Edited by
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Artificial Kidney, Artificial Liver, and Artificial Cells

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International Symposium, McGill University, April 20, 1977

Preface

There is a rapid increase in interest related to novel approaches in artificial kidneys, artificial liver, and detoxification. Recent research has included the successful clinical applications of the principle of artificial cells for adsorbent hemoperfusion. Since it is 20 years ago at McGill that the first report on "Artificial Cells" was presented, I thought it might be useful to get together a small group of speakers and participants for a day before the ASAIO meeting to discuss some recent advances in the area of the clinical applications of artificial kidney, artificial liver and artificial cells with emphasis on adsorbent hemoperfusion. However, the enthusiastic supports of distinguished speakers, session chairmen and participants were such that the original projection of 100 participants had expanded to a preregistration total of 250, from Australia, Canada, England, France, Germany, Israel, Italy, Japan, The Netherlands, Scotland, Sweden and U.S.A. The program also expanded to include a review section on hemodialysis, dialysate regeneration, hemofiltration, resin hemoperfusion and oxystarch given by their respective originators. The remaining of the symposium emphasizes the status of the art on different encapsulated adsorbent hemoperfusion approaches. I would like to apologize to those who we could not accommodate because of space limitations. It is hoped that this symposium volume may be useful for them and for others who are interested in this area.

Special thanks are due to Ms Joanne Toms for her excellent secretarial assistance for the conference and Mrs. Carol Fautrel for her help in the preparation of this volume; Dr. A. Chawla for organizing the audiovisual aspects; Professor F.C. MacIntosh for his suggestions in organizing the post conference special events; and the McGill Conferences and Special Events especially for organizing the reception and banquets. The members of the Artificial Organs Research Unit who have volunteered their help for this symposium included: M. Berman, Dr. A. Chawla, Dr. E. Chirito, G. Colantoni, Dr. J. Cousineau, Dr. J. Grunwald, C. Hayward, N. Kunterian, C. Lister, P. Nasielski, P. O'Keefe, Dr. B. Reiter, E. Resurreccion and J. Toms. Many thanks are due to my wife, Lancy, for preparing the index for this volume.

The research in this Unit has been enriched by past and present collaborators and members, especially: Dr. P. Barre, Mr. D. Cameron, Dr. J. Campbell, Dr. A. Chawla, Dr. E. Chirito, Dr. S. Chung, Dr. J. Coffey, Dr. C. Cole, Dr. J. Cousineau, Prof. J. Dirks, Mrs. P. Douglas, Dr. H. Duff, Mrs. C. Fautrel, Dr. A. Gonda, Dr. J. Grunwald, Dr. M. Habib, Mrs. C. Hayward, Mrs. M. Hewish, Mr. K. Holeczek, Mrs. L. Johnson, Mrs. N. Kunterian, Mrs. T. Lee-Burns, Mr. B. Lessor, Dr. M. Levy, Mr. C. Lister, Dr. K.S. Lo, Prof. F.C. MacIntosh, Mrs. N. Malave, Miss Celeste Malouf, Prof. S.G. Mason, Dr. M. McGoldrick, Miss M. Migchelsen, Mr. P. Nasielski, Dr. M. Poznansky, Dr. S. Prichard, Miss P. O'Keefe, Dr. B. Reiter, Mrs. E. Resurreccion, Dr. A. Rosenthal, Dr. J. Seely, Dr. E. Siu-Chong, Dr. A. Sniderman, Miss A. Stark, Miss J. Toms, Dr. P. Tung, Mrs. A. Versaza, Dr. B. Watson, and Miss W. Yensen. The support and encouragements in the past or at present in other ways by many others are also gratefully acknowledged, especially, Professor D. Bates, Professor J. Beck, Sir Arnold V.S. Bergen, Professor A. Burton, Professor R.F.P. Cronin, Professor O. Denstedt, Professor S. Freeman, Professor W. Kolff, Professor F.C. MacIntosh, Professor S.G. Mason, Professor G. Malcolm Brown, Professor M. McGregor, Professor R.J. Rossiter, Dr. P. Selkej and many others.

The collaboration of Plenum Publishing Corp. in agreeing to publish this symposium volume is appreciated.

