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EVALUATION OF A TISSUE CAGE MODEL FOR USE IN CATTLE*

By

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BENGTSSON, BJÖRN, JAN LUTHMAN and STEN-OLOF JACOBSSON: *Evaluation of a tissue cage model for use in cattle.* Acta vet. scand. 1984, *25*, 480—494. — Three different types of subcutaneous tissue cages were evaluated as sources of tissue fluid in cattle. The biochemical composition of fluid sampled at various intervals after insertion was analysed and compared to corresponding serum values. It was shown that steel netting cages were quickly obliterated by ingrowing tissue and therefore unsuitable. The two types of silicone rubber tubing cages, on the other hand, were not obliterated and could be sampled repeatedly for volumes of about 2 ml tissue cage fluid (TCF) up to at least 32 weeks after insertion. Repeated sampling in a 12 h period was also possible. The levels of total protein and albumin in TCF were lower than in serum, and were shown to decline in the first 12 weeks after insertion to a level of about 35 % of the serum concentration. Calcium and magnesium levels were also lower in TCF as compared to serum. The levels of chloride and potassium were slightly higher in TCF than in serum. For sodium no difference was observed and the results for inorganic phosphorous were not uniform. Repeated sampling did not alter the total protein and albumin level in TCF. It was also shown that cages with larger open areas had lower total protein content.

proteins; tissue cage fluid; tissue fluid.

Guyton (1963) orginally introduced tissue cages in order to gain access to the interstitial space and fluid by implanting perforated capsules of various shape and material subcutaneously and intramuscularly in dogs. The inner walls of the capsules became covered by tissue that grew in through the perforations leaving a fluid-filled hollow in the middle. After similar experiments performed in rabbits, *Calnan et al.* (1972) suggested that

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the fluid in the capsules was "representative of the general body interstitial fluid". *Eickenberg* (1978) came to the same conclusion after experiments with a tissue cage model in dogs. This opinion has, however, been a matter for discussion. *Liberman et al.* (1972) proposed that the tissue cage fluid (TCF) is not a sample of the "true" interstitial fluid but rather of a local interstitial fluid, whose composition is related to the local metabolism of the tissue in and around the cage. *Haljamäe et al.* (1974) expanded this opinion after comparing the cage model with a "liquid paraffin cavity" technique for sampling tissue fluid. He concluded that the latter method gave a fluid whose composition better fits the requirements of a hypothetical interstitial fluid. Nevertheless tissue cages of various shape and meterial have been used in a number of investigations, mainly of pharmacokinetical nature (e.g. *Carbon et al.* 1977, *Henning & Cars* 1982, *Holm et al.* 1978).

The tissue cage technic has been used mainly in experimental animals such as rats, dogs and rabbits but also to a very limited extent in large animals (*Piercy* 1978, *Stanton et al.* 1982). The aim of the present investigation was to evaluate the tissue cage model for use in cattle and particularly to study the chemical composition of the fluid obtained in the implanted cages.

MATERIAL AND METHODS

Three different types of tissue cages were used in the experiments (Fig. 1). The type A cage was a model previously used in rabbits (*Rylander et al.* 1978). This cage was made of stainless steel netting, cylindrical in shape, 20 mm long and with a diameter of 20 mm. The open surface of the cage was about 50 % of the total area.

The type B and C cages were made of silastic rubber tubing, 100 mm in length and with an inner diameter of 15 mm. In the type B cages about 80 holes with a diameter of 3 mm were punched out in each end leaving 40 mm in the middle of the cage unperforated. The open surface of this cage was about 30 %. The type C cage had about 60 holes in each end leaving 50 mm in the middle of the cage unperforated. The open surface was about 20 %. The ends were sealed with silicone rubber plugs. Cages of similar shape and material have been previously used in rabbits, dogs, rats and also cattle (*Calnan et al.* 1972, *Chisholm et al.* 1973, *Piercy* 1978, *Stanton et al.* 1982).

