This paper is a translation from the Japanese paper which appeared in the High Performance Membranes '90 supplement volume of Kidney and Dialysis, p. 13, 1990.

Development and Future Prospects of Polymethyl-methacrylic High-Flux Membranes

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Variability of PMMA membranes

Polymethyl methacrylic (PMMA) membranes are characterized by the fact that membranes with considerable variations in pore structure can be obtained by manipulating the manufacturing conditions of the membranes. Since before development of high-flux membranes (HFMs), PMMA membranes with differing degrees of water permeability, from the dialysis membrane B2 and B1 series to the hemofiltration membrane HF series, have been in clinical use. Fig. 1 shows the structural positions of these membranes and the subsequently-

developed BK series. The horizontal axis shows water permeability, and the indices on the vertical axes proportional to pore radius and the number of pores were obtained by differential scanning calorimetry (DSC) analyzing the thermal fusion behavior of the water in the pores.[1] The BK series aimed for the use in dialysis mode employs membranes which have larger pore size than the HF series for hemofiltration mode.

Trends in academic associations and course of development of PMMA HFM

Development of PMMA HFMs was initiated based on the report by Saitoh et al.[2] suggesting that the protein-losing hemofilter was effective against several long-term dialysis complications such as anemia, pruritus, irritation, and ectopic calcification (tentative model during a period of development: TK-401, commercial model: Filtrizer BK). After this, based on the study by Hirasawa et al.[3], indicating that β_2-microglobulin (β_2-MG) is adsorbed by PMMA membranes and the one by Gejyo et al.[4], reporting that the main component of deposits at the affected region in carpal tunnel syndrome is β_2-MG, optimization as a β_2-MG removal membrane proceeded, and the BK-U and BK-P types were manufactured on a commercial basis.

In the course of this development, it became apparent that the BK membrane was capable of removing Al·DFO complexes[5] and substances related to fulminant hepatitis.[6] In the last several years, studies on the clinical significance of long-term continuous use of HFMs have been conducted at numerous institutions.

The above course is shown in the Table.

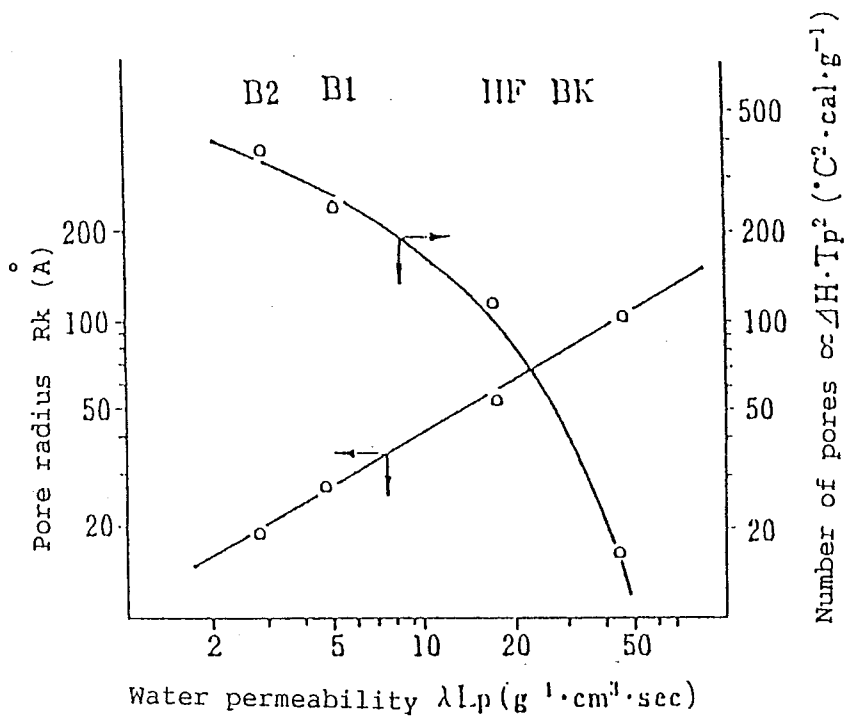


Fig. 1. Structural positions of various PMMA membranes

β_2-MG removal characteristics of PMMA HFMs

Removal of β_2-MG by PMMA HFMs takes place mainly by adsorption. Fig. 2 shows the results of *in vitro* perfusion experiments using PMMA hollow fiber membranes of various water permeability.[7,8] In all of the perfusion periods, maximum areas were observed in adsorption amount per membrane surface area. As shown in the illustration, as pore size is smaller, it is more difficult for β_2-MG to enter the pores, and on the other hand, as pore size is larger, pore surface area for adsorption of B_2-MG is thought to become smaller, and the optimum region of β_2-MG removal is thought to lie between these two extremes. β_2-MG permeation with the BK is observed in the latter half of dialysis, but permeation clearance after 4 hours is of the order of 20% of total clearance.[9]

