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THERAPY OF BOVINE MASTITIS: THE INTRAMAMMARY TISSUE COMPATIBILITY OF MASTITIS REMEDIES ADMINISTERED INTRACISTERNALLY TO COWS

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ABSTRACT

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Eight different mastitis remedies were administered intracisternally on a rotational basis to the 48 quarters of 12 mastitis negative cows. The resulting intramammary reactions were monitored by determining the Somatic Cell Count (SCC) and Bovine Serum Albumin (BSA) levels in milk. The reactions observed indicate that the intramammary cellular reactions frequently elicited by the local treatments in the treated and sometimes even in the untreated quarters of the treated udders are not necessarily inflammatory in nature. Evaluation of the intramammary tissue compatibility of a mastitis remedy mainly in terms of SCC values therefore seems unreliable. Moreover, it may do injustice to a product unless the SCC values are augmented by BSA or other determinations providing a more accurate indication of truly mastitic reactions. The investigation also implies that the patterns of cellular reactions related to individual mastitis remedies require further elucidation before they can be used as indications of an advantageous or disadvantageous intramammary tissue compatibility of a product. Intramammary tissue compatibility, as such, of mastitis remedies and comparable agents requires definition. It seems more expedient, however, that such a definition and the necessary standardization of mastitis remedies in terms of their intramammary tissue compatibility be attempted by the International Dairy Federation (IDF).

Résumé

THÉRAPEUTIQUE DE LA MASTITE BOVINE: COMPATIBILITÉ AVEC LE TISSU INTRAMAMMAIRE DE REMÈDES INJECTÉS PAR VOIE INTRAMAMMAIRE

On à utilisé huit remèdes anti-mastitiques différents, qu'on a injectés à tour de rôle par voie intramammaire dans 48 quartiers de 12 vaches mastite-négatives. Les réactions intramammaires qui en ont résulté ont été suivies en effectuant dans le lait le comptage des cellules somatiques (SCC) et la détermination du taux de sérum-albumine bovine (BSA). Les observations indiquent que les réactions cellulaires intramammaires fréquemment élicitées par des applications locales dans les quartiers traités, et parfois même dans les quartiers non traités du même pis, ne sont pas nécessairement de nature inflammatoire. Il semble dès lors qu'évaluer la compatibilité intramammaire du'un remède anti-mastitique en se basant principalement sur les valeurs du SCC n'est pas un procédé fiable. On risquerait par surcroît de condamner un produit à tort, sauf si les valeurs du SCC sont corroborées par des taux de BSA ou autres déterminations qui indiquent de manière plus précise l'existence de réactions vraiment mastitiques. Cette enquête mène également à la conclusion que les schémas de réactions cellulaires liés à l'administration de remèdes anti-mastitiques particuliers doivent être mieux éclaircis avant de pouvoir servir d'indicateurs quant à la compatibilité intramammaire plus ou moins grande d'un produit. Du reste, cette compatibilité des remèdes anti-mastitiques et d'agents du même ordre avec le tissu intramammaire demande à être définie comme telle. Il semble plus opportun toutefois de laisser à la Fédération Laitière Internationale le soin de formuler pareille définition et de s'attaquer à la standardisation nécessaire des remèdes anti-mastitiques sous le rapport de leur compatibilité avec le tissu intramammaire.

INTRODUCTION

Bovine mastitis is mainly treated with a wide range of antibiotic formulations administered intracisternally either during lactation or at the commencement of the dry period. It seems reasonable, therefore, to expect that mastitis remedies should show *in vivo* maximal antibacterial efficacy and cause minimal damage to the mammary parenchyme (Walser, 1958), and that extensive data should be available on intramammary tissue compatibility of locally administered mastitis remedies.

Much information on so-called intramammary irritations caused by local mastitis therapy is, in fact, available. The data were established either by means of clinical methods alone (Seelemann & Neumann, 1949; Rackow, 1950; Pellander, 1950; Götze, 1951; Graf, 1954) or by clinical and laboratory methods combined (Baumgartner, 1947; Walser, 1958; Brunschwiler, 1961; Cott, 1961; Giesecke, 1965; Schmidt, 1967; Majic, 1972).

However, owing to the absence of a standardized method of investigation, the data usually cannot be compared and consequently the term "irritation of the udder" remains undefined. The criteria of "minimal intramammary damage" demanded by Walser (1958) are left undetermined and, furthermore, it is very doubtful whether the methods used are really suitable for the determination of truly mastitic reactions. This applies especially to data based mainly on changes of the SCC/ml of milk, since there is evidence that elevated SCC values in milk do not necessarily indicate mastitis (Giesecke, 1974; 1975a, b; Giesecke & Van den Heever, 1974; Giesecke & Viljoen, 1974). The same data also indicate that in work on bovine udder health during lactation it would be advantageous to distinguish between true and non- (or pseudo-)inflammatory conditions, such as pre-inflammatory leucocytosis and premature regression.

Because these distinctions were not made during the earlier work, it seemed desirable to determine whether intramammary irritation due to local treatment is, in fact, synonymous with mastitic damage and whether SCC values are a reliable indication of the intramammary tissue compatibility of mastitis remedies administered intracisternally.

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MATERIALS AND METHODS

Experimental animals

The 12 Friesian cows used for the investigation belonged to the same dairy herd, were kept under identical conditions of feeding and management and were milked by machine twice daily. The cows were 2–4 months in lactation, free from tuberculosis, brucellosis and mastitis; they were also clinically healthy in other respects and in good condition. The cows differed, however, in age, number of lactations and daily milk yields.