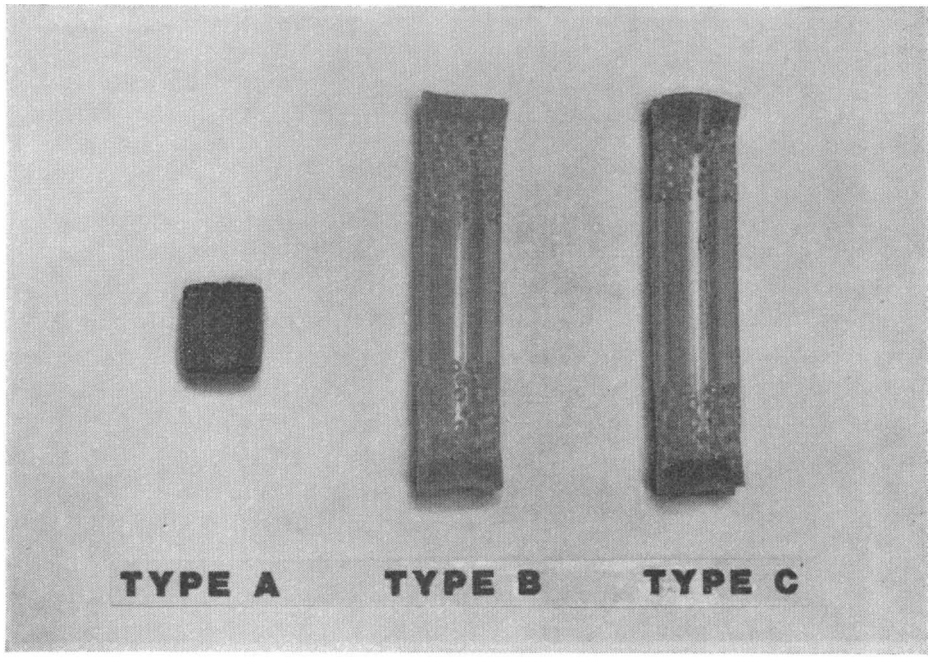

Figure 1. The 3 types of tissue cages used in the experiments.

The animals used in the experiments were 5 cows and 24 calves of the Swedish Red and White breed and the Swedish Friesian breed. The calves were between 3 and 7 months old when the cages were implanted, the cows were over 3 years old. Before the implantation of the cages the animals were given a sedative (Rompun®, Bayer) and the operation areas were shaved and washed with a disinfectant. Implanation sites were anaesthetised by subcutaneous injection of lidocain hydrochloride (Xylocain®, Astra). The cages were inserted in a tunnel which was bluntly dissected subcutaneously through a skin incision. The skin incision was closed by a continous intracutaneous suture. The cages were implanted in the lateral neck region and in the upper flank region. The type A cage was implanted in 4 calves. Each animal carried 4 cages. Type B and C cages were used simultaneously in 5 cows and 4 calves. The animals carried 3 cages of each type, 1 cage on either side of the neck and 2 cages on either side in the upper flank region. In 16 calves type B cages alone were used, each animal carried 4 cages.

The cages were sampled for tissue cage fluid (TCF) by puncturing the midsection of the cage with a syringe and a 0.6 mm needle. Sampling started 1 week after implantation and was continued, when possible, once a week for the first 7 weeks and there after at 10, 12, 14, 18 and 22 weeks. As the animals were simultaneously used in a pharmacokinetical investigation all animals were not available for sampling at the times given above. No sample for determination of biochemical composition was taken until at least 1 week after a previous sampling. All samples showing visible signs of hemorrhage or infection were discarded. Blood samples were collected by puncture of the jugular vein simultaneously with the TCF sampling.

The TCF and serum were analysed for total protein, albumin, sodium, chloride and potassium. In 10 calves, calcium, magnesium and inorganic phosphorus were also included in the analyses. In order to evaluate the effect of repeated sampling type B cages carried by 8 calves with 4 cages each were collected for 1 ml TCF 8 times in a 12 h period. At the beginning and end of the 12 h period TCF from all cages carried by each calf was pooled and analysed for total protein and albumin. This experiment was performed 6 weeks after implantation of the cages. All analyses were performed at the Department of Clinical Chemistry, Swedish University of Agricultural Sciences, Uppsala, Sweden, according to the standard methods of the department.

Tissue from type B and C cages removed 7, 14 and 32 weeks after implantation were examined histologically.

Student's t-test for paired and unpaired means was used in the statistical calculations.

RESULTS

General features of the cage models

An oedematous swelling usually occurred at the site of implantation. The swelling disappeared a couple of days after the operation, at which time the cages were neatly lined out under the skin and did not seem to irritate the animals. Of the 134 cages totally implanted 13 became infected following surgery or in the course of the experiments.