Fig. 3 shows the significance of adsorption in removal of β_2-MG. Clearance of β_2-MG is extremely high in the initial dialysis period compared to clearance extrapolated based on the molecular weight dependency of clearance of other model substances, and around the 5th hour it coincides nearly with the extrapolation line. It is assumed that because the concentration gradient in the membrane is maintained at a high level due to adsorption, removal of β_2-MG is accelerated.

Table. Trends of academic associations and course of development of PMMA HFM

Trends of academic associations		Development of PMMA HFM
Protein Losing Hemofilter (by SHINSEIKAI)	'81	
	'82	BK (TK-401) Clinical trial (at SHINSEIKAI and Tokyo Women's Medical College)
$ß_2$-MG adsorption to PMMA membrane (by SHINRAKUEN)	'83	
Al removal with PMMA HFM (by Kyoto 1st Red Cross)	'84	Membrane structural analysis method (DSC)
CTS affected region deposit is $ß_2$-MG (by Niigata University)	'85	Sale of BK-1.0H and BK-2.0
First meeting of High Performance Membrane Research Association	'86	Optimization as a $ß_2$-MG removal membrane
	'87	Sale of BK-U and BK-P
Elucidation of significance of continuous use of HFM (by Kyoto 1st Red Cross, Niigata University, etc.)	'88	

