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Building 518
Division of Artificial Organs

OFFICE MEMORANDUM

TO: W.J. Kolff, E. Thor-Atkin, H. Klinkmann, D. VanDura, K. Kablitz, and S. Jacobsen

DATE: 7-15-74

FROM: J.D. Andrade

SUBJECT: Report on Charcoal Hemoperfusion clinical trial 4-25-74

Background

Application was made to the Human Experimentation Committee of the College of Medicine for authorization to conduct clinical trials on extracorporeal sorbent hemoperfusion of both endogeneous and exogenous toxins under the direction of W.J. Kolff. Plans had been made by Thor-Atkin, Klinkmann, VanDura, Andrade for the trials to be performed on Tuesday and Thursday, April 23 and 25, 1974. Permission was obtained on April 24, 1974 and the trial scheduled for 8:00 a.m., April 25, 1974.

Two fresh cartridges were made by W. Rohloff; all components were extensively extracted and pieces of each material in the circuit were submitted to Professor Nicholes in Microbiology for cell culture toxicity, endotoxin reactions, and sterility. All components for the clinical trial were non toxic to cell cultures (except the Tygon tubing), were endotoxin - Negative and were sterile.

Arrangements had been made earlier, (April 2 and 3 at the ASAIO meeting in Chicago) by Andrade and R. Numeroff and Ronel of Hydro Med Sciences (HMS) to obtain Hydron-coated carbon for the clinical trial. The coated carbon and a sample of uncoated material were delivered on United Air Lines on the evening of April 9, and picked up by Andrade.

The carbon was observed to be very clean and nearly particle free. On April 10, Mrs. Mary Stegall unpacked the carbon and refrigerated it. It had been autoclaved by HMS prior to shipping. Extraction, washing, and creatinine depletion studies were conducted by Mary Stegall from April 3 to April 5. The standard washing test showed no detectable particles after a 90 minute wash (< 20 micrograms). This compares with around 200 micrograms for earlier carbons. The carbon was relatively particle clean. The invitro creatinine depletion results were disappointing - creatinine removal was slow, implying that the carbon would not be very effective for invivo creatinine uptake.

The carbon as received (both coated and uncoated) were submitted to Dr. Nichols in Microbiology for cell culture toxicity and endotoxin reaction. The carbons were not cytotoxic and were endotoxin negative. Solution extraction studies were conducted for physiologic ions and the determinations made by a local independent lab.

The carbon was washed in two batches and placed in the cartridge Tuesday morning, April 16, 1974. The system was then steam sterilized (wet cycle) under the supervision of Dietz VanDura and Dennis Coleman. A sample of the material in the cartridge was not submitted for toxicity or pyrogen testing.

The sterile cartridge was stored at room temperature until Thursday morning, April 18, 1974, when Dietz VanDura began assembling the circuit for clinical trial. Our previous sterility tests indicated that wet autoclaved material is sterile.

Clinical Trial

The circuit was assembled by 7:45 a.m. on April 18, 1974 and heparin/saline primed at 8:20 a.m. Debubbling went smoothly and was easier than with previous cartridges, though the patient and her husband were somewhat nervous about the need for debubbling.

8:55 a.m. - A slight leak in tubing set, repaired by D. VanDura.
9:10 a.m. - Blood samples taken.
9:32 a.m. - Extracorporeal flow began into inlet chamber of cartridge
9:34 a.m. - Blood flow observable at top of carbon column, initially around perimeter. Flow appeared quite uniform. The flow rate was about 100 ml/min. due to fistula problems.
9:38 a.m. - About 320 ml of priming fluid was drained. Circuit completely filled with blood.
9:50 to 10:20 a.m. - Considerable problems with blood access, foaming due to low flow, and a minor circuit leak. It was observed during this period that the carbon bed expanded about 3 mm during flow and settled down at low flow.
10:21 a.m. - Dr. Kablitz noticed outflow blood was slightly darker than inflow - could it be somewhat deoxygenated?
10:25 a.m. - Patient begins feeling cold and nauseated.
10:31 a.m. - Begin switching flow to dialyzer - Saline rinse initiated
10:32 a.m. - Blood gas samples taken.
10:37 a.m. - Saline begins clearing top of column - rinsing looks good.
10:40 a.m. - Carbon perfusion off.
10:45 a.m. - Patient still cold - fistula problems still present
10:50 a.m. - Post-perfusion blood samples taken.
10:55 a.m. - Patient feels better
10:57 a.m. - Cartridge removed from circuit