The type A cages could be sampled for small volumes of up to 0.5 ml of a clear or straw coloured fluid at 1 and 2 weeks after implantation. Thereafter no samples could be obtained from any

of these cages. The ingrowth of tissue was very fast. Only minor compartments remained in the center of the cages 3—4 weeks after implantation and the obliteration was usually complete after 5 weeks. The type A cages were usually compressed and deformed after some time in situ.

The type B and C cages made of silastic tubing could be sampled for a clear or straw coloured fluid from 1 week and up to 22 weeks after implantation when the sampling was terminated. As much as 2 ml of TCF could usually be collected from a single cage at each sampling. Repeated sampling of 1 ml TCF 8 times in a 12 h period was performed several times and usually did not cause any problem. At the end of the sampling period the number of blood tingled samples increased.

Histological examination of the tissue inside B and C cages removed at various intervals following implantation revealed that a highly vascularised granulation tissue had formed at the perforated parts inside the cages. In the early stages perivascular infiltrates of inflammatory cells were seen and later on the granulation tissue became more collagen rich with only a few mononuclear cells present. The "plugs" of granulation tissue at the ends of the cage were connected by a fibrinous strand located

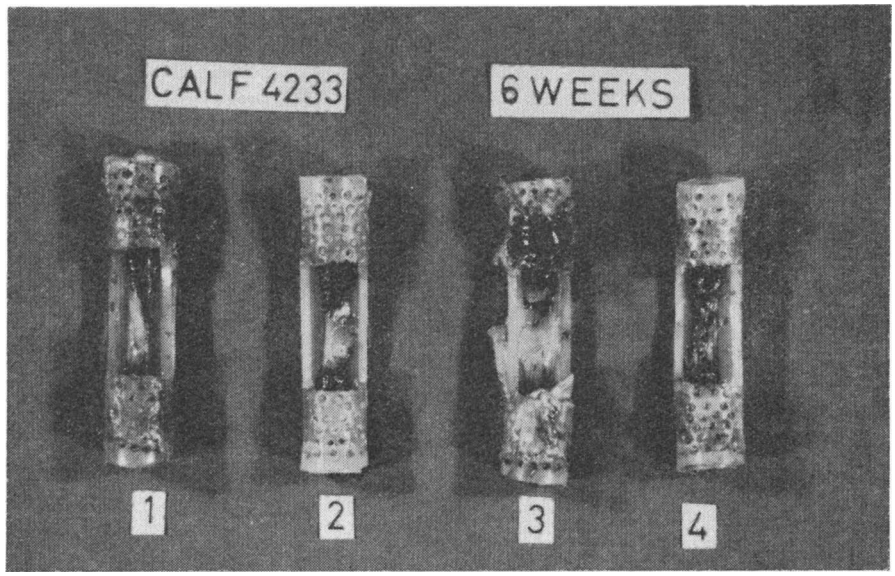

Figure 2. Type B cages removed 6 weeks after insertion and cut open to show the central fibrinous strand connecting the "plugs" of granulation tissue in the perforated parts of the cage.

in the center of the unperforated part (Fig. 2). The size of the fibrinous strand varied among cages and was not obviously greater in cages left in situ for longer periods of time. A mild calcification of the fibrinous strand was, however, present at 14 weeks. The calcification increased with time and was severe at 32 weeks. The B and C cages were not obliterated even 32 weeks after implantation.

Type B versus type C

No visible difference was observed between type B and C cages in the amount of tissue in the unperforated parts 7 weeks after implantation. The perforated parts of the cages were obliterated by granulation tissue; the amount of tissue was greater in the type B cages which had a larger perforated zone.

