

To date, with the exception of nasopharyngiocarcinoma and Epstein-Barr virus, hepatocellular carcinoma and hepatitis B virus, and human T-cell leukemia virus and acute leukemias, the evidence for virally induced human cancers is suggestive but still elusive. After 17 to 19 years of surveillance, children who were inadvertently exposed to SV40 in polio vaccine did not have an increased incidence of cancer,¹ yet SV40 sequences have been detected in one of seven human brain tumors.² Furthermore, DNA sequences homologous to the BK virus — a virus related to SV40 that was originally isolated from a patient with progressive multifocal leukoencephalopathy — were detected in a human adenoma of pancreatic islet-cell origin.³ SV40 and the BK virus can induce many different tumors in rodents. It is therefore plausible that similar agents can induce different tumors in human beings. Whether the familial clustering of cancer cases is due to an exposure to such a virus or to an increased genetic susceptibility to such a virus is open to conjecture. The results of the study by Farwell and Flannery add one more clue to the elucidation of the causes of human carcinogenesis.

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: Dr. Sokal is correct in pointing out that some first-degree relatives have a shared environment as well as a shared genetic endowment. In our study, controls were matched to cases for town of birth, and the relatives of controls did not have the excess incidence of certain neoplasms that the relatives of cases had. We believe that this eliminates macroenvironmental variables — water supply, atmosphere, and soil — as a cause. It is possible that a carcinogen in a particular family's home (for example) was responsible for the development of cancer in two siblings, one soon after the other. Such an environmental causative association is less creditable in the many instances we observed in which a central nervous system tumor developed in a child and 30 years later leukemia or a central nervous system tumor developed in a parent.

For similar reasons, we believe that our observations about the familial incidence of cancer would be difficult to explain on the basis of relatives' shared exposure to a viral cause. We agree with Dr. Zeldis that the possibility of viral causation of central nervous system tumors is intriguing. We have found a strong association between antenatal exposure to SV40 and the development of medulloblastoma during childhood* (the number of patients followed by Mortimer and his associates was too small to allow detection of an increase in the incidence of central nervous system tumors smaller than 200 per cent). However, the number of sibling pairs with cancer is quite similar to the number of parent-child pairs, although in nearly all instances the siblings acquired cancer within a few years of one another but the parents acquired the disease in middle age, several decades later. This chronologic separation is much more consistent with a genetically determined increased susceptibility to cancer than with common exposure to a virus.

Cancer did not develop in the spouses of any of our probands.

We did not investigate the occurrence of cancer in adoptive family members of adopted children.

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*Farwell JR, Dohrmann GH, et al. Effect of SV₄₀ virus contaminated polio vaccine on the incidence and type of CNS neoplasms in children: a population-based study. *Trans Am Neurol Assoc* 1979; 104:261-4. abstract.

ACCELERATED ATHEROSCLEROSIS OF BYPASSED CORONARY ARTERIES

To the Editor: Pathological (microscopical) examination of bypassed coronary arteries reveals progressive intimal proliferation leading eventually to total occlusion of the vessels and their transformation into fibrous cords.

This phenomenon should not be considered accelerated atherosclerosis but rather an intimal proliferative response to a diminution or absence of blood flow. It is uniformly found in varying degrees in bypassed coronary arteries and accounts for obliteration of the ductus arteriosus and the umbilical vessels soon after birth.*

Consider a blood vessel with a normal pressure and velocity of blood flow. The diameter will vary between normal limits, depending on the systolic and diastolic pressure in the vessel. If at a given site the blood flow is permanently altered by disease, external pressure, or surgical intervention so that the systolic and diastolic pressures are reduced, both the diameter and the length of the vessel will be correspondingly reduced by the contraction of elastic tissue in the wall. If the blood flow is further reduced so that patency cannot be maintained by the blood pressure, the lumen will collapse or become gradually obliterated by endothelial and fibroblastic proliferation. This process should not be considered a form of atherosclerosis but rather a reparative biologic response of the intima that serves to occlude an unused lumen, such as the ductus arteriosus and the umbilical vessels, and to transform these vessels into fibrous cords. This appears to be the mechanism for the occlusion of bypassed coronary arteries that have a diminished blood flow proximal to the site of insertion of a graft.

It is apparent that a normal physiologic range of blood volume requires a normal range of diameter and velocity of flow ($Q = AV$) to minimize intimal proliferation due to excessively high or excessively low blood velocity.

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*Texon M. The hemodynamic basis of atherosclerosis. New York: Hemisphere, 1980.