Samples

After being disinfected before milking, the udders were thoroughly dried with disposable paper towels and the teats, and especially their tips, were vigorously swabbed with 70% ethanol. The first 3 jets of milk from each quarter were aseptically collected into individual sterile McCartney bottles. Samples were taken regularly at the morning milking.

Compounds administered

The following 8 commercial products described in the manufacturers' declaration of contents were tested on 3 cows each—

(i) Compound A—20 ml of an aqueous solution containing 15,5% m/v serum protein with 85% immunoglobulin, 200 000 i.u. penicillin G and 250 mg dihydrostreptomycin sulphate;
(ii) Compound B—1 tube of 5 ml with 150 mg penethamate hydroiodide; 150 mg dihydrostreptomycin sulphate, 50 mg framycetin sulphate and 5 mg prednisolone in vegetable oil base;
(iii) Compound C—1 tube of 5 ml containing 300 000 i.u. penethamate hydroiodide and 300 mg dihydrostreptomycin sulphate in a vegetable oil base;
(iv) Compound D—1 tube of 3 g with 500 mg cloxacillin as benzathine salt suspended in a long-acting base with 3% aluminium monostearate;
(v) Compound E—1 tube of 3 g containing 200 mg cloxacillin as sodium salt monohydrate suspended in a long-acting base;
(vi) Compound F—1 tube containing 5,9% m/v rolitetracycline;
(vii) Compound G—1 tube of 7 g with 200 mg chlortetracycline hydrochloride, 200 mg neomycin sulphate and 100 mg dihydrostreptomycin sulphate;
(viii) Compound H—1 tube of 14,2 g containing 426 mg oxytetracycline HCl in propylene glycol at a concentration of 30 mg/g.

Treatments

After the 48 quarters of the 12 cows had been checked on 3 successive days (Day-2 to 0), the compounds to be tested were intracisternally administered immediately following the afternoon milking on Day 0. The completely milked udders and teats were thoroughly dried, the teat tips disinfected and the compound administered once only into 1 of the 4 quarters of each cow, leaving the remaining 3 quarters to serve as untreated controls. The compounds remained in the treated quarters until the subsequent morning milking (Day 1) when, after an interval of 15 h, the first post-treatment samples were collected from treated and untreated quarters alike. The daily examinations were repeated thereafter until the SCC and/or BSA values of the treated quarters reverted to pre-treatment levels for 2 successive days. The subsequent treatment with another compound commenced in the quarter positioned diagonally opposite to the quarter treated last. Thus treatments were performed on a rotational basis and the shortest interval occurring between the 1st and 2nd treatments of the same quarter was not less than 5 weeks.

Laboratory examinations

The fresh milk samples were subjected within 30 min of sampling to cytological, bacteriological and immunochemical laboratory examinations as described by Giesecke & Viljoen (1974).

Results

The cellular reactions

The SCC values (Table 1) observed before the treatments (Day-2 to 0) were all lower than the critical threshold value of 500×10^3 cells/ml of milk. However, the values fluctuated considerably within this normal limitation, especially in the cows subsequently treated with Compounds A, B, C and D. Such patterns of the individual normal fluctuations were changed by the treatments, which apparently caused some cellular reaction not only in the treated but also in the untreated quarters.

The cellular reactions of the treated quarters as a rule resulted in SCC values elevated above the pre-treatment values, or even above the critical threshold value of 500×10^3 cells/ml of milk, and showed rather variable patterns of development briefly characterized as follows:

(i) an initial, abnormally elevated peak level gradually decreased during the following 3 days and dropped thereafter to normal and pre-treatment levels (Compound A);
(ii) an initial, abnormally elevated peak level suddenly dropped during the following 3 days to normal but fluctuating values, and decreased thereafter to pre-treatment levels (Compounds B and E);
(iii) an initial, slightly abnormal value gradually rose to an abnormally high peak level, then gradually returned to pre-treatment values (Compound C);
(iv) an initial, distinctly abnormal value rose further to an abnormally high peak level and then rapidly dropped to pre-treatment values (Compound G);
(v) an initial, gradual rise to a moderate peak level within normal limitations was followed by a more rapid decrease to pre-treatment values (Compound H); and
(vi) an initial, very moderate peak level within normal limitations was eventually followed by rather fluctuating but also normal values (Compounds D and F).

In contrast, the cellular reactions of the untreated quarters showed the following characteristics:

(i) a distinct drop to consistently lower and less fluctuating normal levels than those observed before treatment (Compound A);
(ii) a slight drop to mostly lower and more fluctuating normal values than those observed before treatment (Compound B);
(iii) a slight drop to mostly lower and less fluctuating normal levels than those observed before treatment (Compound D);
(iv) a slight drop to mostly lower and markedly more fluctuating levels than those observed before treatment (Compound C);
(v) a distinct elevation to mostly higher and more fluctuating normal values than those observed before treatment (Compound E); and
(vi) a slight elevation to sometimes higher and more fluctuating normal values than those observed before treatment (Compounds F, G and H).

The fluctuations of the SCC values before and after treatments and the differences between the cellular reactions of the treated and untreated quarters are illustrated in Fig. 1 & 2.