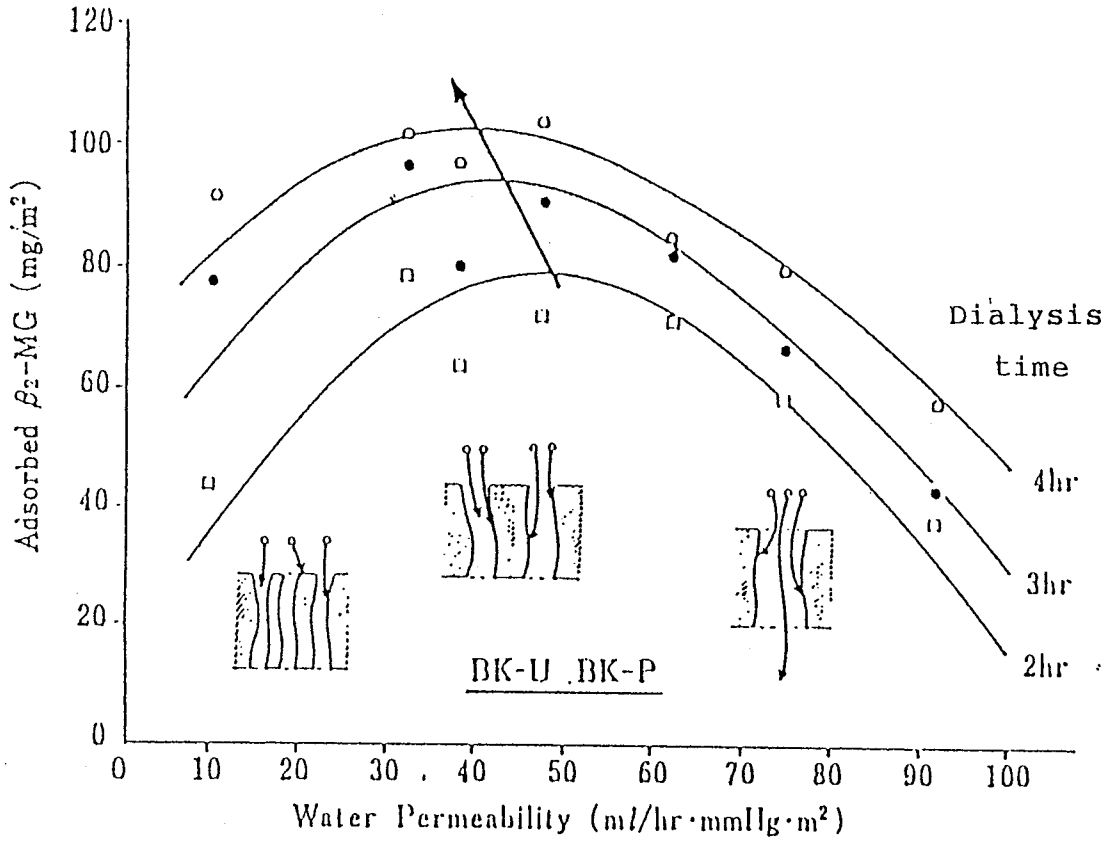


Fig. 2. Relationship between water permeability and amount of β_2-MG adsorption per m^2

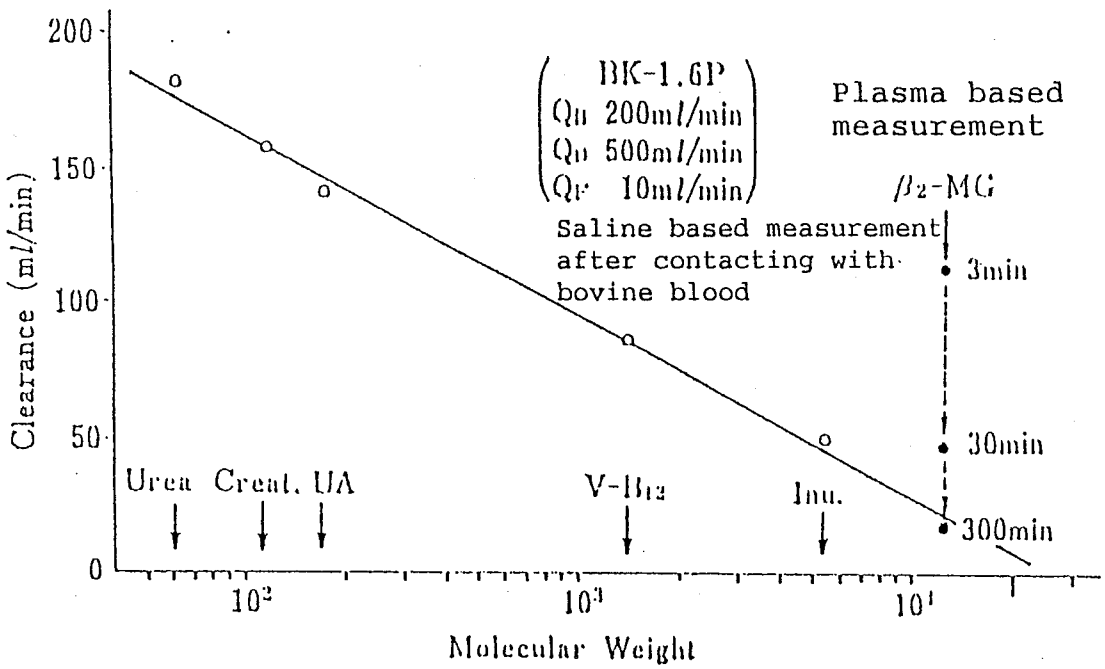


Fig. 3. Effect of adsorption on β_2-MG removal

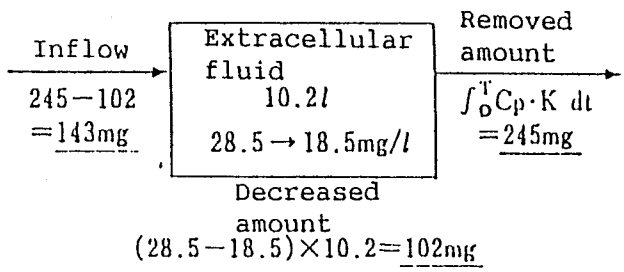
In vivo Pharmacokinetics of β_2-MG

Evaluation of β_2-MG removal is carried out using the parameters of removal rate, removal amount, clearance, maintenance level in long-term use, etc. Clearance is an indicator directly specified by the dialyzer, but because there are changes during dialysis time in the case of PMMA HFMs, as mentioned above, this cannot easily be evaluated. The other indicators may lead to erroneous assessments in cases where the *in vivo* pharmacokinetics of β_2-MG have not been sufficiently understood.