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Thomas Ming Swi Chang

Contents

OTHER ADSORBENT HEMOPERFUSION APPROACHES

COMMUNICATIONS

ADDRESS OF WELCOME

L. Yaffe

Vice Principal, McGill University

Montreal, Quebec, Canada

I am very happy to welcome you here on behalf of Principal Bell and the Board of Governors. McGill is extremely proud of its Faculty of Medicine. McGill also prides itself on the fact that it has a tradition of excellence. In these days of egalitarianism, democratic society, etc., it is virtually considered elitist to be excellent, but I think your presence here today at a conference like this, shows that you yourselves are committed to this very same principle of excellence. Without this, scholarship in any discipline, especially in the sciences, could never survive. I want to congratulate Professor Chang on attracting such a distinguished group of people but I also want to congratulate the audience because when I took a look at the program and the length and content of the program, I recognized that it would take a certain kind of stamina to be able to endure this. I would be interested to see what you look like at about 5:30 or 6:00 this afternoon. I know you did not come here to hear me. You have a very long and a very good program. May I wish you a great deal of success in this conference. Thank you very much.

INTRODUCTION

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HEMODIALYSIS

Introduction

In 1913, Abel et. al. demonstrated that using the principle of hemodialysis, they were able to remove diffusible substances from the circulating blood of rabbits. This principle of hemodialysis remained as an experimental curiosity until about 30 years later when Kolff successfully developed a hemodialyser that can be used effectively for the treatment of patients with renal failure (Kolff, 1944, 1947, also in this volume). However, long-term maintenance of patients was associated with the difficulty of repeated accesses to the blood vessels. It took another 15 years for Scribner's group (Quinton et. al., 1961) to develop the arteriovenous shunt which makes it possible for long-term intermittant accesses to blood vessels of patients. Since that time the use of hemodialysis for the long-term maintenance of patients with chronic renal failure has become an established procedure. At present there are many patients who have been maintained alive for more than 10 years by long-term hemodialysis. The standard hemodialysers are based on the principle of, (1) dialysis for the removal of diffusible molecules and (2) ultrafiltration for the removal of water and sodium chloride (Fig. 1). Although hemodialysis has been conclusively demonstrated to be effective for the maintenance of chronic renal failure patients there are a number of problems related to its use. The major problems are related to the complexity and size of the machine and the cost and time required for treatment (6-12 hours three times a week).

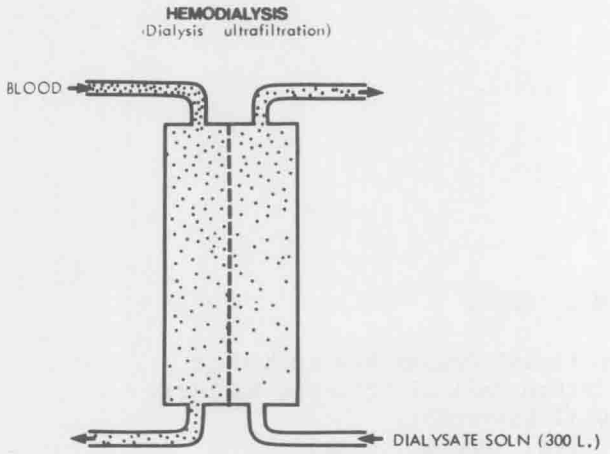

Figure 1

At present the exact type of toxic molecules that has to be removed and the essential molecules which should not be removed still have not been established. Hemodialysis though useful in treating some form of drug intoxication (Maher and Schreiner, 1969) can be further improved. The standard hemodialysers have not been demonstrated to be effective for treating liver failure. A large amount of research has therefore been carried out in the areas of artificial kidney, artificial liver and detoxifiers. Most of the developments have been related to the improvements, modificiations and extensions of the principle of hemodialysis. Thus, the earlier developments involved the use of different membrane configurations in the form of coils, plates, and capillaries. This has resulted in substantial improvements in the membrane component of the hemodialysis machine. A great deal of advance has also been made in the monitoring system. The development of the internal AV fistula (Brescia et. al., 1966) has overcome a number of the problems related to the external A-V shunts. The single needle approach (Kopp et. al., 1972) has lessened problems related to needle puncture in internal AV fistula.

