ceeds the intake, and there is a shift of the major excretion from the stool to the urine.

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Antipyretic Action of Magnesium Chlorid Alone and Combined With Amidopyrin.

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The temperature reducing properties of magnesium salts in doses below the threshold for the well known Meltzer narcosis, have been described by J. Schütz,[1] for normal rabbits. Rabbits artificially fevered with *β-tetra-hydro-naphthylamin* also exhibited antipyresis with magnesium. The latter, however, has apparently never been investigated hitherto with regard to the reduction of fever of bacterial origin. In animals with hay-infusion fever, it is not difficult to demonstrate a marked antipyretic action with doses of magnesium salts far below the toxic range. This can be especially well shown with magnesium chlorid in rabbits previously injected with hay-infusion incubated 48 hours, at 37° C.

Healthy adult rabbits after fasting over night were injected subcutaneously with 1 cc. (per kilo) hay-infusion. A rise in temperature amounting to at least 1.5° F. was found within about 2 hours, in approximately two-thirds of the injected rabbits. The antipyretic agent was injected subcutaneously, usually 2 to 3 hours after the fever injection; at least 2 well fevered rabbits were retained for controls.

In the present work $MgCl_2$ was used in 5% solution, amidopyrin in 4% solution. When "combined" the same solutions were used, one immediately following the other; whether injected at the same or different sites was found immaterial.

The results as shown in the curves (Figs. 1 and 2) represent differences in body temperature between treated animals and untreated fever controls, the zero temperature being the temperature at the time (zero hour) of giving the magnesium chlorid.

To produce definite magnesium antipyresis in hay-infusion fever rabbits, about 200 mg.* of the chlorid per kilo are required, as il-

[1] Schütz, J., *Arch. f. exper. Pathol. u. Pharmakol.*, 1916, lxxix, 285.

* All Mg calculations are made in terms of anhydrous salts.

lustrated in Fig. 1, which shows the effect of 12 injections varying from 150 to 300 mg. per kilo. The difference between the fever control curves and those resulting from 150 mg. per kilo magnesium chlorid represents approximately the maximum variation to be expected with inadequate doses.

It has been shown in this laboratory[2] that 700 mg. per kilo represents approximately the minimal lethal dose of magnesium chlorid for rabbits.

Augmentation of Amidopyrin Antipyresis by Magnesium Chlorid.

Having shown that fevered rabbits respond to doses of magnesium chlorid amounting to less than one-third of the lethal dose, we combined magnesium with another type of antipyretic drug—amidopyrin (pyramidon). Several series of experiments were performed; typical resulting curves appear in Figs. 2 to 4. A comparison of the 3 sets of curves shown in Fig. 2, shows that a very marked antipyretic effect can be elicited by 150 to 200 mg. per kilo of amidopyrin, 100 mg., however, giving a somewhat doubtful effect.

But when to this weak amidopyrin dose is added magnesium chlorid 150 mg. per kilo, these 2 ineffective components produce in combination a profound fall in temperature. The maximum decrease obtained in an average of 9 rabbits was 3.9° F. This is greater than the effect which can be produced separately by either 200 mg. per kilo amidopyrin or 300 mg. per kilo magnesium chlorid. Hence the antipyretic combination exhibits true potentiation or synergism.

With repeated doses, we attempted a closer estimation of the therapeutic equivalent of amidopyrin in terms of its combination with magnesium chloride. In the 4 series of experiments shown in Fig. 3, 5 doses were given each rabbit at half-hourly intervals. In both amidopyrin series, the dosage was 50 mg. per kilo (every half-hour); the averages of 2 sets of 3 rabbits each, showed close agreement (maximum temperature fall about 4° F.). The combination of drugs which was compared with amidopyrin consisted of a mixture of 1 part of amidopyrin with 2 parts of magnesium chlorid. The equivalent of the amidopyrin given alone was found to lie between 50 and 75 mg. per kilo of the combination (Fig. 3).

In a further series, therefore, the 50 mg. amidopyrin dose was compared with 67.5 mg. per kilo of the combination. Injections at half-hourly intervals were performed in the 2 series which each consisted of 3 rabbits. As will be seen from Fig. 4, the combination

[2] Barbour, H. G., and Taylor, W. F., (unpublished experiments).

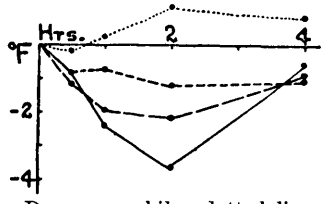

FIG. 1.

Effects of magnesium chlorid given subcutaneously, upon body temperature of fevered rabbits.