Analysis of TCF sampled simultaneously from all 6 cages carried by an animal revealed no significant difference in concentration of albumin, sodium, chloride or potassium between the 2 cage types. The total protein concentration in TCF from

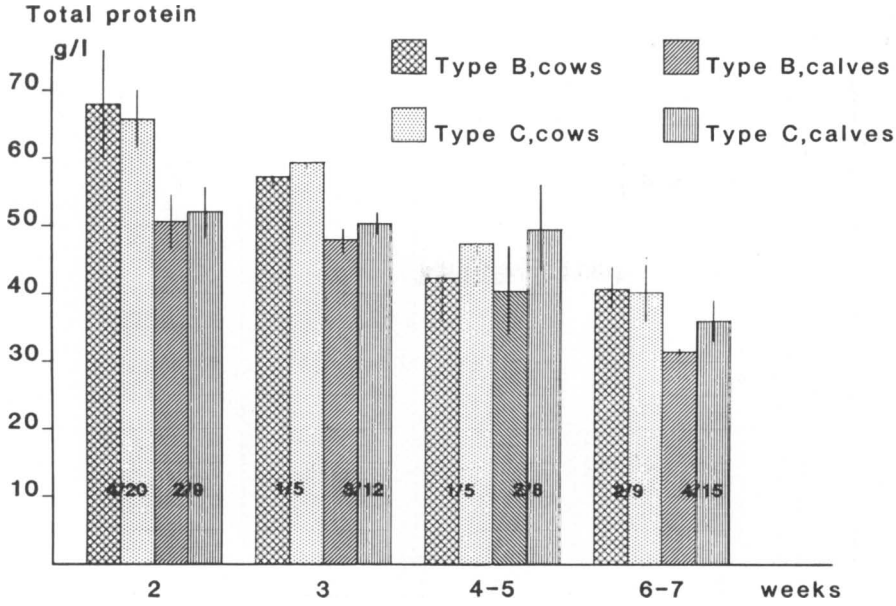

Figure 3. Comparison of total protein content of TCF from type B and C cages sampled at various intervals after insertion. Values are mean ± s.e.m. The number of animals (n) and cages (m) sampled are given as n/m inside the columns.

type B cages was, however, significantly lower ($0.01 < P < 0.05$) than in fluid from type C cages (Fig. 3). As the difference was numerically small the TCF from both cage types is in the following treated as being equal.

Composition of TCF

Analysis of TCF from a total of 86 cages (59 types B and 27 type C) carried by 17 animals (5 cows and 12 calves) forms the basis for the results given in Tables 1—3 and Figs. 4—5.

As can be seen in Figs. 4 and 5 the concentrations of total protein and albumin in TCF were consistently lower than the corresponding serum concentrations and declined with the age of the sampled cages. The decline continued throughout the sampling period and statistically significant differences between serum and TCF in the calf samples could be demonstrated from 5 weeks and onwards for total protein ($P < 0.001$) and from 2 weeks and onwards for albumin ($P < 0.001$). In the cow samples the differences for both parameters were significant from 6 weeks and onwards ($0.001 < P < 0.01$). Twelve weeks after implanta-

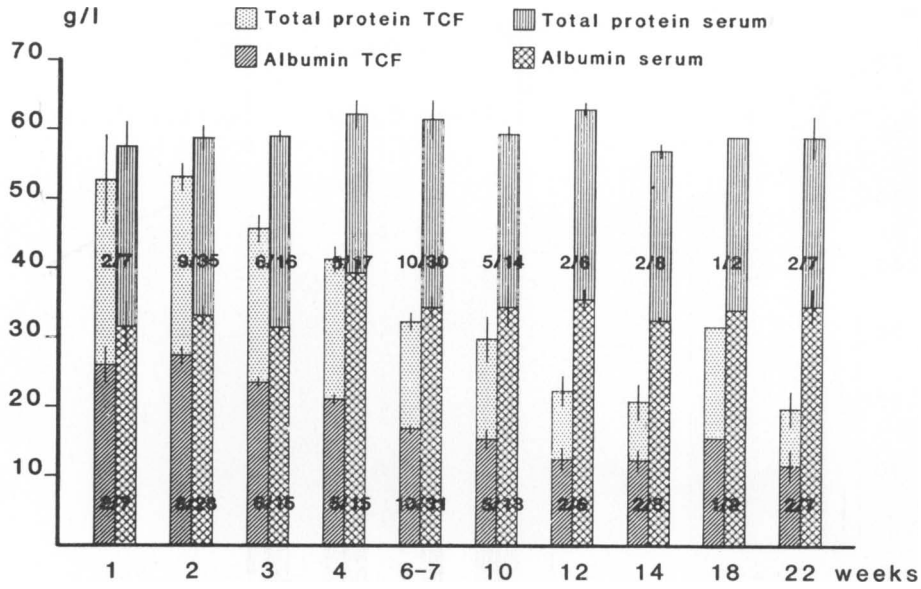

Figure 4. Total protein and albumin content of TCF and serum from calves at various intervals after insertion of type B and C cages. Values are mean ± s.e.m. The number of animals (n) and cages (m) sampled are given as n/m inside the columns.