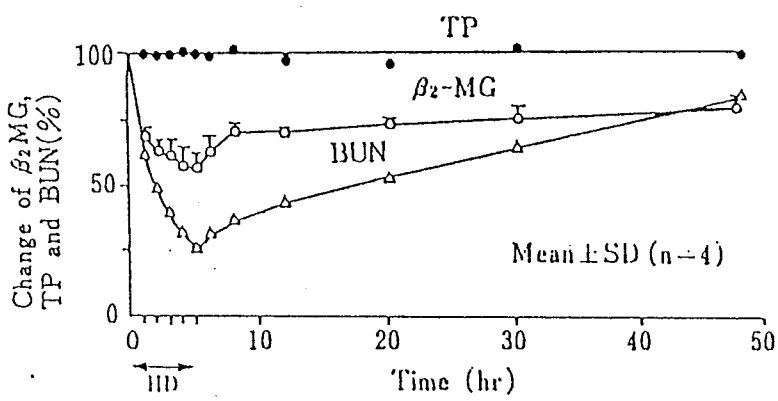
In vivo pharmacokinetics of β_2-MG may be estimated from plasma concentration and clearance. An example of this is shown in the top portion of Fig. 4.[9] In a clinical case using BK-2.1U, plasma clearance of β_2-MG was measured during dialysis at 30, 60, 120, and 240 minutes, and the product of these values and plasma concentrations at the various times was cumulated to determine the amount removed (245 mg). The amount of in flow to extracellular fluid during 4 hours dialysis (143 mg) can be calculated from the removed amount and the decreased amount in the extracellular fluid (taken as 20% of average body weight). The bottom portion of Fig. 4 shows the pharmacokinetics of β_2-MG after dialysis.[10] Compared to the rate of elevation of BUN after dialysis, that

of β_2-MG is high, and it is presumed that there is considerable inflow for several hours after dialysis.

Thus before discussing the relationship between β_2-MG and dialysis-related amyloidosis, one must have a better understanding of the *in vivo* pharmacokinetics of β_2-MG itself.



[Saiseikai Kawaguchi General Hospital, BK-2.IU, 51kg][9)]



[Kyoto First Red Cross Hospital, BK-2.0][10)]

Fig. 4. ***In vivo*** pharmacokinetics of β_2-MG

A case of analysis using an extracellular fluid model (top) and course of plasma concentration after dialysis (bottom)