Abscissae, time after administration of antipyretic.

Ordinates, temperature changes °F, not absolute but calculated as difference from control fevered rabbits. Five fever controls.

Dosage per kilo: dotted line, 150 mg. (average of 4 rabbits); short dash line, 200 mg. (av. 2 rabbits); long dash line, 250 mg. (av. 2 rabbits); continuous line, 300 mg. (av. 2 rabbits).

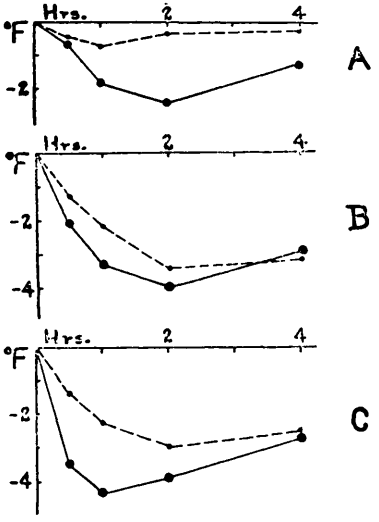

FIG. 2.

Effects of amidopyrin with and without magnesium chlorid, in fevered rabbits.

Dosage per kilo: Continuous lines, effects of amidopyrin 100 mg. plus $MgCl_2$ 150 mg. (A, 2 rabbits; B, 2 rabbits; C, 5 rabbits); broken lines, amidopyrin alone (A, 100 mg. 2 rabbits; B, 150 mg. 2 rabbits; C, 200 mg. 4 rabbits).

A, 2 fever controls; B, 1 fever control; C, 2 fever controls.

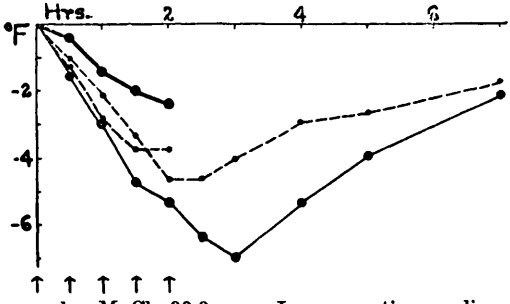

FIG. 3.

Effects of repeated doses of amidopyrin alone and combined with magnesium chlorid, in fevered rabbits.

Temperature changes absolute, no fever controls. Each curve represents the average result from 3 rabbits. Doses given half-hourly shown by arrows.

Dosage per kilo: Upper continuous line, amidopyrin 16.7 mg. plus $MgCl_2$ 33.3 mg. Lower continuous line, amidopyrin 25 mg. plus $MgCl_2$ 50 mg. Both broken lines, amidopyrin alone 50 mg.

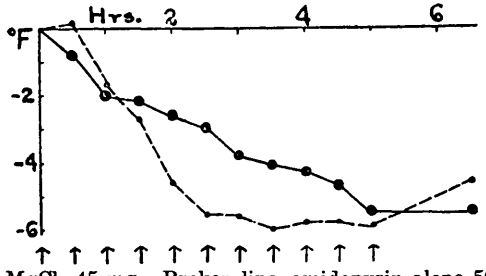

FIG. 4.

Effects of repeated doses of amidopyrin alone and combined with magnesium chlorid, in fevered rabbits.

Temperature changes absolute, no fever controls. Each curve the average from 3 rabbits. Doses given half-hourly shown by arrows.

Dosage per kilo: Continuous line, amidopyrin 22.5 mg. plus $MgCl_2$ 45 mg. Broken line, amidopyrin alone 50 mg.

maintained some advantage over amidopyrin for over an hour, that is, until the third dose was beginning to take effect, and an average fall of 2° F. had been attained. From this point on, a decidedly greater temperature fall was seen in the amidopyrin rabbits than in those given the combination.

These results are very significant inasmuch as they indicate for the magnesium-amidopyrin combination a twofold advantage over that dose of amidopyrin, causing an equal fall in 2 hours. (1) This effect was achieved more rapidly by the *combination.* (2) Further temperature reduction, signifying a *transition from the therapeutic into toxic action,* was accomplished more rapidly by the *single drug.* The latter also attained the lowest temperature.

Thus the magnesium combination exhibits both higher therapeutic efficiency and lower toxicity than does amidopyrin alone. The relative toxicity is borne out by the subsequent history of the most heavily injected rabbits (Fig. 4), for a death occurred among the 3 given amidopyrin alone, while all of those given the combination survived.

Relative Toxicity of Magnesium and Amidopyrin Alone and in Combination.