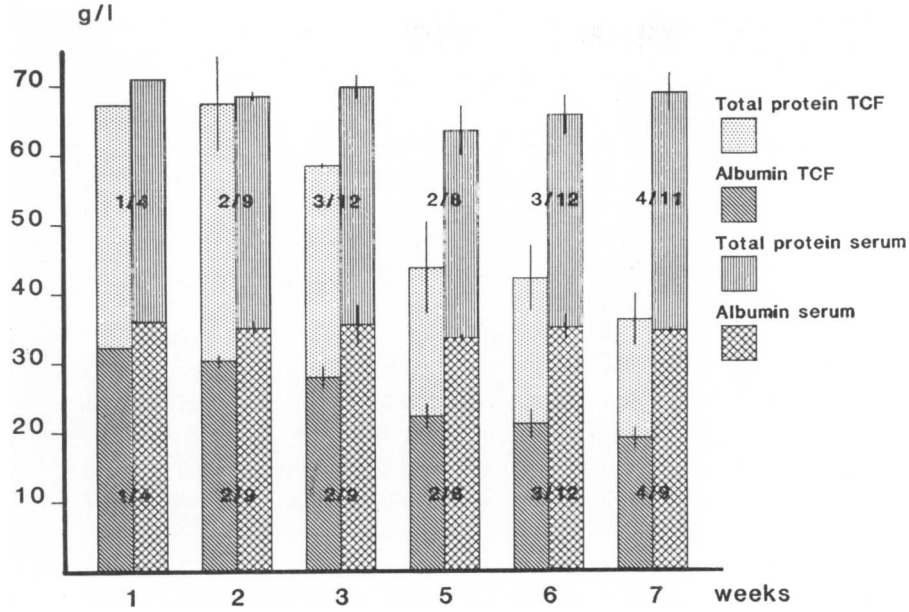

Figure 5. Total protein and albumin content of TCF and serum from cows at various intervals after insertion of type B and C cages. Values are mean ± s.e.m. The number of animals (n) and cages (m) sampled are given as n/m inside the columns.

tion the total protein and albumin content of TCF from calves reached a more or less steady level of about 35 % of the serum concentrations. Throughout the investigation the albumin/total protein ratio was about 0.55 in both TCF and serum.

The concentration of both calcium and magnesium was lower in TCF than in serum (Table 2). The calcium level was significantly lower from 3 weeks and onwards ($0.01 < P < 0.05$) and the magnesium level from 6—7 weeks ($0.01 < P < 0.05$).

The concentration of sodium did not at any time differ significantly from the corresponding serum concentration (Tables 1 and 3). Chloride and potassium had higher levels in TCF than in serum. The difference was significant for potassium only at 3 weeks in the cow samples ($0.001 < P < 0.01$), and for chloride at 10 weeks in the calf samples ($0.01 < P < 0.05$). For inorganic phosphorus the results were not uniform.

Table 1. Composition of TCF and of serum from calves at various intervals after implantation of type B and C cages. Number of calves = n. Number of cages = m. Mean ± s.e.m.

