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ΦΑΡΜΑΚΟΛΟΓΙΑ.—**Action of bromides to the body temperature and pyrogen test,** *by G. Logaras**. Ἀνεκοινώθη ὑπὸ τοῦ κ. Γ. Ἰωκείμογλου.

In routine testing of parenteral solutions for pyrogens we have observed that a solution containing 3 % $CaBr_2$ and 5 % Calcium gluconate, lowers the body temperature of rabbits by 1 to 3° C below the initial temperature. This fall of the normal temperature has been also recorded by others in isotonic solutions of sodium chloride (1) but amounts only to 0.1—0.3° C. This fact is important and it should be taken note of in testing for pyrogens. In the experiments we are reproducing below we were concerned to find out a) whether this effect prevents the pyrogen from causing a rise in body temperature b) how this effect could be abolished and c) whether bromides have an antipyretic effect.

* ΓΕΩΡΓ. ΛΟΓΑΡΑΣ: Ἐνέργεια τῶν βρωμιούχων ἐπὶ τῆς θερμοκρασίας τοῦ σώματος.

METHODS

Pyrogens. To test for pyrogens the U.S.P. XIII method on rabbits was used.

Antipyretic effect. Rats of a Wistar strain and both sexes, weighing 200 — 300 gm, were used.

Pyrexia was induced by subcutaneous injection of 10 cc/kg body weight of a 15 % suspension of dried yeast. Calcium bromide and acetylsalicylic acid were administered intraperitoneally or subcutaneously.

RESULTS

It is necessary to take into account the toxicity of $CaBr_2$ and sodium salicylate and allow a sufficient margin between the doses employed in pyretic animals and the maximum dose tolerated by normal rats. Intraperitoneally the following results have been obtained.

3 per cent $CaBr_2$+5 per cent Ca gluconate	Number of rats injected	Number died
$CaBr_2$ 0.87 gm per kg	10	10
$CaBr_2$ 0.7 gm per kg	5	5
$CaBr_2$ 0.52 gm/kg	4	4
$CaBr_2$ 0.35 gm/kg	15	10
$CaBr_2$ 0.26 gm/kg	20	3
$CaBr_2$ 0.15 gm/kg	10	0
10 % Sod. salicylate		
0.05 gm/kg	9	0
0.1 gm/kg	15	10
0.15 gm/kg	15	13

The results are tabulated in tables I, II, and III and figures 1 and 2.

Figure 1 reproduces several temperature curves in normal rabbits after intravenous injection of a solution of $CaBr_2$ 3.0 %+5 % Calcium gluconate in a dose of 10 cc/kg body weight. By diluting the solution with sterile pyrogen free water 1 : 5 or 1 : 10 the antipyretic effect is no more noticeable and only the pyrogenic effect shown (Figure 2 and Table III).

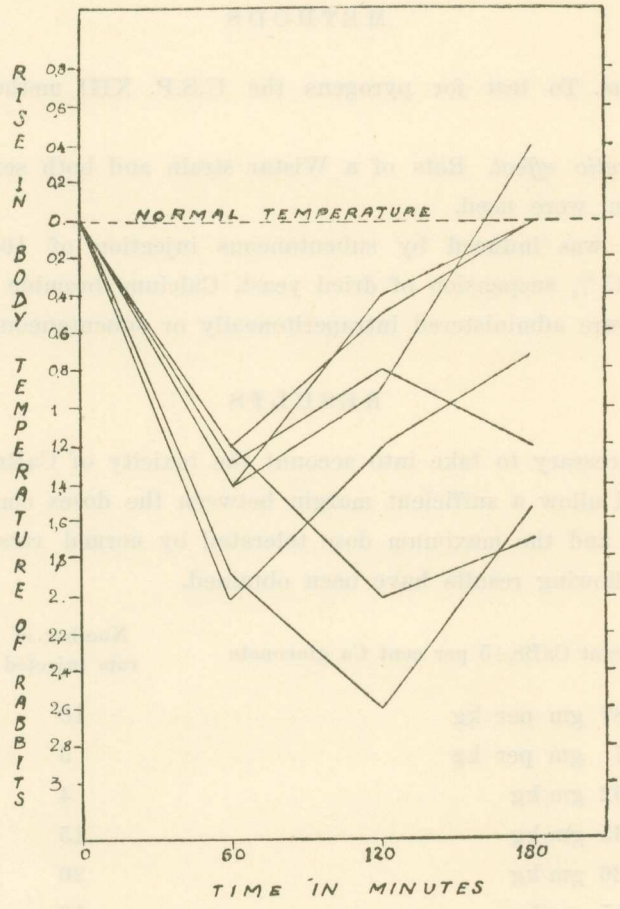

Fig. 1.

