Activated Carbon and Blood Perfusion: A Critical Review

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Activated carbon is a very high surface area adsorbent with the property of adsorbing relatively non-polar molecules, even from aqueous solution (Bock, 1920; Anderson, 1946). It adsorbs creatinine, uric acid, salicylates, barbiturates and a variety of other important compounds (Blaney et al, 1966; Sparks et al, 1966; Dedrick & Beckmann, 1967). It is often used as an oral antidote for ingested poisons (Holt & Holz, 1963; Fiser et al, 1971). Activated carbon has been studied for dialysate optimisation (Kolobow & Dedrick, 1965) and is now in commercial use in a recirculating dialysate system (Gordon et al, 1969). Yatzidis (1964) pioneered the use of activated carbon in direct contact with blood. A large number of investigators have followed Yatzidis' lead in studying and applying charcoal haemoadsorption.

This paper is a brief critical review of the literature experience with activated carbon haemoadsorption, with emphasis on the characteristics, properties and cleanliness of the activated carbons employed.

**ACTIVATED CARBON**

Adsorbent haemoperfusion requires the use of particles which can be contained without difficulty in an extracorporeal circuit. This largely eliminates carbons of very small particle size, unless such carbons are encapsulated or otherwise contained. Granular and pelletised carbons are available in size ranges suitable for blood perfusion (about 0.5mm in diameter or larger).

The properties of activated carbon are a function of the raw material from which it is prepared (coconut shells, bone, coal, peat, wood, petroleum, etc), the method of activation (see Smisek & Cerny, 1970), the surface area (expressed as square m/g), the pore volume (expressed as ml/g), the ash content, and the pore size distribution (pores in the 100 to 300 nm diameter range are the most useful for compounds of interest in uraemia and acute intoxication). In addition, one should know the mechanical properties of the carbon, ie its tendency to fragment or fracture. The presence of fine-
ultra-fine particles attached to the carbon surface, which are potential charcoal emboli, must also be determined and characterised. Unfortunately, such data are rarely, if ever, available from industrial activated carbon suppliers. Most of the activated carbons we have considered are inadequately characterised. Andrade et al (1972) have presented a table listing the USA granular and pelletised carbons and their properties. The authors would appreciate similar data for European and other activated carbons.

NON-COATED ACTIVATED CARBON

Yatzidis (1964) packed about 200 g of a granular (0.50-0.75 mm diameter) Merck carbon into a 6 x 20 cm siliconised glass cylinder filled with 100 mesh filters. He states that the system is "... well washed with deionised tap water" and then sterilised. A flow of 140 ml/min can be maintained through the low resistance device by arterial pressure. The device was evaluated on 5 dogs and a number of patients (20 perfusions). Temperature elevations and blood pressure drops were noted initially in a few of the cases. Extensive chemical determinations were made. Haematological studies were also performed — platelet and fibrinogen drops were noted. There was no mention of fine particles, possible fine carbon emboli generation or pathological examinations. There was no mention of other carbon types or why that particular carbon was selected. Yatzidis (1965) did mention that a number of side effects of the perfusion might be "attributable to sulphur compounds which are liberated from the charcoal. By careful washing of the charcoal with ammonia before use, these reactions can be partly avoided".

Dunea and Kolff (1965) utilised a system very similar to that of Yatzidis (1964). Eighteen haemoadsorptions were performed on three patients. They utilised a Union Carbide Corp. carbon, coconut base, 12/28 mesh, acid washed, and of 0.045% ash content. The carbon was gas sterilised with ethylene oxide in dichlorodifluoromethane. One must expect some desorption of these compounds on the carbon — desorption could be quite slow. The device was assembled and 4 to 8 l of saline "... were run through the cylinder to remove fine dust". This description of carbon properties and washing procedure is one of the best to be found in the haemoadsorption literature, yet it is very inadequate. One must question the suitability of gas sterilisation and the very inadequate washing procedure (see Andrade et al, 1972). Dunea and Kolff noted caking of the carbon and significant platelet drops. Clearance data for creatinine, uric acid, and salicylate were very good initially but dropped rapidly during perfusion. They concluded: "Haemoperfusion appeared to be a safe procedure. Side effects were few. Nausea and vomiting occurred several times. No pyrogenic reactions were noted". No mention was made of fine particles or pathological studies.