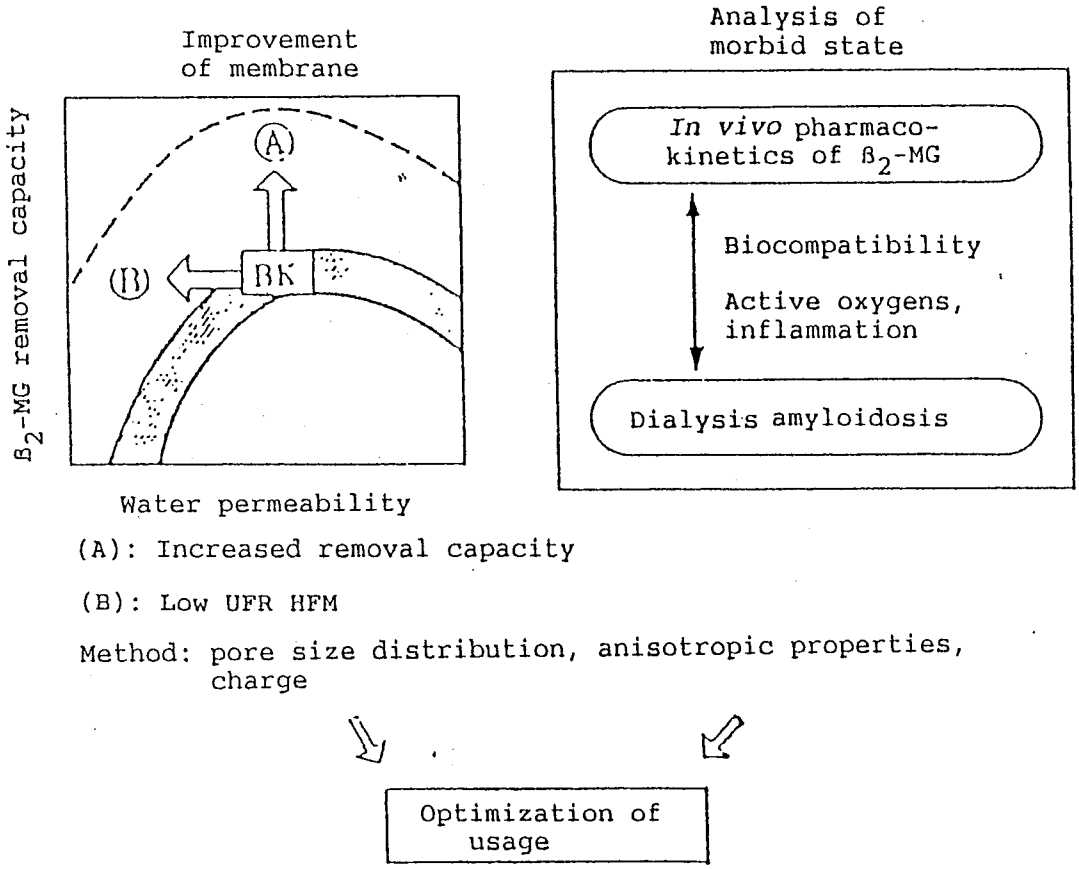


Fig. 5. Direction of future study of $ß_2$-MG removal

Future prospects for removal of pathogenic substances such as $ß_2$-MG

Fig. 5 illustrates our views on how studies will be conducted in the future on treatment for the purpose of removing $ß_2$-MG. The two directions aimed for in development of PMMA membranes are direction (A), in which removal capacity is improved while water permeability remains unchanged, and direction (B), in which removal capacity is maintained and water permeability decreases. In the case of direction (B), the development of HFMs which allow dialysis without using an

ultrafiltration rate controller or HFMs resistant to back-filtration is aimed. Possible means towards realizing these goal are optimization of the membrane in pore size distribution, anisotropic properties and introduction of electric charge.

It is expected that water permeability and β_2-MG removal properties will vary due to the effect of changes in membrane structure resulting, in the case of pore size distribution from sharpening thereof, in the case of anisotropic properties from adjustment of density of the internal and external surface layers, despite the fact that PMMA membranes have a more uniform structure than other membranes, and in the case of electric charge from adjusting the electricity of the membrane material. Concerning the effect of electricity, it is expected that selectivity will increase due to interaction of the electricity of the membrane and the electricity of β_2-MG. Whichever techniques are pursued, possible direction will be between (A) and (B) considering mechanical strength of the membrane.

On the other hand, on the clinical side, elucidation of the morbid states should proceed in parallel, including a deeper understanding of the *in vivo* pharmacokinetics of β_2-MG, identification of the trigger by which β_2-MG is deposited

leading to amyloidosis, and conversely, investigation of whether or not there are means for decreasing this deposited amyloid.

Through improvement of membranes and elucidation of the morbid states, it will be possible to proceed with optimization of the usage, such as blood flow rate, ultra filtration rate, dialysis time, appropriate time of using HFM, combined use with means for dissolving amyloid, etc.

So far, we have taken dialysis amyloidosis and removal of β_2-MG as examples, but if the pathogenic substances causing long-term dialysis complications such as anemia, bone and joint disorders, and pruritus are elucidated, membranes for their removal could be studied in a similar manner. In this case, it might be preferable that membranes would have a pore size larger than that of current HFM.

Impermeability of endotoxins

When HFMs are used in dialysis, it has been expressed that there is a possible risk that endotoxins in the dialysate may enter the blood side due to back-diffusion, back-filtration, etc. To elucidate this, we conducted a back-filtration experiment under harsh conditions. The results are shown in Fig. 6. Phosphate-buffered solution, acetate dialysate, and bicarbonate dialysate were prepared to 12 L

with untreated tap water. For the first 3 hours, circulation was carried out on the dialysate side only, and for the next 2 hours, back-filtration to the blood side was carried out with a total volume of 12 L. Endotoxin concentration in the blood side after 3 hours was at or below the detection limit, and no signs of back-diffusion were observed. Under back-filtration conditions, there were cases in which low concentrations of endotoxins were detected, but these concentrations were identical to those in normal plasma and physiological saline.