TABLE I.

Antipyretic effect of Calcium bromide.

Number of rats	dosage	Average maximum rise in temperature ° C
7	suspension of dried yeast	+0.8
15	Yeast+$CaBr_2$ 0.015 g./ 100 g. body weight	−0.70
7	Yeast+0.01 g. Acetyl-salicylic acid	−1.75

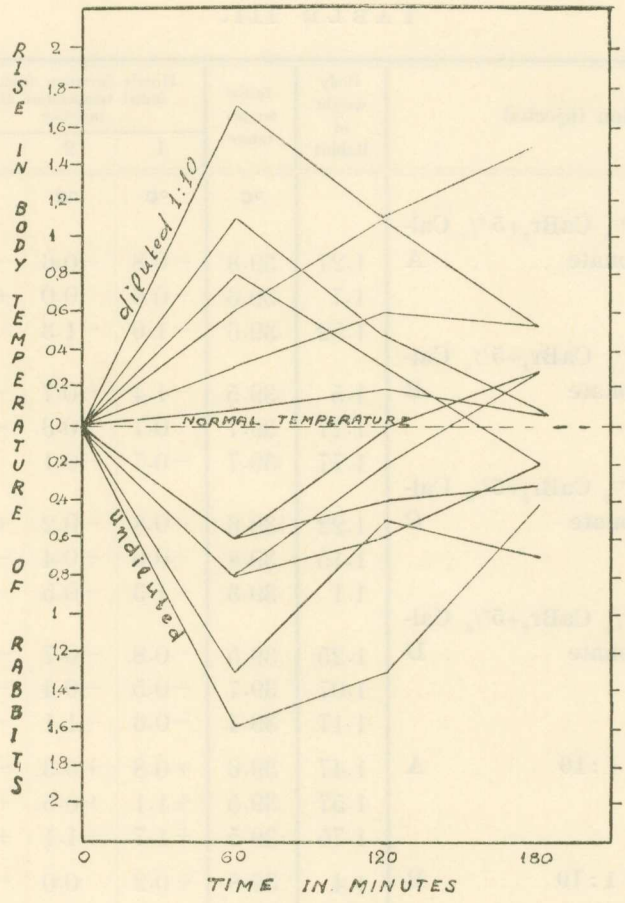

Fig. 2.

TABLE II.

Antipyretic effect of Potassium bromide

Number of rats	Dosage	Average maximum rise in temperature ° C
8	0.015 g/100 g KBr	+ 0.7
5	Controls suspension of dried yeast	+ 1.3
5	0.01 g/100 g Acetyl-salicylic acid	+ 0.3

TABLE III.