	Weeks	Sodium (mmol/l)	Chloride (mmol/l)	Potassium (mmol/l)
TCF	1	141.4 ±1.35	98.7 ±0.35	4.91 ±0.23
Serum		142.5 ±2.50	103.5 ±8.50	5.30 ±0.80
n ; m		2 ; 7	2 ; 7	2 ; 7
TCF	2	140.5 ±0.81	97.3 ±0.99	4.78 ±0.06
Serum		138.3 ±2.70	94.1 ±3.23	4.39 ±0.14
n ; m		9 ; 31	9 ; 35	9 ; 31
TCF	3	141.3 ±0.38	101.8 ±1.02	4.63 ±0.08
Serum		142.2 ±0.48	100.5 ±2.62	4.67 ±0.11
n ; m		6 ; 17	6 ; 16	6 ; 16
TCF	4	142.6 ±0.51	96.5 ±1.25	4.71 ±0.07
Serum		144.5 ±1.66	95.5 ±4.42	4.83 ±0.17
n ; m		5 ; 17	5 ; 17	5 ; 17
TCF	6—17	142.8 ±0.60	99.8 ±0.95	4.59 ±0.05
Serum		143.1 ±0.61	98.4 ±0.65	4.47 ±0.09
n ; m		10 ; 29	10 ; 30	10 ; 30
TCF	10	142.4 ±0.46	98.9 ±1.49*	4.44 ±0.07
Serum		140.6 ±0.68	94.4 ±1.89	4.70 ±0.09
n ; m		5 ; 14	5 ; 14	5 ; 14
TCF	12	142.0 ±0.50	95.9 ±2.60	4.39 ±0.09
Serum		142.5 ±1.50	95.0 ±4.00	4.50 ±0.20
n; m		2 ; 6	2 ; 6	2 ; 6
TCF	14	140.8 ±0.50	100.2 ±0.65	4.23 ±0.03
Serum		141.0 ±1.00	94.5 ±2.50	4.65 ±0.05
n ; m		2 ; 8	2 ; 8	2 ; 8
TCF	18	143.5 ±0.50	96.8 ±0.75	4.25 ±0.25
Serum		144.0 ±0.00	93.5 ±0.50	4.45 ±0.15
n ; m		2 ; 2	2 ; 3	2 ; 2
TCF	22	139.9 ±0.60	98.0 ±0.00	4.28 ±0.08
Serum		138.5 ±0.50	93.5 ±0.50	4.55 ±0.05
n ; m		2 ; 7	2 ; 7	2 ; 7

* Statistically significant difference between TCF and serum, $0.01 < P < 0.05$.

Repeated sampling

Repeated sampling in a 12 h period did not give any statistically significant alterations in the levels of total protein and albumin in TCF.

Table 2. Composition of TCF and of serum from calves at various intervals after implantation of type B and C ages. Number of calves = n. Number of cages = m. Mean ± s.e.m.

	Weeks	Magnesium (mmol/l)	Calcium (mmol/l)	Inorganic phosphorus (mmol/l)
TCF	1	0.88 ±0.33	2.46 ±0.02	3.12 ±0.20
Serum		0.94 ±0.09	2.65 ±0.05	2.20 ±0.84
n ; m		2 ; 7	2 ; 7	2 ; 6
TCF	2	0.95 ±0.04	2.40 ±0.02	3.08 ±0.06
Serum		0.93 ±0.05	2.58 ±0.10	2.71 ±0.22
n ; m		5 ; 14	5 ; 14	5 ; 14
TCF	3	0.90 ±0.04	2.31 ±0.06*	3.00 ±0.08
Serum		0.93 ±0.03	2.65 ±0.03	3.01 ±0.09
n ; m		5 ; 11	5 ; 11	5 ; 13
TCF	4	0.84 ±0.04	2.17 ±0.09**	2.55 ±0.13
Serum		0.88 ±0.06	2.84 ±0.04	2.39 ±0.54
		5 ; 17	5 ; 17	3 ; 9
TCF	6—7	0.86 ±0.02*	2.01 ±0.06***	2.85 ±0.11
Serum		0.92 ±0.02	2.62 ±0.02	2.79 ±0.10
n ;m		8 ; 20	8 ; 20	8 ; 20
TCF	10	0.85 ±0.04**	1.94 ±0.06***	2.62 ±0.12**
Serum		0.93 ±0.04	2.70 ±0.07	2.85 ±0.13
n ; m		5 ; 14	5 ; 14	5 ; 14
TCF	12	0.83 ±0.01	1.96 ±0.14	3.14 ±0.24
Serum		0.97 ±0.02	2.80 ±0.01	3.00 ±0.28
n ; m		2 ; 6	2 ; 6	2 ; 6
TCF	14	0.85 ±0.02	2.09 ±0.09	2.96 ±0.03
Serum		0.95 ±0.00	2.81 ±0.02	3.10 ±0.02
n ; m		2 ; 8	2 ; 8	2 ; 8
TCF	18	0.83 —	2.15 —	2.78 ±0.11
Serum		0.93 —	2.82 —	2.90 ±0.30
n ; m		1 ; 2	1 ; 2	2 ; 3
TCF	22	0.85 ±0.03	2.10 ±0.21	2.81 ±0.15
Serum		0.91 ±0.00	2.60 ±0.01	2.81 ±0.17
n ; m		2 ; 7	2 ; 7	2 ; 7

* Statistically significant difference between TCF and serum, $0.01 < P < 0.05$.