TABLE 1 Changes in the somatic cell count (SCC) $\times 10^3$/ml of milk before and after intramammary treatments of mastitis negative cows with Compounds A–H

Treatments		Day of investigation								
		Before treatment			After treatment					
Compounds	Quarters	—2	—1	0	1	2	3	4	5	6
		Mean SCC $\times 10^3$ per ml of milk								
A.....	Untreated.....	105*	110	111	58**	54	67	63	71	79
	Treated***.....				9 813	5 113	1 625	713	788	350
B.....	Untreated.....	72	66	57	56	54	83	72	50	50
	Treated.....				1 217	217	250	267	117	50
C.....	Untreated.....	132	90	115	50	89	50	50	233	94
	Treated.....				633	667	1 033	1 567	2 417	700
D.....	Untreated.....	52	70	52	272	172	122	67	133	106
	Treated.....				1 267	1 700	250	233	100	67
E.....	Untreated.....	75	64	85	50	75	71	75	67	63
	Treated.....				50	250	75	100	88	100
F.....	Untreated.....	56	50	50	50	89	50	50	50	72
	Treated.....				50	300	150	50	50	50
G.....	Untreated.....	50	50	50	72	78	50	50	50	50
	Treated.....				883	1 217	300	50	50	50
H.....	Untreated.....	50	50	50	58	67	104	58	50	50
	Treated.....				113	225	463	125	50	50

* n=12 quarters
** n= 3 quarters
*** n= 9 quarters

TABLE 2 Changes in the BSA levels of milk before and after intramammary treatments of mastitis negative cows with Compounds A–H

Treatments		Day of investigation								
		Before treatment			After treatment					
Compounds	Quarters	—2	—1	0	1	2	3	4	5	6
		Mean diameter (mm) of precipitation zone of BSA								
A.....	Untreated.....	4,18	4,21	4,25	4,58	4,08	4,25	3,92	3,58	4,08
	Treated.....				9,25 (4,75)	5,50	4,50	4,00	3,75	4,25
B.....	Untreated.....	4,67	4,70	4,67	3,11	3,67	3,67	4,00	3,67	3,00
	Treated.....				3,00	3,67	3,67	4,25	3,67	3,00
C.....	Untreated.....	4,00	4,05	4,00	3,00	3,44	4,00	4,78	4,78	4,78
	Treated.....				3,33	3,67	5,89	6,67	6,67	6,67
D.....	Untreated.....	4,06	4,00	4,00	4,00	4,00	4,00	3,33	3,78	3,89
	Treated.....				4,25	5,67	5,60	3,67	4,00	4,00
E.....	Untreated.....	3,46	4,00	3,38	3,50	3,58	3,58	4,00	4,00	4,00
	Treated.....				3,50	3,75	3,50	4,00	4,00	4,00
F.....	Untreated.....	3,00	3,00	3,00	3,67	3,33	3,56	4,08	4,56	5,44
	Treated.....				5,67	4,33	5,00	4,67	5,00	5,67
G.....	Untreated.....	4,00	4,00	4,00	3,67	3,67	3,67	3,67	3,67	3,67
	Treated.....				6,00	5,00	4,33	3,67	3,67	3,67
H.....	Untreated.....	4,00	3,67	4,00	4,08	3,58	4,00	3,75	3,58	4,00
	Treated.....				4,50	5,00	5,00	4,25	4,00	4,00