The patient developed a fever later and was admitted to the hospital in mid afternoon for observation. Her temperature was down to normal that evening, but back up to about 100° F on Friday morning, April 19, 1974. She felt fine at that time. Her blood cultures (taken around noon on April 18, 1974) were negative. She was later released with no ill effects.

Analysis

I believe the general concensus of the physicians was that the patient suffered a classical pyrogen reaction, possibly due to endotoxin. Although all components of the circuit had been tested individually for endotoxin, the final assembled circuit was not tested just prior to sterilizing. It is possible that the carbon became contaminated with pyrogen during the washing process.

Analysis of the cartridge right after removal from the circuit indicated no sludging or packing, and no fibrin deposits. In general the carbon and cartridge was very clean - much cleaner than observed in the animal

experiments. The two attached photos document this observation.

The labratory results, summarized by Dr. Kablitz, are on the next page. Creatinine removal was disappointing but not unexpected due to the poor invitro creatinine removal and the low blood flow during the procedure. The decrease in blood enzymes is of interest. There was a 17% decrease in platelets and a very large decrease in white cells - though the white cell samples may have been taken from the dialyzer outflow and may not be representative of the carbon column. There was a definite decrease in pO_2, confirming the observation on slight blood color change during perfusion.

Conclusions

1. The priming volume of the system is much too high (320 ml) and must be greatly reduced.

2. The coated carbon, though good from a particulate point of view, was grossly inadequate for creatinine removal.

3. The patient suffered a reaction, probably due to pyrogens introduced during the carbon washing proceedure. Room temperature storage of the circuit for two days may have added to the problem.

4. Enzymes changes, oxygen adsorption and white blood cells interactions may be problems and must be studied in more detail.

Action

1. The cartridge has been redesigned, primarily by Jacobsen and Porter with some input by Lentz and Andrade. The cartridge will have a lower priming volume for the same amount of carbon and will be vacuum moldable.

2. Our studies on carbon coating, creatinine removal, particulate analysis have been expanded. We are also continuing discussion with HMS in order for them to develop an optimum coated carbon.

3. A Barnsted Biopure Still for the continous preparation of guaranteed pyrogen-free and sterile water has been ordered and should arrive within two weeks. A laminar flow filtered air bench is now being assembled adjacent to the still and the autoclave for the sterile assembly of cartridge circuit components. This facility is being installed in Room 2044 F in the Merrill Engineering Building.

4. Enzymes, blood gases, total and diferential white cells, and platelets will be monitored on subsequent animal experiments with the new cartridge system.

J. Andrade
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FIGURE 1. Photograph of carbon and cartridge components after perfusion and brief tap water rinse to remove blood. No clots, fibrin, or other evidence of blood intolerability was observed in the carbon, on the screen, or in the other circuit components. The inflow screen is on the left and is perfectly clean, as is the outflow screen on the right.