It is frequently found that the toxicity of a combination of 2 drugs differing somewhat in action, is lower than would be predicted from the known action of its components. For example, animals are likely to survive the simultaneous administration of one-half each of the fatal doses of 2 such drugs. This is readily understood from consideration of the fact that the *loci* of toxic action are more extensive. As will be seen from Table I, the minimum lethal doses have been found as follows:

$MgCl_2$	1.05 gm. per kilo.
Amidopyrin	325 mg. per kilo.
Amidopyrin + $MgCl_2$ (1:1 ratio)	500 mg. per kilo.
Amidopyrin + $MgCl_2$ (2:3 ratio)	625 mg. per kilo.

From the first 2 determinations one finds that the predicted minimum lethal doses for the 2 combinations would be 496 and 595 mg. respectively,† from which some antagonism is evident in the case of the 2:3 ratio. Thus in normal mice as well as in fevered rabbits, there is evidence in favor of a decrease in toxicity, as a result of adding to the amidopyrin quantities of magnesium chlorid which increase its efficiency.

† Prediction formula: $ab\ (A+B)/Ab+Ba$ where A parts of a drug having m.l.d.$=a$ are combined with B parts of a drug having m.l.d.$=b$.

TABLE I. *Toxicity in Normal White Mice.*

Drug*	Mg. per kilo.	Number of mice	
		Survived	Died
$MgCl_2$	1,000	2	0
	1,050	1	3
	1,100	0	4
	1,200	0	2
	1,300	0	2
	1,400	0	2
	1,500	0	2
	2,000	0	2
Amidopyrin	250	3	0
	300	7	1
	325	1	1
	350	6	4
	375	2	1
	400	7	4
	450	2	5
	500	3	4
Amidopyrin + $MgCl_2$ (2:3)	500	2	0
	562	9	1
	625	9	3
	688	8	3
Amidopyrin + $MgCl_2$ (1:1)	300	1	0
	400	2	0
	450	4	0
	500	8	2
	550	3	1
	600	0	1

*1% solutions.

Summary. 1. Magnesium chlorid proved effectively antipyretic in hay-infusion fever rabbits in doses of 200 mg. per kilo and upwards.

2. By combining doses of magnesium chlorid and amidopyrin, which separately are ineffective, marked antipyresis was produced in such rabbits.

3. The antipyretic efficiency of amidopyrin 100 mg. per kilo plus $MgCl_2$ 150 mg. per kilo was greater than the efficiency of either amidopyrin 200 mg. per kilo or $MgCl_2$ 300 mg. per kilo given separately. (Synergism.)

4. Comparing repeated doses exhibiting equivalent efficiency after 1 or 2 hours, the combination first lowered the temperature more rapidly; nevertheless the amidopyrin later produced a more rapid and extreme (toxic) effect.

5. The amidopyrin-magnesium combination (2:3) proved slightly less toxic to normal white mice than would be predicted from the known toxicity of the 2 component drugs.

Conclusion. Combinations of amidopyrin with magnesium chlorid in experimental animals exhibit antipyretic synergism, and, to a lesser extent, diminished toxicity.

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Influence of Magnesium Salts Upon the Toxicity and Antipyretic Action of the Salicylates.

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In the preceding paper we have shown that magnesium chlorid is antipyretic to rabbits in hay-infusion fever. Furthermore the antipyretic efficiency of amidopyrin was found considerably potentiated by combination with magnesium chlorid, although in the same combination the toxicity appears slightly decreased.

The synergistic action of magnesium combined with antipyretic drugs is further illustrated by the following experiments upon magnesium combinations with salicylates. The work will be described under 3 heads: (1) toxicity in normal mice of sodium salicylate alone and in combination with $MgCl_2$; (2) antipyretic action in fevered rabbits of sodium salicylate alone and combined with $MgCl_2$; (3) antipyretic action in fevered dogs of aspirin alone and in combination with magnesium oxide.

1. Toxicity.

In normal white mice, the m.l.d. (minimal lethal dose) of sodium salicylate was found to be about 600 mg. per kilo (Table I). Similarly, the m.l.d. of a combination of 2 parts sodium salicylate with 3 parts magnesium chlorid (anhydrous) was found to be approximately 975 mg. per kilo (Table II). Our criterion for judging the m.l.d., as will be seen, does not include an occasional fatality within that range of dosage where survival is obviously the rule.

In the previous report, it was shown that the m.l.d. for magnesium chlorid is approximately 1.05 gm. per kilo. Thus the predicted m.l.d. for the present combination with sodium salicylate would be 807.5* mg. per kilo. Inasmuch as 975 mg. were, with 1 exception, actually required, there is evidently an antagonism between the 2 drugs favorable to survival. The combination is about

* For prediction formula see other paper.