** Statistically significant difference between TCF and serum, $0.001 < P < 0.01$.

*** Statistically significant difference between TCF and serum, $P < 0.001$.

Table 3. Composition of TCF and of serum from cows at various intervals after implantation of type B and C cages. Number of animals = n. Number af cages = m. Mean ± s.e.m.

	Weeks	Sodium (mmol/l)	Chloride (mmol/l)	Potassium (mmol/l)
TCF	1	140.0 —	not done	4.47 —
Serum		141.0 —		4.40 —
n ; m		1 ; 3		1 ; 3
TCF	2	140.8 ±1.75	99.4 ±0.35	4.70 ±0.10
Serum		143.0 ±1.00	98.5 ±5.50	4.45 ±0.35
n ; m		2 ; 9	2 ; 9	2 ; 10
TCF	3	141.5 ±1.39	98.5 ±1.17	4.63 ±0.11**
Serum		142.7 ±1.33	96.0 ±2.08	4.37 ±0.12
n ; m		3 ; 12	3 ; 12	3 ; 12
TCF	5	140.2 ±0,15	98.8 ±0.75	4.42 ±0.14
Serum		143.0 ±2.00	97.5 ±2.50	4.20 ±0.30
n ; m		2 ; 8	2 ; 8	2 ; 8
TCF	6	141.1 ±2.75	100.0 ±2.31	4.67 ±0.15
Serum		141.7 ±0.88	99.0 ±1.53	4.30 ±0.21
n ; m		3 ; 12	3 ; 12	3 ; 12
TCF	7	142.2 ±1.11	99.9 ±1.90	4.67 ±0.34
Serum		142.5 ±1.50	99.5 ±5.50	4.10 ±0.00
n ; m		4 ; 9	4 ; 10	2 ; 4

** Statistically significant difference between TCF and serum, $0.001 < P < 0.01$.

DISCUSSION

The present investigation showed that the type A cage, made of steel netting, was unsuitable for use in cattle because it was completely obliterated by ingrowing tissue 3—5 weeks after implantation. This type of cage, when used in rabbits, could be sampled for at least 12 weeks after implantation and the tissue covering the inner wall of the cage never exceeded 0.2 mm (*Rylander et al.* 1978). The type B and C cages on the other hand were not obliterated even after 32 weeks and could be sampled repeatedly from 1 week and onwards for volumes up to 2 ml. Repeated sampling in a 12 h period was also possible. There was no obvious difference in the sample volumes from the type B and C cages nor in the speed of tissue ingrowth. *Stanton et al.* (1982) reported similar results in calves with a cage model almost identifical to type B. The cages could be sampled for at least 12

months in their study. Volumes of 0.5—1.5 ml could be obtained at each sampling. *Piercy* (1978) used, in calves and sheep, a silicone rubber cage of the same size as in the present study. The open surface was, however, greater (40—50 %). This cage model yielded sample volumes of 1—2 ml in experiments performed 4—10 weeks after implantation. The silicone rubber tubing cage thus seems to be a high yielding and long lasting cage also when used in large animals. The present results, and those reported by *Stanton et al.* and *Piercy*, also indicate that the open surface of tissue cages is of little importance for their usefulness as a source of TCF in cattle, at least when the open surface is in the range 20—50 % and the cages have an unperforated midsection. The size of the cages is probably also of importance. When used in cattle small cages will be quickly obliterated by the excessive formation of granulation tissue which occurs in this species.

The tissue in B and C cages was found to be a highly vascularized granulation tissue maturing with time. This description corresponds well with previous reports (*Calnan et al.* 1972, *Haljamäe et al.* 1974, *Eickenberg* 1978, *Piercy* 1978, *Ryan* 1978, *Rylander et al.* 1978). The tissue in our cages was still highly vascularized and maturing after 32 weeks in situ. Of interest is the fibrinous strand in the center of the cages, which after 14 weeks was mildly calcified. The calcifications was quite prominent at 32 weeks and possibly a sign of degeneration in the tissue.