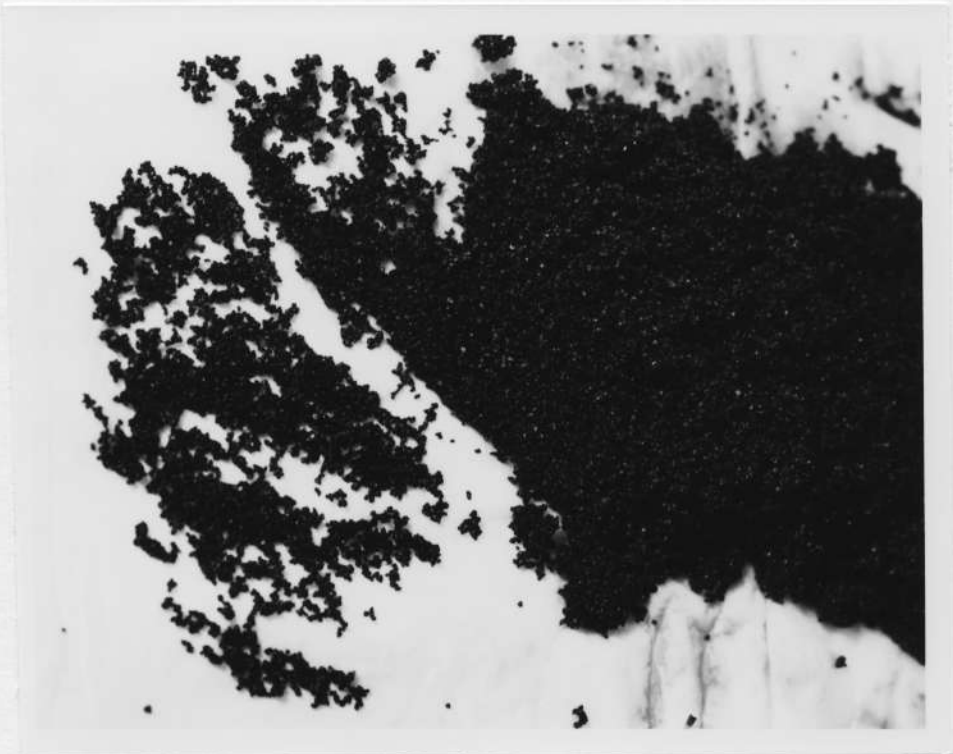

FIGURE 2. Close up of carbon in Figure 1. The carbon was loose. There was no evidence of sludging or packing.

CHARCOAL-HEMOPERFUSION ROMA PROCTOR 4/25/1974 #1

LABORATORY RESULTS	PRE	POST	
CREATININE	12.4	11.7	mg/100ml
BUN	95	95	"
URIC ACID	6.3	6.0	"
GLUCOSE	114	120	"
B ILIRU BIN DIR.	0.1	0.0	"
BILIRUBIN TOTAL	0.4	0.3	"
CHOLESTEROL	220	220	"
CALCIUM	9.7	10.0	"
PHOSPHORUS	2.9	2.4	"
SODIUM	139	140	mEq/l
POTASSIUM	5.5	4.7	"
CHLORIDE	95	102	"
CO2	24	20	"
TOTAL PROTEIN	7.2	7.0	gm/100 ml
ALBUMIN	4.2	4.2	"
ALK.PHOSPHATASE	61	46	mu/ml
LDH	165	150	"
SGOT	15	12	"
PLATELET COUNT	187,000	155,000	/mm3
WBC COUNT	6.0	0.9	$x10^3/mm3$
HEMATOCRIT	23.0	22.6	%
FREE PLASMA HGB	?	12.2	mg/100ml

ESR on flow line?

4/26 a.m. 4/26 p.m.

? → 24 → 20.3

(post hemoperfusion ± dialysis)

BLOOD GAS	PRE(ART.LINE)	POST(ART.LINE)	POST(VEN.LINE)
pH	7.45	7.38	7.41
pCO2	31	29	29
pO2	71	64	50
O2 SAT	94.2	91	85
BE	-2.0	-7.2	-5.4
HCO3	21.3	16.8	18.2
mHct	24.3	21.7	20.5

Total blood flow (poorly estimated): ~ 4785 ml

mean blood flow (" "): ~ 100 ml/min