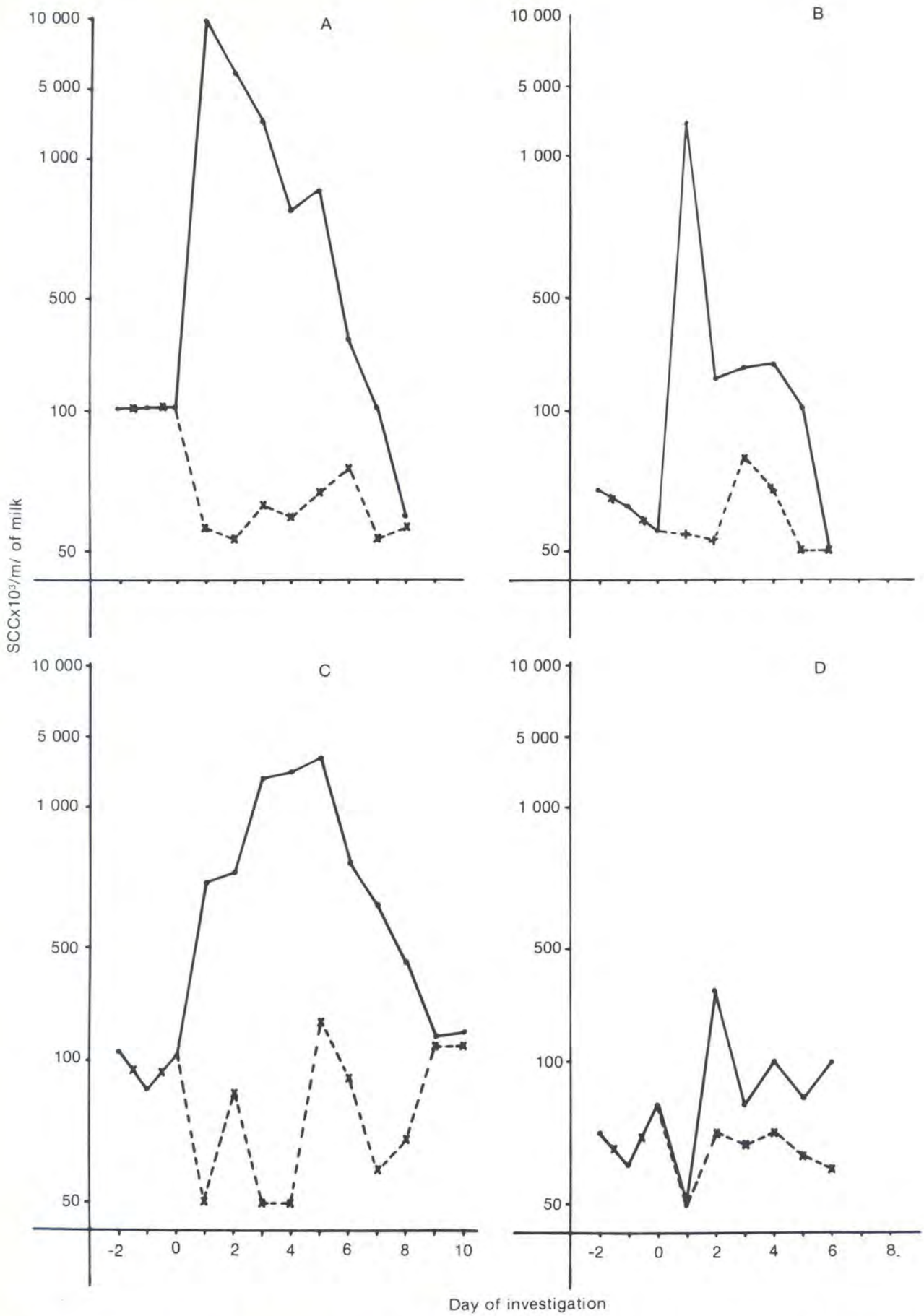

FIG. 1 Mean SCC values before and after intracisternal administration of Compounds A, B, C and D, respectively. x- - - - - -x = untreated quarters; •————• = treated quarters

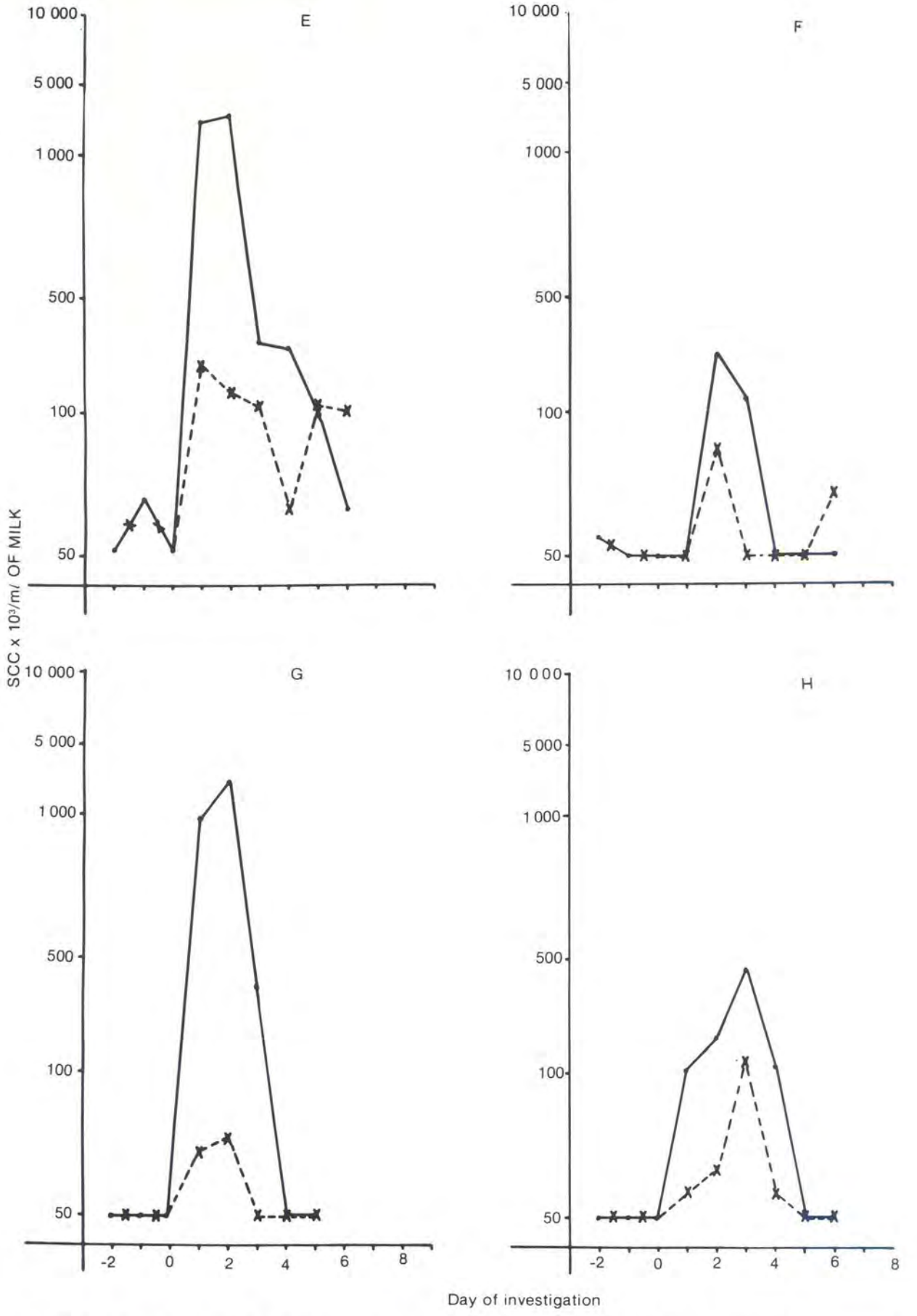

FIG. 2 Mean SCC values before and after intracisternal administration of Compounds E, F, G and H, respectively. x------x = untreated quarters; •————• = treated quarters