The first histopathological study of activated carbon haemoperfusion was
removal was demonstrated, and they state "...the clearance of urea ... by this method has already been proved". This is misleading. Some urea is removed, but not nearly enough to make carbon perfusion attractive for urea removal. Histopathological studies were performed. Carbon deposits were noted in the lungs, liver and kidney when they used 15/30 mesh carbon, though they claimed that when 5/15 mesh carbon was used "...no further carbon emboli were encountered". Platelet decreases were also noted.

Barakat and MacPhee (1971) have used charcoal perfusion for the removal of bilirubin and alkaline phosphatase. These results are intriguing, as they are quite different from those of other investigators. Yatzidis (1964) and Andrade et al (1971) found negligible removal of bilirubin. The pH changes encountered in Barakat and MacPhee's (1971) in vitro experiments perhaps indicate that an acid-washed carbon was used. One of the final statements in their paper deserves mention. They state "we were disappointed to observe that ammonia was not adsorbed by the wet carbon column".

Activated carbon is not a magical sponge which will adsorb and thereby remove anything we desire. It can exhibit some ion exchange behaviour depending on the surface treatments to which it has been exposed. Adsorption of gases on activated carbons can be rather non-specific. Adsorption from aqueous solution is another and much more complex matter. Grades of activated carbon used for treating aqueous solutions and often called decolourising carbons tend to adsorb apolar, relatively insoluble compounds. Different carbons may have substantially different adsorption properties, particularly for creatinine (see Andrade et al, 1972).

It is of interest to note that we have reviewed the work of seven groups (11 papers) and in all cases the properties of the carbon were inadequately known or at least inadequately discussed. In all cases the washing procedure was inadequate or inadequately discussed. In all the studies cited in this section there was no mention of evaluating different carbon types.

Merrill, in a recent editorial (Merrill, 1971), indicated substantial concern over the blood damage and emboli (fine particle) problems associated with activated carbon haemoperfusion. Andrade et al (1972) have shown that there are substantial differences in the cleanliness and, more importantly, the "washability" of various USA carbons. One might expect that the same would be true of European carbons.

**COATED ACTIVATED CARBON**

Properly coated or encapsulated activated carbon may minimise the blood damage and fine particle emboli problems associated with carbon haemodialysis.

Yatzidis (1966) used cellulose acetate-coated carbon, claiming that such coated carbon almost completely eliminated the undesirable ill effects noted
with uncoated carbon. He could not detect any fine carbon particles in the rinsing fluid from a 200 g column of coated carbon. He further claimed that the coating did not significantly affect the adsorptive power of the carbon. Six patients with acute barbiturate poisoning and 11 chronic renal failure patients (29 perfusions) were treated. The results were quite dramatic and similar to those reported earlier (Yatzidis, 1964; Yatzidis et al., 1965). In vitro adsorption data were also reported. Yatzidis (1966) also discussed the adsorption of "non-dialysable toxic factors" on activated carbon.

Rosenbaum et al. (1968) also evaluated cellulose acetate-coated carbon (a different coating procedure to that used by Yatzidis, 1966) using the apparatus and carbon previously described. The coated carbon was apparently ethylene oxide sterilised and washed in the same manner as the uncoated carbon previously discussed. Though the coating technique was well described, little description of washing procedure was presented.

Rosenbaum et al. (1968) were much less enthusiastic about carbon or coated carbon perfusion than Yatzidis (1964). Severe drops in platelet and in leucocyte counts were noted. Charcoal emboli were readily observable in the pulmonary arterioles, just as with uncoated carbon. They conclude that "the emboli are not prevented by cellulose coating or the use of blood filters". Rosenbaum et al. (1968) may have had a carbon with low washability (see Andrade et al., 1972) which was then inadequately washed, or the coating method which they utilised may not have produced a good, strong encapsulation.

Neither Yatzidis (1966) nor Rosenbaum et al. (1968) discussed the properties of their coating, the extent of encapsulation, or the cleaning processes they may have used before and after coating.