Solution injected	Body weight of Rabbit	Initial temperature	Hourly deviation from the initial temperature after injection			maximum rise or fall in temperature
			1	2	3	
		°C	°C	°C	°C	
Solution of 3 % $CaBr_2$+5 % Calcium gluconate . . . . . A	1.27	39.8	− 0.8	− 0.6	− 0.2	− 0.8
	1.7	39.6	− 0.6	0.0	+ 0.3	− 0.6
	1.52	39.6	− 1.6	− 1.3	− 0.4	− 1.6
Solution of 3 % $CaBr_2$+5 % Calcium gluconate . . . . . B	1.5	39.5	− 1.4	− 0.7	− 0.4	− 1.4
	1.77	39.7	− 0.7	− 0.3	− 0.4	− 0.7
	1.77	39.7	− 0.7	− 0.1	0.0	− 0.7
Solution of 3 % $CaBr_2$+5 % Calcium gluconate C	1.22	39.6	− 0.8	− 0.2	+ 0.3	− 0.8
	1.15	39.8	− 0.6	− 0.4	− 0.3	− 0 5
	1.1	39.3	− 1.3	− 0.5	− 0.7	− 1.7
Solution of 3 % $CaBr_2$+5 % Calcium gluconate . . . . . D	1.25	39.5	− 0.8	− 0.7	− 0.2	− 0.8
	1.07	39.7	− 0.5	− 0.4	− 0.2	− 0.6
	1.17	39.4	− 0.6	− 1.1	− 0.9	− 1.1
Same diluted 1 : 10 . . . . . A	1.47	39.6	+ 0.8	+ 0.3	− 0.2	+ 0.8
	1.57	39.5	+ 1.1	+ 0.5	+ 0.1	+ 1.1
	1.75	39.5	+ 1.7	+ 1.1	+ 1.5	+ 1.7
Same diluted 1 : 10 . . . . . B	1.4	39.8	+ 0.2	0.0	− 0.2	+ 0.2
	1.3	39.9	0.0	0.0	− 0.3	0.0
	1.4	39.5	− 0.1	+ 0.1	+ 0.1	0.1
Same diluted 1 : 10 C	1.12	39.2	+ 0.6	+ 1.1	+ 0.5	+ 1.1
	1.1	39.8	+ 0.3	+ 0.6	+ 0.5	+ 0.6
	1.12	39.7	+ 0.1	+ 0.2	+ 0.1	+ 0.2
Same diluted 1 : 5 . . . . . D	1.0	39.3	+ 0.2	− 0.2	− 0.3	+ 0.2
	1.15	39.6	− 0.3	− 0.3	− 0.2	− 0.3
	1	39.2	+ 0.1	+ 0.3	+ 0.3	+ 0.3
10 % sodium salicylate	1.43	39.3	0.0	− 0.6	− 0.9	− 0.9
	1.75	39.5	− 0.2	− 0.5	− 0.9	− 0.9
	1.45	39.6	− 1.6	− 1.8	− 1.8	− 1.8
Same diluted 1 : 10	1.32	39.7	0.0	− 0.2	− 0.4	− 0.4
	1.25	39.7	− 0.1	− 0.1	− 0.2	− 0.2
	1.62	39.4	+ 0.5	+ 0.4	+ 0.1	+ 0.5

DISCUSSION

As it is well known convulsant drugs (picrotoxin, strychnine etc.) produce changes in heat regulation. Small doses increase heat loss, larger doses further increased loss of heat and paralytic doses diminish the heat production greatly. The temperature is changed accordingly· paralytic doses lower it greatly (Sollman 2). No such effect is described in the literature we had in our access for sedative drugs as it is our case. Recently it has been shown by J. ten Cate and J. Boeles 3) that pentothal and nembutal lower the body temperature of rats.

We know of course that the bromides show many of the actions which are typical of the depressant drugs of the hydrocarbon anaesthetics. The action of the bromide ion on the central nervous system is one of depression.

The experiments of Januschke cited by Bürgi (4) have demonstrated that sodium bromide and calcium bromide abolish the clonic spasms which cocaine causes to rabbits. The necessary amounts are smaller than the required to provoke sleep.

Our experiments show that the depressant action of the bromide ion which lowers the body temperature in rabbits can be abolished by diluting the solution to be tested 1:5 or 1:10 with pyrogen free distilled water. The same is true for sodium salicylate solutions. One could object that by diluting the solution, the concentration of pyrogen is also diluted. From theoretical point of view this objection is correct, but it has no practical value, because the minimal effective dose of pyrogen for humans is several hundred times greater than the dilution we make (5).

Further the antipyretic action of bromides on rats has been demonstrated. This antipyretic effect is enhanced by calcium ions. The calcium itself has no such effect as we have observed in very great number of pyrogen tests.

We suggest that if the same technique is applied to antipyretic drugs may prove itself useful for pyrogen tests. The problem is further complicated by the discovery of Wylie and Todd (6) that Proteus vulgaris and Pseudomonas fluorescens can produce a depressant substance, which either lowers the body temperature to below normal, or prevents the pyrogen from causing a rise in body temperature. The modifying effect of the depressant

was abolished by heating the solution between 30° and 40° C for about 10 minutes before the injection.