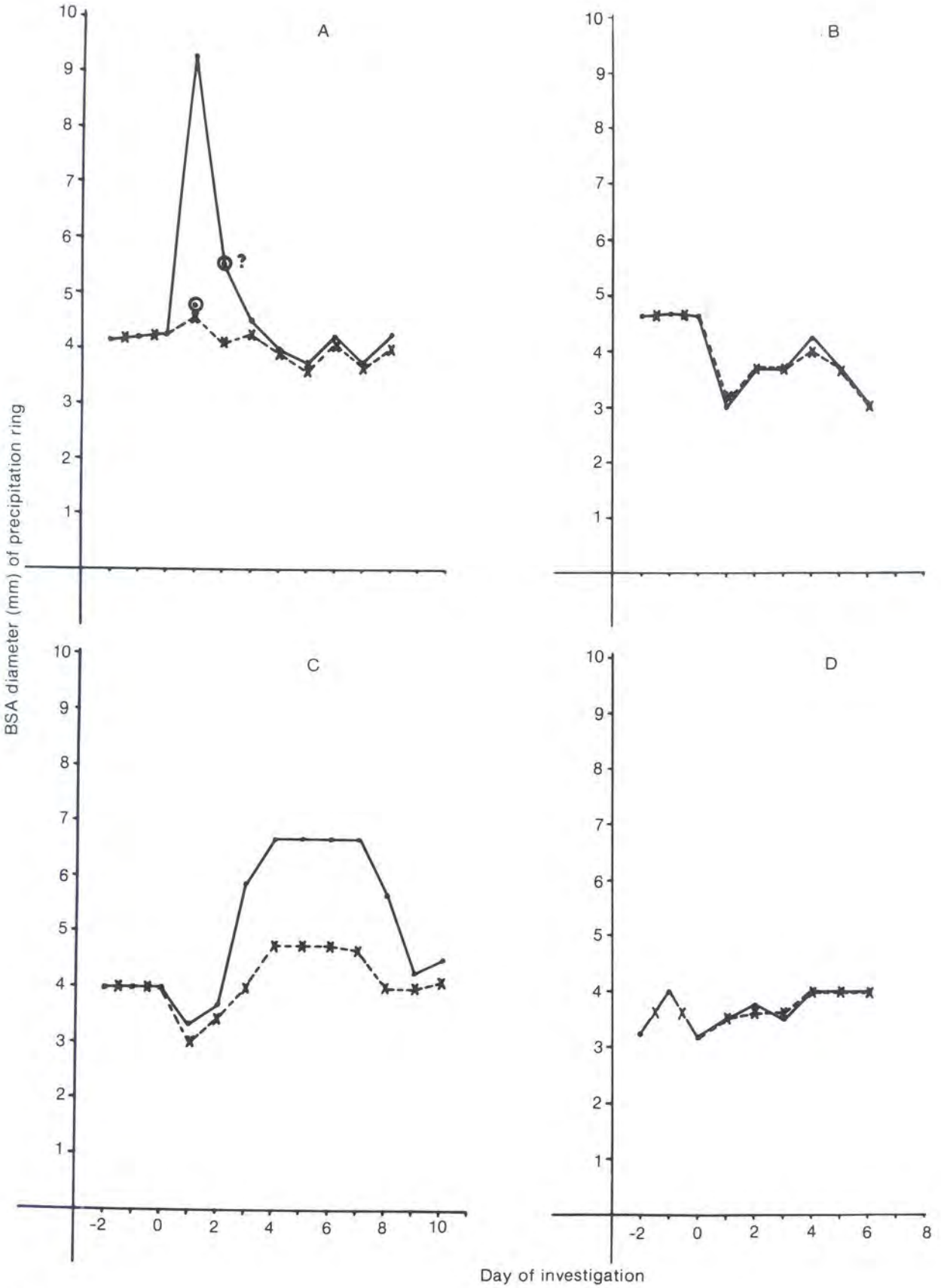

FIG. 3 Mean BSA values before and after intracisternal administration of Compounds A, B, C and D, respectively. x------x = untreated quarters; •————• = treated quarters; ○ = corrected BSA value; O? = uncorrected doubtful BSA value