The most extensive, complete and well characterised study of coated activated carbon haemoperfusion is that by Chang et al. (1966-1972). Chang (1966) has pioneered the field of microencapsulation (artificial cells) for medical applications. Chang et al. (1968) evaluated three different encapsulation materials (nylon, collodion and heparin-complexed collodion) for blood compatibility, concluding that the nylon material showed the greatest platelet and WBC decrease. The heparin-complexed collodion surface showed no effect on platelet or WBC levels. Chang noted early in his work (1966) that deformable capsules were not suitable for use in a large column, as they would pack closely, producing a very high resistance to flow. Chang et al. (1968) thus coated activated carbon in a manner similar to that of Yatzidis (1966). Heparin-complexed collodion was used, and the coating procedure is well-documented (Chang et al., 1968). Dog experiments showed that platelet levels remained approximately normal during and after perfusion over coated carbon, while uncoated carbon produced a 50% drop in arterial platelet levels. A relatively small amount of carbon (40 g) was used and the flow
rate was 100 ml/min. These results clearly indicated that activated carbon could be coated in such a manner as to greatly minimise blood damage with haemoadsorption. In vitro adsorption data, clearance data and fine carbon particles were not evaluated. The carbon was not identified.

Chang (1969) used 300 g of 6/14 mesh Fisher scientific carbon in a study of toxin removal. Collodion, heparin-collodion and collodion-adsorbed albumin coatings were studied. The coating procedures were well described. Carbon was washed before and after coating with 6 l of saline per 300 g of carbon. In vivo (dog) adsorption and platelet data were presented for all three coatings. The collodion-albumin system proved to be the best compromise for creatinine removal and platelet compatibility. He did note that fine carbon particles were observed in the effluent blood from the shunt when uncoated carbon was used "... but none was found in that of the microencapsulated activated charcoal shunts". Excellent removals of pentobarbital were also obtained. No rationale was given for the selection of the Fisher carbon nor for the washing conditions used. No histopathological analyses were reported.

Chang and Malave (1971) have reported on the first clinical use of their system. They again used the Fisher Scientific carbon - 6/14 mesh, coconut base, encapsulated with collodion-albumin. The coated carbon was "... washed repeatedly with distilled water through a sieve (40 mesh) until all free particles which have escaped microencapsulation are removed". In vitro adsorption and clearance studies were reported. Twenty bilaterally nephrectomised dogs were perfused with 300 g of encapsulated carbon. The 10-30 mg/100ml initial creatinine level was decreased by more than 35 % after 2 hours of perfusion at a flow rate of 120ml/min. Uncoated, collodion-coated and collodion-albumin coated carbon all showed roughly the same creatinine removal. Uric acid, urea, and other molecules were also studied. Haematological findings were comparable to those previously reported by Chang (1969). Chang and Malave (1971) studied a number of sterilisation methods for activated carbon in preparation for clinical trials, finally settling on autoclaving.

Histological studies of organs of dogs perfused with collodion-albumin coated carbon which had been carefully washed following autoclaving showed no evidence of charcoal particles in the lungs, liver, spleen, or kidney. Following these promising results, an initial clinical trial was conducted utilising 300 g of collodion-albumin activated carbon, and a 90 min perfusion. The perfusion was successful. After 60 min of perfusion the creatinine level had only dropped from 16.5 to 14.8 mg/100 ml - uric acid went from 12.9 to 9 mg/100 ml. No significant decrease in formed elements was noted.

Chang et al reported their clinical trials in 1971 and 1972. A detailed description of the washing and coating procedure is available (1971). Creatinine
and uric acid clearances were found to be linear with flow rate. Data were 
presented for nembutal, salicylate, glutethimide and guanidine. Chang et al 
(1971) have managed to design and construct a system of very low resistance, 
which can function adequately from arterial inflow without a blood pump. 
Resistances and clearances of various dialysers were compared with carbon 
perfusion.

Further clinical experience with coated activated carbon haemoadsorption 
was reported by Chang et al (1972a, b). Chang and his group have there-
fore evaluated various coatings and cartridge designs in the development of 
a system for haemoadsorption. They have extensively studied the system in 
vitro and with experimental animals. Finally, they have documented the 
safety and efficiency of coated activated carbon haemoperfusion in a series of 
continuing and expanding clinical trials.

