreement with the results obtained on the effects of steroids on the normal

animal receiving dicumarol, where high mortality was observed with dicumarol and desoxycorticosterone, whereas there was no significant mortality with dicumarol plus cortisone or dicumarol plus hydrocortisone. It is evident that cortisone and hydrocortisone can protect the adrenalectomized animals from hemorrhage in the presence of dicumarol but do not appear to be able to protect the animals under stress. This is not in agreement with general findings, that it is possible to inhibit the effects of stress by previous administration of cortisone. There is of course, a difference in these experiments in that in the adrenalectomized animal the subject is receiving daily injections of cortisone, whereas in the stress experiment the animal received only a single injection. However, in the second experiment of table 2, a significant mortality was seen even though cortisone was given daily.

The results may be interpreted along the following lines. Adrenalectomized rats lack cortisone-hydrocortisone (-corticosterone?) required for normal hemostasis. Hence, they die of hemorrhage when hemostasis is further impaired with dicumarol. Some animals 2 to 4 days after stress also suffer a relative deficiency of the same corticosteroids and likewise die of hemorrhage. The administration of desoxycorticosterone does not protect the adrenalectomized rats and increases the mortality of normal rats through an antagonistic action, as is already known in the case of inflammation. The effect of ACTH then can be explained by the fact that a single dose of ACTH, while causing an immediate rise in circulating corticosteroids, is followed by a fall in blood level below normal, so that there is a deficiency of corticosteroids. This presumably is responsible for the hemorrhage. Finally, the hemorrhage with STH is related to the corresponding effect of desoxycorticosterone (11).

Summary

1. Rats receiving dicumarol were given injections of desoxycorticosterone, cortisone, hydrocortisone, ACTH, somatotrophin, sodium salicylate, adrenaline, reserpine, histamine, 10% sodium chloride intraperitoneally. A high incidence of hemorrhagic death was observed with desoxycorticosterone, ACTH, STH, sodium salicylate, 10% sodium chloride, histamine, adrenaline, reserpine. Little hemorrhage was observed with cortisone and hydrocortisone.

2. The mortality resulting from 10% sodium chloride stress in dicumarolized rats was not depressed by dial, or phenergan, or pretreatment with cortisone. The mortality was prevented by treatment with vitamin K_1 before giving the stress agent.

3. The mean prothrombin time with dicumarol in rats appeared to be increased by the administration of ACTH, sodium salicylate, 10% sodium

chloride, desoxycorticosterone, adrenaline and histamine. No modification was observed by cortisone, dial, reserpine. With hydrocortisone — there was an increase the day after giving the steroid, but the prothrombin time was nearly normal 2 days later.

4. Steroids were tested for their ability to protect adrenalectomized rats from hemorrhage with dicumarol. Desoxycorticosterone had no action in this regard. Cortisone and hydrocortisone were effective with cortisone being more active.

Résumé

1. Chez le rat, l'administration concomitante de dicoumarol d'une part, de désoxycorticostérone, d'ACTH, de STH, de salicylate de soude, de chlorure sodique, d'histamine, d'adrénaline ou de réserpine d'autre part entraîne la mort par hémorragies viscérales. L'hydrocortisone ou la cortisone sont-elles injectées dans les mêmes conditions, les animaux survivent sans présenter d'hémorragies décelables.

2. Chez les rats traités par dicoumarol, l'injection de dial, de phénergan ou de cortisone prélablement au stress par le chlorure sodique hypertonique ne diminue pas l'influence que ce dernier exerce sur la mortalité. Par contre, l'injection d'une dose de vitamine K_1, qui ramène le taux de prothrombine au voisinage de la normale, protège les animaux contre l'action léthale de ce stress.

3. L'ACTH, le salicylate de soude, le chlorure sodique, la désoxycorticostérone, l'adrénaline ou l'histamine entraînent chez les rats traités par dicoumarol, un accroissement de la valeur moyenne du temps de prothrombine. La cortisone, le dial et la réserpine ne possèdent pas cette action.

Chez les rats soumis à l'action de l'anticoagulant, puis injectés d'hydrocortisone, le temps de prothrombine est accru par rapport aux contrôles, le jour qui suit l'administration de l'hormone. Il est, par contre, au voisinage de la normale deux jours plus tard.

4. Les rats surrénalectomisés traités par dicoumarol meurent d'hémorragie.

Divers corticostéroïdes ont été administrés aux animaux surrénalectomisés pour tester leur pouvoir de protection contre l'action du dicoumarol. La désoxycorticostérone est sans effet. Par contre, l'hydrocortisone et surtout la cortisone se sont révélées efficaces.

Zusammenfassung

1. Dicumarol-behandelte Ratten erhielten intraperitoneal Desoxycorticosteron, Cortison, Hydrocortison, ACTH, Somatotrophin, Natriumsalicylat,

Adrenalin, Histamin oder 10% Natriumchlorid. Nach Desoxycorticosteron, ACTH, STH, Natriumsalicylat, 10% Natriumchlorid, Histamin, Adrenalin und Reserpin wurde ein hoher Prozentsatz tödlicher Blutungen beobachtet. Nach Cortison und Hydrocortison hingegen traten nur geringfügige Blutungen auf.

2. Durch Dial, Phenergan oder Cortison-Vorbehandlung ließ sich die Mortalität nach Natriumchlorid „Stress" bei der Dicumarol vorbehandelten Ratte nicht senken. Eine Vitamin-K1-Behandlung vor Verabfolgung des Stress auslösenden Agens verhinderte den tödlichen Ausgang.

3. ACTH, Natriumsalicylat, 10% Natriumchlorid, Desoxycorticosteron, Adrenalin und Histamin erhöhen die durchschnittliche Prothrombinzeit nach Dicumarolverabreichung. Cortison, Dial und Reserpin hingegen beeinflussen diese nicht. Hydrocortison verursachte eine Erhöhung am Tage nach der Verabreichung, zwei Tage später war die Prothrombinzeit fast wieder normal.

4. Die Möglichkeit, adrenalektomierte Ratten mit Steroiden gegen eine tödliche Dicumarolblutung zu schützen, wurde überprüft. Desoxycorticosteron erwies sich hier im Gegensatz zu Hydrocortison und dem aktiveren Cortison als unwirksam.

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