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ΠΕΡΙΛΗΨΙΣ

Κατὰ τὴν δοκιμασίαν διὰ τὴν ἀνίχνευσιν πυρετογόνων ἐντὸς διαλυμάτων περιεχόντων μεῖγμα 3% $CaBr_2$ καὶ 5% γλυκονικοῦ ἀσβεστίου εὕρομεν ὅτι ἡ θερμοκρασία τῶν κονίκλων κατέρχεται κατὰ 1 — 3° C κάτω τῆς ἀρχικῆς τοιαύτης. Σκοπὸς τῆς παρούσης ἐρεύνης ὑπῆρξεν ἡ διαλεύκανσις τῶν ἑξῆς τριῶν σημείων: 1) ἐὰν ἡ ἐνέργεια αὕτη τῶν βρωμιούχων ἀναστέλλει τὴν ὕψωσιν τῆς θερμοκρασίας ἐκ πυρετογόνων οὐσιῶν. 2) διὰ ποίας μεθόδου δύναται νὰ ἀνασταλῇ ἡ ἐνέργεια αὕτη καὶ 3) ἐὰν τὰ βρωμιοῦχα ἔχουν ἀντιπυρετικὴν ἐνέργειαν.

Ἀποτελέσματα: Εὑρέθη πρῶτον ἡ μέση θανατηφόρος δόσις DL 50 ἐπὶ ἐπιμύων.

1) τοῦ μείγματος 3% $CaBr_2$ καὶ 5% γλυκονικοῦ ἀσβεστίου.
2) τοῦ σαλικυλικοῦ νατρίου.
3) τοῦ ἀκετυλοσαλικυλικοῦ ὀξέος.

Ἀπὸ πειράματα ἐπὶ ἐπιμύων εἰς τοὺς ὁποίους προεκλήθη πειραματικῶς πυρετὸς εὑρέθη ὅτι πράγματι τὰ ἀνόργανα ἅλατα τοῦ βρωμίου ἔχουν ἀντιπυρετικὴν ἐνέργειαν εἰς τὰς χρησιμοποιηθείσας δόσεις. Τὴν ἐνέργειαν ταύτην ἐπαυξάνει ἡ σύγχρονος χορήγησις ἐνώσεων ἀσβεστίου.

Διὰ πειραμάτων ἐπὶ κονίκλων εὑρέθη ὅτι ἡ ἐνέργεια τῶν βρωμιούχων ἐπὶ τῆς θερμοκρασίας τοῦ σώματος ἀναστέλλει τὴν ἐνέργειαν τῶν πυρετογόνων οὐσιῶν ἐπὶ τῆς θερμοκρασίας, οὕτω δὲ συσκοτίζεται τὸ ἀποτέλεσμα τῆς δοκιμασίας

διὰ τὴν ἀνίχνευσιν πυρετογόνων. Δι' ἀραιώσεως τοῦ ὑπ' ἐξέτασιν διαλύματος 1 : 5 ἢ 1 : 10 δι' ὕδατος ἀπεσταγμένου καὶ ἐλευθέρου πυρετογόνων οὐσιῶν, δὲν παρατηρεῖται πλέον ἡ ἐνέργεια αὕτη τῶν βρωμιούχων ἢ σαλικυλικῶν ἐπὶ τῆς μοκρασίας, οὕτω δὲ τὸ ἀποτέλεσμα τῆς ἐξετάσεως διὰ πυρετογόνους οὐσίας δὲν διαταράσσεται. Ἡ παρατήρησις ὅτι δι' ἀραιώσεως τοῦ διαλύματος ἀραιοῦται καὶ ἡ πυκνότης εἰς πυρετογόνους οὐσίας δὲν ἔχει πρακτικὴν ἀξίαν, διότι ἡ ἐλαχίστη δόσις ἥτις προκαλεῖ πυρετογόνον ἀντίδρασιν ἐπὶ ἀνθρώπων εἶναι πολλαπλασία τῆς λαμβανομένης ἀραιώσεως.

Γεωργ. Μαρίνου, Συνθῆκαι γενέσεως τοῦ ὀρυκτοῦ Οὐβαροβίτου ἐντὸς χρωμιτικοῦ κοιτάσματος παρὰ τὸν Δομοκόν *.

* Θὰ δημοσιευθῇ κατωτέρω.