There are still many unanswered questions, however. Our group (Andrade 
et al, 1971, 1972) has studied other coating systems, carbon types and car-
tridge designs. An extensive study of granular, decolourising USA-activated 
carbons was carried out (Andrade et al, 1972). In vitro adsorption data for

*Figure 1. Wilco Chemical Company Activated Carbon, as received. Note the surface 
pores and the fine particles. Scanning Electron Micrograph, 5000 x original magnification.*

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creatinine and other solutes were determined. Extensive washing and washability studies were also conducted, concluding that Witco 517 activated carbon (Figure 1) was perhaps the best. A detailed washing protocol is available. We evaluated three different coatings — glutaraldehyde cross-linked albumin; polyhydroxyethyl methacrylate (polyHEMA) prepared in place by direct monomer polymerisation; and Hydron Biomedical Polymer (trademark of HydroMed Sciences, Inc., New Brunswick, New Jersey, USA), prepared by cross-linking polyhydroxyethyl methacrylate (Figure 2). The latter two coatings are representative of the hydroxy alkyl methacrylate hydrogels, materials now well known for their biological compatibility (Wichterle & Lim, 1960). All exhibited good platelet compatibility and excellent in vitro and in vivo adsorption. The advantage of the polyHEMA and Hydron Biomedical Polymer coatings is that it is quite simple to prepare and is autoclavable. The coated carbon is thus relatively easy to prepare and sterilise.

Andrade et al (1972) concluded that:

1 Perfusion of blood over about 200 g of coated activated carbon can reduce blood creatinine values in 70-80 kg sheep from 15 mg/100 ml to 4 mg/
100 ml in less than three hours of perfusion. Clearances for creatinine can be maintained at over 100 ml/min for three hours for a 15 mg/100ml inflow concentration. Salicylate clearances can be maintained at over 60 ml/min for two hours for a 100 mg/100 ml inflow concentration.

2 Albumin and PolyHEMA coated carbon is relatively resistant to packing and sludging, albumin being better than the PolyHEMA. Hydron Biomedical Polymer coated activated carbon is also resistant to packing and sludging.

3 Albumin coated carbon produces a platelet drop of 20-50% in the first hour of perfusion.

4 PolyHEMA and Hydron Biomedical Polymer-coated carbon produce a platelet drop of the order of 20% or less in one hour of perfusion.

5 There is no optimum particle size in the 12-24 mesh range.

6 A single compartment cartridge is just as effective as a multi-compartment-fluidised one.

7 Charcoal which is properly and thoroughly washed does not produce readily detectable charcoal emboli — particularly when such charcoal is encapsulated. This is a tentative conclusion.

8 High resolution electrophoresis patterns of perfused blood reveal no protein changes. Inflow and outflow samples show no differences. Serum amino acid chromatograms also show no differences.

9 Activated carbon which is encapsulated may be even more effective than uncoated carbon in removing material from blood due to the lack of sludging and packing.

10 Witco 517 activated carbon appears to be superior to all others tested with respect to cleanliness and washability. It is comparable to many others for the in vitro adsorption of creatinine, salicylic acid and pentobarbital.

11 Hydron Biomedical Polymer-coated activated carbon (Witco) may be suitable for use in clinical adsorbent haemoperfusion applications.

The work discussed on coated carbon, particularly the work of Chang et al (1966-1972) and Andrade et al (1971-1972) clearly demonstrates that a number of the problems cited in the editorial by Merrill (1971) have been successfully overcome.

DISCUSSION AND CONCLUSIONS

There is no doubt that activated carbon is an extremely effective adsorbent for creatinine, uric acid, guanidine, salicylates, barbiturates, glutethimide,
amphetamine, and a number of other compounds of interest in chronic urae-
mia and acute drug intoxication.

There is no doubt that perfusion over columns of most commercial activ-
ated carbons will produce readily detectable fine-particle emboli in the
organs and in effluent blood smears, unless the carbon is extensively and
thoroughly washed. Well-washed, properly washed carbon, particularly one
of the more easily "washable" types, does not appear to produce fine carbon
emboli. There is ample evidence that properly washed and properly coated
carbon exhibits no signs of carbon emboli.