In the present investigation the total protein, albumin, calcium and magnesium concentrations of TCF were found to be lower than in serum. This agrees with previous reports on the composition of TCF from laboratory animals (e.g. *Calnan et al.* 1972, *Chisholm et al.* 1973, *Haljamäe et al.* 1974, *Eickenberg* 1978). Most investigators have reported lower potassium concentrations in TCF than in serum. In our experiments we found higher levels in TCF although significant differences could only be demonstrated in the cow samples taken at 6 weeks. The chloride level in TCF was slightly higher than in serum. Significant differences could only be demonstrated at 1 occasion. In laboratory animals there is usually a larger difference. Sodium and inorganic phosphorus in TCF did not differ significantly from corresponding serum levels. Generally the sodium concentration of TCF from laboratory animals has been reported to equal the serum concentration. For inorganic phosphorus the

results are not uniform. *Liberman et al.* (1972) found higher and *Ryan et al.* (1979) lower values in TCF than in serum.

A significant difference $0.01 < P < 0.05$ could be demonstrated between the total protein content of TCF from type B and C cages. The only difference in the construction of the cages was the size of the open area. It is difficult to explain, why the cage with less open area had a higher protein content. Nevertheless this result indicates that the shape, size and open surface of a tissue cage model is of importance for the composition of the fluid. Therefore it may not be correct to compare results of investigations performed with different types of cages, at least if the difference in cage models is prominent. This has been demonstrated by *Holm et al.* (1978), who in a pharmacokinetical experiment used rabbits carrying two cage types simultaneously. The concentrations of a given antibiotic in TCF differed between the 2 cage models.

Repeated sampling of cages did not influence the level of total protein and albumin. This is of great importance when the model is used for pharmacokinetical experiments with highly protein bound drugs.

When a tissue cage model is used in pharmacokinetical investigations it is of vital importance to know not only the composition of the TCF, but also if and when this composition is stable. In the present investigation it was shown that the total protein and albumin content of TCF changed with time. In the calf samples the level of protein declined approximately 50 % in the period from 3 to 12 weeks after which a more or less steady level of about 35 % of the serum level was reached. Albumin declined in a similar way. Also calcium and magnesium levels in TCF were found to change with time. Alterations of the protein content in TCF following implantation of cages in rabbits have been reported previously (*Carbon et al.* 1977). Stable protein levels in TCF from rabbits were found in the period 2—10 months (*Calnan et al.* 1972). On the other hand *Gardner et al.* (1973) reported relatively stable conditions during the first 3 weeks in experiments performed in rats.

From the present investigation it is obvious that the composition of TCF from cages implanted in cattle, with respect to total protein, albumin, calcium and magnesium, changes with time. A likely explanation for this phenomenon is that the changing composition reflects the maturing of the tissue inside and around the

implanted cages. The maturation process, including changed permeability, and altered metabolism of the granulation tissue, thus alters the conditions in the cages and probably also influences the results obtained in pharmacokinetical experiments. Therefore if results of pharmacokinetical experiments are to be compared, consideration must be given not only to which experimental animal is used, but also to the type of tissue cage and at which time after implantation the experiments are performed.

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SAMMANFATTNING

Utvärdering av en vävnadskammar-modell på nötkreatur.

Tre olika typer av subkutana vävnadskammare som källa för vävnadsvätska från nötkreatur har utvärderats. Den biokemiska sammansättningen av vätska samlad vid olika tidpunkter efter implantation av kamrarna har analyserats och jämförts med samtidiga serumnivåer. Stålnätskammare visade sig vara olämpliga då de snabbt igensattes av inväxande vävnad. De 2 typerna av silikongummikammare kunde däremot användas i minst 32 veckor. Provvolymer upp till 2 ml vävnadsvätska kunde samlas vid varje provtagningstillfälle. Upprepad provtagning under en 12-timmarsperiod var också möjlig. Nivåerna av totalprotein och albumin var lägre i vävnadsvätska än i serum och sjönk under de första 12 veckorna efter implantationen till en nivå av ungefär 35 % av serumkoncentrationen. Även kalcium och magnesium hade lägre nivåer i vävnadsvätska än i serum. Klorid och kalium hade något högre koncentrationer i vävnadsvätska än i serum medan ingen skillnad sågs för natrium. Oorganiskt fosfor gav varierande koncentrationer. Upprepad provtagning under en 12-timmarsperiod påverkade inte totalprotein och albuminnivåerna i vävnadsvätska. Koncentrationen av totalprotein var större i kammare med större öppen yta.

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