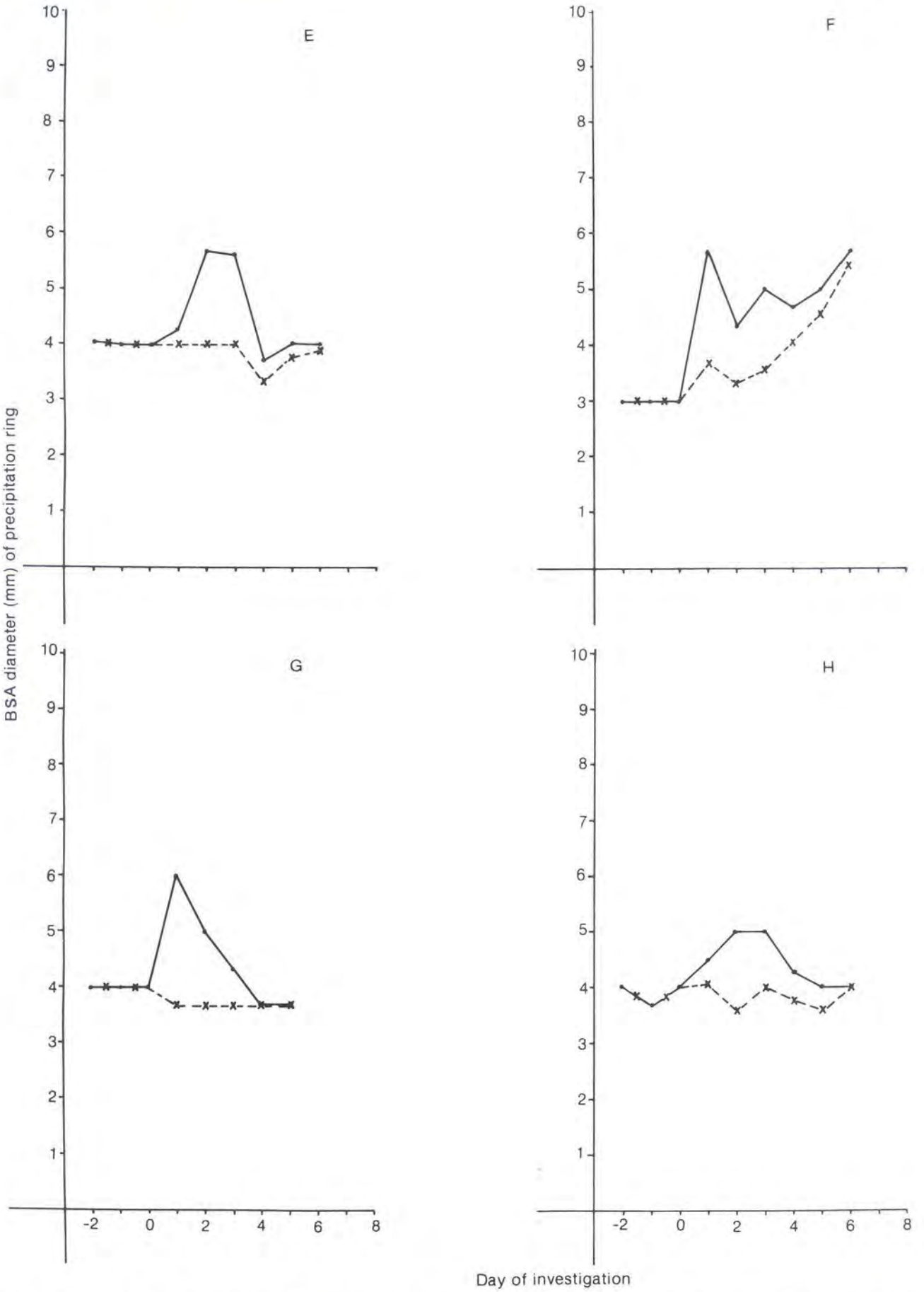

FIG. 4 Mean BSA values before and after intracisternal administration of Compounds E, F, G and H, respectively. x------x = untreated quarters; •————• = treated quarters

The BSA reaction

The BSA values (Table 2) observed before and after administration of the intramammary treatments (Day-2 to 0) were all lower than the critical threshold value indicated by a precipitation zone of BSA with a diameter of 8 mm. The treatment resulted generally in fluctuations of the BSA values, that were considerably less distinct than the corresponding cellular reactions. This also applies to Compound A which contained serum proteins including BSA at a level that resulted in a precipitation zone with a diameter of 4,5 mm. As a result the milk of the cows, treated with Compound A, on Day 1 showed a BSA level which produced a zone of precipitation with a diameter of 9,25–4,50=4,75 mm. The corresponding BSA value of 5,5 mm on Day 2 (Table 2) cannot be corrected in the same way because it could be related to the BSA contents of Compound A as such and/or a slight increase of the BSA level of milk caused by some effect of the compound on the mammary epithelium.

TABLE 3a Mean values, standard deviations and coefficients of variation of the SCC $\times 10^3$/ml of milk before and after intramammary treatments of mastitis negative cows with Compounds A–H

Compounds investigated	SCC $\times 10^3$/ml of milk								
	Before treatments			After treatments					
	All quarters together			All untreated quarters			All treated quarters		
	Mean value	Standard deviation	Coefficient of variation (%)	Mean value	Standard deviation	Coefficient of variation (%)	Mean value	Standard deviation	Coefficient of variation (%)
A	109,18	13,49	12,35	65,28	9,00	13,78	3 066,67	3 768,64	121,91
B	65,35	13,41	20,52	60,93	13,70	22,49	352,49	431,33	122,26
C	112,76	23,27	20,63	94,44	71,06	75,23	1 169,45	706,04	60,37
D	75,56	11,40	15,08	66,67	9,50	14,25	110,42	70,89	64,20
Subtotal 1	90,71	25,84	28,49	71,82	36,85	51,30	1 174,82	2 143,35	182,44
E	58,65	9,86	16,81	145,37	71,09	48,90	602,78	699,40	116,02
F	52,04	4,99	9,58	60,19	16,64	27,64	108,33	102,06	94,21
G	50,00	0,0	0,0	58,33	13,03	22,33	425,00	504,84	118,78
H	50,00	0,0	0,0	64,58	20,37	31,54	170,83	156,66	91,70
Subtotal 2	52,67	6,30	11,96	82,11	51,79	63,07	326,73	458,82	140,42
Total values	71,69	26,76	37,32	76,97	44,77	58,16	750,78	1 592,10	212,05

TABLE 3b Mean values, standard deviations and coefficients of variations of the BSA levels of milk before and after intramammary treatments of mastitis negative cows with Compounds A–H