Dialysate Regeneration

One of the major problems of standard hemodialysis machine is

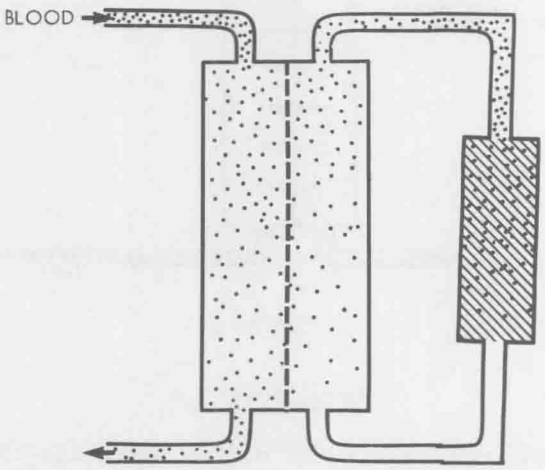

Figure 2

the dialysate required for removing uremic metabolites (Fig. 1). Approximately 300 litres of fluid is required for each treatment. This means that about 900 litres per week is required for the 3 times a week treatment. In addition to the very high cost of dialysate, there are other problems related to possible trace element being absorbed by the patients from this large volume of fluid. The principle of dialysate regeneration is a successful attempt to decrease the dialysate volume required by using sorbents in the dialysate fluid compartment to remove the uremic metabolites (Fig. 2) (Gordon et. al., 1969, also in this volume). This principle has been used for the construction of a "wearable artificial kidney" (Kolff, in this volume).

Middle Molecules

The proposal that uremic toxins are molecules in the middle molecular weight range(Babb et. al., 1972) has led to modifications of hemodialysers. Thus the total membrane area has been increase to facilitate the removal of these "middle molecules". Membranes with high permeability to middle molecules (e.g. Rhone-Poulone) have also been developed.

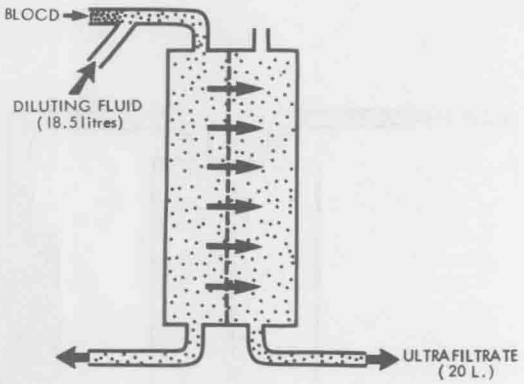

Figure 3

Hemofiltration

Another approach related to middle molecules is the use of the principle of hemofiltration whereby instead of using a combination of dialysis and ultrafiltration (Fig. 1) only ultrafiltration is used (Fig. 3) (Henderson et al., 1967; Henderson, in this volume). Hemofiltration (Fig. 3) is based on the principle that, unlike dialysis, permeant molecules of different molecular weight can move across a membrane at the same rate in ultrafiltration. This way, middle molecules can be removed as effectively as the smaller molecules. The ultrafiltrate removed has to be replaced very accurately with diluting solution in order not to deplete or overload the fluid volume of the patients.

Reviews

Some of these recent novel approaches related to new extension and modifications of hemodialysis will be reviewed by their originators.

ADSORBENTS

Many adsorbents like activated charcoal, oxystarch, ion-exchange resins, and others have been used. Activated charcoal is used in the dialysate regeneration system described above. It has also been used for hemoperfusion (Yatzidis, 1964) however, complications related to embolism and platelet depletion has prevented its clinical use as free granules for hemoperfusion. The use of oxystarch (Giordano, in this volume) and amberlite (Rosenbaum, in this volume) will be reviewed by their original proponents in this volume.

ARTIFICIAL CELLS

Introduction

With the thought that most of the novel approaches in artificial kidney have been extensions and modifications of hemodialysis; and also with the thought that perhaps completely different approaches may also contribute to the further development of artificial kidney, artificial liver and detoxification, a new area of research was started here. This involved investigations into the possible uses of artificial cells (microencapsulation) as the basis for the construction of artificial liver, artificial kidney and detoxifier(Fig.4) (Chang, 1964, 1966, 1972). The ultrathin membrane and the large surface to volume relationship of artificial cells is such that a very small volume of suspension allows for extremely high transport rates of metabolites. Studies carried out to use enzyme systems in the artificial cells for the removal and conversion of metabolites have recently been reviewed in more detail elsewhere (Chang, 1977).

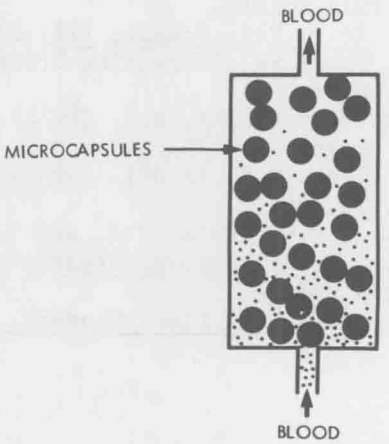

Figure 4

Microencapsulated Adsorbents

This volume reviews in some detail the use of artificial cells or other extensions to encapsulate adsorbents for clinical applications as artificial kidneys, artificial livers, and detoxifiers. Most centers working in this area at present have contributed to this volume.

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