As concentrations of endotoxins in clinical dialysate just before the dialyzers are reported to range from several tens to several hundreds of pg/ml, concentrations which are lower by 2 digits or more than those in the experiment shown in Fig. 6, even if endotoxins enter the blood side, the concentration is on the order of 0.01 pg/ml, and one could say that there is absolutely harmless.

Thus there is virtually no possibility of contamination on the blood side by the back filtration of endotoxins using PMMA HFMs. As we have mentioned above, however, it is predicted that pore size will be increased in the future depending on the substances to be removed, and in this case, it will be necessary to reexamine the permeation of endotoxins.

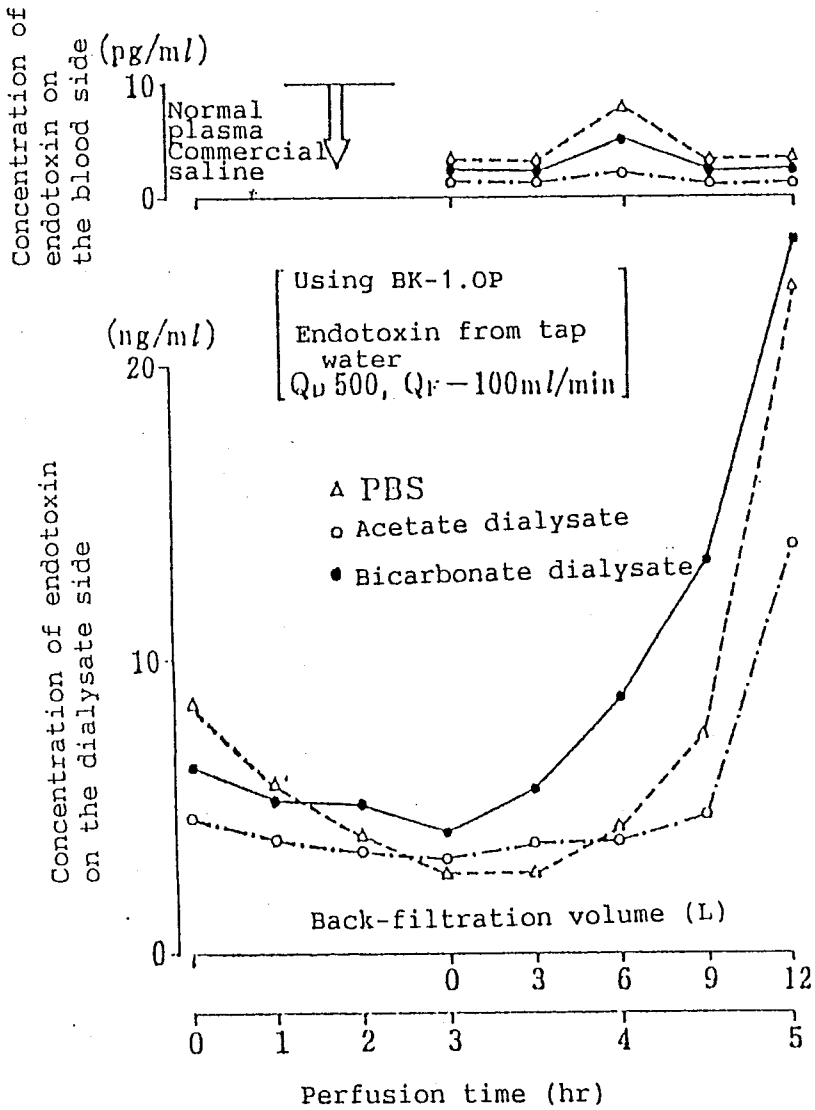


Fig. 6. Results of experiment on perfusion and back-filtration--impermeability of endotoxins

The future of dialysis systems

Development of membranes which will improve the $ß_2$-MG removal capacity and remove pathogens causing long-term dialysis complications such as anemia, bone disorders, and pruritus will proceed in the future.

We concluded that there is virtually no endotoxin contamination on the blood side using the current membranes, but in order to further increase the general safety of dialysis, and in order to make the development of future membranes possible, there should be parallel development of

backup technologies such as systems for removing endotoxins from dialysate.

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