Compounds investigated	Diameters (mm) of precipitation zone of BSA								
	Before treatments			After treatments					
	All quarters together			All untreated quarters			All treated quarters		
	Mean value	Standard deviation	Coefficient of variation (%)	Mean value	Standard deviation	Coefficient of variation (%)	Mean value	Standard deviation	Coefficient of variation (%)
A	4,20	0,0	1,0	4,1	0,3	8,2	4,5	0,6	13,9
B	4,60	0,0	0,5	3,5	0,3	10,9	3,5	0,4	13,4
C	4,00	0,0	0,1	4,1	0,7	18,8	5,4	1,5	28,4
D	3,60	0,3	8,7	3,7	0,2	6,5	3,7	0,2	6,4
Subtotal 1	4,10	0,4	10,1	3,9	0,5	13,3	4,3	1,1	26,1
E	4,0	0,0	1,1	3,8	0,2	6,8	4,5	0,8	19,2
F	3,0	0,0	0,0	4,1	0,7	19,1	5,0	0,5	10,5
G	4,0	0,0	0,0	3,6	0,0	0,0	4,3	0,9	21,6
H	3,8	0,1	4,3	3,8	0,2	5,8	4,4	0,4	10,2
Subtotal 2	3,7	0,4	11,7	3,8	0,4	11,1	4,6	0,7	15,9
Total values	3,9	0,4	11,9	3,9	0,5	12,1	4,5	0,9	21,2

TABLE 4 The observed SCC and BSA values calculated as percentages of their corresponding critical threshold values

Nature of samples and diagnostic parameters used	Compounds investigated and the relative (%) deviations from the critical threshold values of the diagnostic parameters used							
	A	B	C	D	E	F	G	H
All quarters before treatment ... SCC	21,84± 2,70	13,07± 2,68	22,55± 4,65	11,73± 1,97	15,11± 2,28	10,41± 1,00	10,00	10,00
... BSA	52,50	57,50	50,00	50,00	45,00± 3,75	37,50	50,00	47,50± 1,25
All untreated quarters after treatment ... SCC	13,06± 1,80	12,19± 2,74	18,89± 14,21	29,07± 14,22	13,33± 1,90	12,04± 3,33	11,67± 2,61	12,92± 4,07
... BSA	51,25± 3,75	43,75± 3,75	51,25± 8,75	47,50± 2,50	46,25± 2,50	51,25± 8,75	45,00	47,50± 2,50
All treated quarters after treatment ... SCC	613,33±753,73	70,56±86,27	233,89±141,21	120,56±139,88	22,08±14,18	21,71±20,41	85,00±100,97	34,17±31,33
... BSA	56,25± 7,50	43,75± 5,00	67,50± 18,75	56,25± 10,00	46,25± 2,5	62,50± 6,25	53,75± 11,25	55,00± 5,00

Unlike the cellular reactions, the fluctuations of the BSA levels were too slight to give any indication of significant changes before and after treatments, although the BSA values of the treated quarters were apparently slightly more variable than those of the corresponding untreated controls. This tendency is more clearly shown in Fig. 3 & 4.

The evaluation of intramammary reactions due to local treatments

Instead of making the above detailed daily analysis throughout the prolonged period of a routine investigation, the analysis of such intramammary reactions should preferably be limited to a period of 3 days before and 6 days after treatment. The intramammary effect of a compound during this period can furthermore be characterized by means of the mean value $\bar{x}$, standard deviation (SV) and the coefficient of variation (CV) of the results (Table 3a, b).

The data (Table 3a, b) indicate the mean magnitudes plus the absolute and relative range of fluctuations of the intramammary reactions elicited. All SCC values (Table 3a) observed before treatment showed values of $\bar{x}=71,69\times10^3$ cells/ml of milk, $SD=26,76\times10^3$ cells/ml of milk and $CV=37,32\%$. The corresponding values observed after treatments were $750,78\times10^3$; $1\,592,10\times10^3$; $212,05\%$ and $76,97\times10^3$; $44,77\times10^3$; $58,16\%$ for all treated and untreated quarters, respectively. The mean values indicate, therefore, that intramammary cellular reactions were very low before treatment. The treatments were followed by marked cellular reactions in the treated quarters and to some extent in the untreated quarters. The types of cellular reactions that were apparently elicited fall into 2 major groups. Treatment with Compounds A, B, C and D were followed in the untreated quarters of the treated udders by SCC values that were lower (Table 3a, subtotal 1: $\bar{x}=71,82\times10^3$ cells/ml) than the corresponding values observed before the treatments (Table 3a, subtotal 1: $\bar{x}=90,71\times10^3$), whereas Compounds E, F, G and H produced higher post-treatment SCC values under otherwise identical conditions. The differences between the 2 types of reactions were insignificant, however, at the 5% and 1% levels of statistical significance.

The quantitative data given above only become qualitatively meaningful if evaluated in terms of critical threshold values that distinguish between normal and abnormal features of milk. The critical threshold values for the SCC and BSA values are 500×10^3 cells/ml and a precipitation zone with a diameter of 8 mm respectively. The relationship between intramammary reaction and its corresponding critical threshold value can be given by expressing the SCC and BSA values as percentages of their corresponding threshold values where the latter equal 100%, that is, the limit of normality (Table 4).

The percentage values $\leq100\%$ and $>100\%$ thus observed (Table 4) indicate the degree of normality and abnormality respectively of the intramammary reactions elicited. The combined assessment of SCC and BSA values according to criteria proposed earlier (Giesecke & Viljoen, 1974) indicates that, although several of the treatments resulted in considerable cellular reactions, none of these reactions were truly inflammatory in nature. The data clearly show that SCC values, though considerably elevated and thus indicative of some type of intramammary irritation, (that is, a deviation from the normal status) elicited by a local treatment, are not necessarily indicative of a mastitic damage in the udder.