Activated carbon haemoperfusion cannot be a substitute for haemodialy-
sis, but it can be an effective supplement to dialysis. Activated carbon
removes best what haemodialysis removes the most poorly — creatinine and
uric acid. Two to three hours of activated carbon perfusion can remove quan-
tities of creatinine and uric acid equivalent to a full term haemodialysis. It
is thus conceivable that activated carbon perfusion may permit haemodialysis
treatment times to be cut in half (Scribner, 1971).

The usefulness of activated carbon haemoperfusion in the treatment of
acute drug intoxication is well documented. Such work should be encouraged
and expanded. Haemoadsorption devices suitable for pediatric use are pre-
sently under development and study. Commercialisation of coated activated
carbon perfusion systems is undergoing extensive study.

Unless activated carbons (granules, pellets or fibres) can be produced
to the exacting specifications required for medical applications, particularly
freedom from fine particles, all investigators should consider the use of
properly coated or encapsulated carbons. Coating systems are presently
under development, which should permit haemoperfusion with minimal amounts
of anticoagulation.

Other adsorbents, ion-exchange materials, and biochemically-specific
perfusion systems have not been discussed. These areas are being studied
by a number of groups and merit attention.

This review has emphasized the most ignored parameter in carbon
haemoperfusion — the carbon itself. We hope that future workers will realize
that all activated carbons are not equal — and that all coating systems are not
equivalent.

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REFERENCES

Bock, J. C. (1920) Journal of the American Chemical Society, 42, 1564
Chang, T. M. S. (1972b) Proceedings of the European Dialysis and Transplant Association, 9, this volume
Dedrick, R. L. and Beckmann, R. E. (1967) Chemical Engineering Progress Symposium Series, 63, No. 74: 68
Dutton, R. C., Dedrick, R. L. and Bull, B. S. (1969) Thrombosis et Diathesis Haemorrhagica, 21, 367
Kolobow, T. and Dedrick, R. L. (1965) Transactions. American Society for Artificial Internal Organs, 12, 1
Merrill, J. P. (1971) New England Journal of Medicine, 284, 911
Sparks, R. E., Blaney, T. L. and Lindan, O. (1966) Chemical Engineering Progress Symposium Series, 62: 2
OPEN DISCUSSION

E DENTI (Saluggia): I want to ask Mr Kopp two questions. First, in the experimental work carried on jointly by Sorin Research Centre, Saluggie and by Medical Semiotics Institute of the University of Pisa, we found that the activated carbons commercially produced always contain a more or less significant amount of various impurities that are slowly released into body fluids put into contact with such activated carbons. The main impurities are sodium, calcium, potassium, magnesium, copper, iron; and in some cases also zinc, manganese, aluminium and boron. The amount of impurities is such that the granulated carbons must be purified by complicated and time-consuming washing processes, in order to avoid troubles in the application of absorption techniques on the animals and the humans. I would like, therefore, to ask the author about his own experience of similar problems.

The second question is about the formation of dust from the carbon granules. We have remarked that the transport conditions are the most significant factor, the quantity of dust being of course a function of vibration duration and intensity, with the accompanying attrition between granules. It is difficult, therefore, to define the dustiness of a carbon in comparison with another carbon, without taking into account these modifications taking place during the transport. The same remark applies also, by our own experience, to the cellulose acetate coated granules. To avoid this, only coatings of relatively much greater thickness are useful, as we have found recently in Saluggia and Pisa.

KOPP: Well I am very happy; Dr Denti fully confirms what I said, that not all carbons are equal, and not all washing procedures are equivalent. Thank you, Dr Denti.

T M S CHANG (Montreal): I just want to make the point that the microencapsulation of activated charcoal is just one example of the possible use of the microcapsule artificial kidney. If you do some calculations you will find that 10 ml of microcapsules has the same total surface area as the whole artificial kidney, and thus if anybody comes up with a better absorbent than activated charcoal, then it is possible to make an even smaller 10 ml microcapsule artificial kidney.

KOPP: I think I pointed out that Dr Chang has done probably the very best work on encapsulated carbon. I encourage you very much to see his demonstration downstairs (see page 568, Eds).