Discussion

Walser (1958) proposed that mastitis remedies for intracisternal administration should be highly effective against mastitogenic bacteria *in vivo* but cause minimal damage to the mammary glands. Since then numerous attempts have been made to produce such remedies but the different methods used to investigate the intramammary irritations they cause have apparently led to diverse conclusions. They indicated, for instance, that the locally administered mastitis remedies either (a) elicited no intramammary irritations (Schalm, 1948; McCullock, Kiser & Migaki, 1949; Seelemann & Neumann, 1949; Trussel & Stevenson, 1949a, b; Pellander, 1950; Götze, 1951; Otta, 1953; Bauer, Ferricke & Steigler, 1960), (b) resulted in slight intramammary irritations (Baumgartner, 1947; Beijers, 1947; Kelly & Bell, 1947; Svarc, 1947; Schipper & Petersen, 1952; Graf, 1954; Reul, 1955), or, (c) caused rather variable degrees of intramammary irritations (Kästli, 1944; Benson, 1947; Swanson & Hermann, 1947; Simon Spencer, Kraft & Schenk, 1950; Kästli & Baumgartner, 1951; Richter, 1952; Seelemann & Rackow, 1952; Barnes, 1955; Bulling, 1956; Krippner, 1957; Walser, 1958; Brunschwiler, 1961; Cott, 1961; Giesecke, 1965; Schmidt, 1967; Majic, 1972).

Evaluations of this nature, even under fairly standardized conditions, are difficult, however, because of differences in sensitivity between individual cows, fluctuating SCC values before, during and after treatments, the differences between the formulations administered, a serious lack of detailed information on the qualitative characteristics of the intramammary reactions elicited and other variables. A meaningful comparison of the data available at present is, unfortunately, even more difficult because the various mastitis remedies were not assessed according to a standard procedure, and what represents intramammary damage—let alone minimal damage—or irritation due to local treatments apparently still requires definition. Consequently it is impossible to determine what advances have presumably been made over the past decade(s) in the formulation of mastitis remedies showing improved intramammary tissue compatibility. Moreover, it is doubtful whether the above-mentioned discrepancies are favourable to the future development of mastitis remedies that are improved both therapeutically and in their intramammary tissue compatibility compared with the formulations available at present. Over-reliance on the SCC determinations in milk and the interpretation of elevated SCC values as a symptom of mastitis during the evaluation of a mastitis remedy, should particularly be avoided.

From previous data (Giesecke, 1974; 1975a, b; Giesecke & Van den Heever, 1974; Giesecke & Viljoen, 1974) it is apparent that elevated SCC values in milk do not necessarily indicate mastitis. Continued over-reliance on the usually undifferentiated SCC values might thus hamper the development of mastitis remedies, including immunobiological products, which, for instance, elicit or stimulate in the udder a type of pre-inflammatory leucocytosis that may be very favourable therapeutically or prophylactically. Depending upon the SCC reactions produced, such formulations, though probably harmless to the mammary epithelium, would at present be declared to be as irritant as other formulations that cause elevated SCC values of truly inflammatory origin.

The results presented in this paper show clearly that, although several types of cellular patterns were elicited by the local treatments in untreated and treated quarters, none of these reactions was found to be inflammatory by the BSA determinations (Table 2). The compounds therefore caused some type of cellular irritation that clearly exceeded the normal fluctuations. Such reactions may eventually lead but are not necessarily equivalent to inflammation. When evaluating the irritating effect of a mastitis remedy, it is thus desirable to distinguish between mastitic lesions, other irritations and the normal condition, and relate the reactions observed to the intramammary tissue compatibility of the remedy.

The intramammary tissue compatibility of an agent may be defined as that feature of the agent that determines, during a standard test programme, whether its intracisternal administration in general affects the normal intramammary status when monitored by methods capable of distinguishing between inflammatory, non- (or pseudo-) inflammatory and normal reactions.

This investigation has shown the feasibility of characterizing the intramammary effect of a mastitis remedy sufficiently accurately by means of a procedure starting 3 days before and terminating 6 days after the local treatment. As more detailed data were not required, it seemed sufficient to summarize the corresponding daily observations by means of their mean values and standard deviations (Tables 3a, b). These values indicated clearly that some untreated quarters of the treated udders were also affected by the treatments, presumably because of collateral reactions described previously (Giesecke, 1975b). Such untreated quarters thus became unreliable controls and the degree of intramammary tissue compatibility of the mastitis remedies was established in terms of critical threshold values that distinguish between normal and abnormal features of milk. The critical threshold values for the SCC and BSA levels are 500×10^3 cells/ml of milk (Tolle, 1971) and a precipitation zone with a diameter of 8 mm respectively (Giesecke & Viljoen, 1974). The degree of intramammary tissue compatibility of the mastitis remedies was determined by expressing the mean values and standard deviations of the SCC and BSA levels observed as percentages of their corresponding threshold values which were equated to 100% and regarded as the limit of normality. Percentage values $\leq 100\%$ and $> 100\%$ thus obtained (Table 4) readily indicate degrees of intramammary tissue compatibility and could serve as a practical basis for comparisons between, classifications of or further investigations on the mastitis remedies concerned, provided a standard method is employed to establish the data.

The establishment and promotion of such a standard on the international level, for instance by the IDF, could significantly rationalize present and future attempts at research on and the development and introduction of mastitis remedies with acceptable degrees of intramammary tissue compatibility.

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