COMPLEMENT ACTIVATION DURING HEMODIALYSIS

To the Editor: I was interested to read the report by Hakim et al.¹ in the October 4 issue, and it was also enlightening to review the accompanying editorial comment.² In the latter, however, no mention was made of the possible role of acetate in hemodynamic instability.

During regular hemodialysis (diffusion plus ultrafiltration) a reduction in preload is usually observed. This is generally attributed to removal (ultrafiltration), redistribution (hypo-osmolality), and delayed refilling (low blood viscosity) of the intravascular fluid.^{3,4} The immediate consequence of such a reduction in preload is a decrease in the cardiac output, an effect probably further exacerbated by the negative inotropic action of acetate on cardiac muscle.⁵ As cardiac output decreases, it is necessary for the peripheral vascular resistance to increase in order to maintain the stability of the blood pressure (blood pressure = cardiac output × peripheral resistance). It should be pointed out, however, that in most instances the peripheral vascular resistance does not increase appropriately or is actually reduced during acetate dialysis, thereby causing the blood pressure to decline.^{5,6,9} This inappropriate response of the peripheral resistance may be caused by inadequate vasoconstriction (or vasodilatation) along with an insufficient rise in blood viscosity.⁷ The lack of adequate vasoconstriction (or vasodilatation) may in turn be attributed to the vasodilatory action of acetate or other organic acids resulting from its metabolic degradation.⁸ This is supported by the observation that during hemodialysis with a dialysate containing bicarbonate, peripheral resistance usually increases appropriately and blood pressure remains stable.^{5,6,9}

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To the Editor: Complement activation by cuprophane membranes via the alternative pathway generates C3a and C5a anaphylatoxins, which seem to play an important part in the acute transient neutropenia and pulmonary dysfunction observed during hemodialysis.^{1,3} C3a and C5a may cause these side effects directly by inducing intravascular neutrophil aggregation.² They may also act indirectly after binding to neutrophils,⁴ by stimulating the release of other aggregating agents for these cells, such as 5-HETE.⁵ Activated neutrophils are also capable of stimulating platelets⁶ and may therefore enhance the synthesis of 12-HETE, another chemotactic and aggregating agent for neutrophils.⁵ In the study described below, we obtained supportive evidence that during hemodialysis, complement activation and neutropenia correlate temporally with stimulation of neutrophil oxidative metabolism and increased synthesis of 5-HETE and 12-HETE by neutrophils and platelets, respectively.

Five patients undergoing long-term dialysis with new cuprophane membranes were selected for study, on the basis of a transient decline of the neutrophil count to less than 50 per cent of its predialysis value, within the first 15 minutes of hemodialysis, and a concomitant activation of complement as indicated by the generation of C3 and factor B breakdown products.⁷ Informed consent was obtained. Blood samples were drawn in heparinized tubes either before initiation of dialysis or 15 and 60 minutes later. Neutrophils and platelets were purified as described by Stenson and Parker.⁸ The following analyses were performed: (1) C3b-receptor and Fc-receptor expression on neutrophils were measured according to radioligand-binding assays⁹ using saturating amounts of ¹²⁵I-labeled F(ab')₂ fragments of IgG monoclonal antibody directed against either C3b receptor (Dakopatts, Denmark) or neutrophil Fc receptor (New England Nuclear, Boston); (2) the neutrophil superoxide production rate was determined according to the method of Bellavite et al.¹⁰; and (3) HETE production by neutrophils and platelets was measured by reverse-phase high-performance liquid chromatogra-

phy on a LiChrosorb RP-18 (10 μm) column after incubation of 10⁷ cells for one hour at 37°C with 1 μCi of [³H]arachidonic acid¹¹ (specific activity, 100 Ci per millimole; Amersham International, England).

The results are shown in Table 1. Fifteen minutes after initiation of a hemodialysis session, the specific binding of anti-C3b and anti-Fc receptor antibodies to neutrophils significantly decreased; thereafter, the binding of both antibodies increased and about 45 minutes later reached values significantly higher than predialysis values. Whatever the mechanisms involved, the modulation of expression of Fc and C3b receptors most probably induced neutrophil activation, as indicated by the simultaneous stimulation of the production of superoxide anion and 5-HETE. Indeed, it has been shown that the oxidative metabolism of phagocytes is enhanced by IgG-coated red cells,¹² although their lipoxygenase activity is stimulated by opsonized zymosan.¹³ Like neutrophils, platelets are also activated during hemodialysis, as reflected by the increased production of 12-HETE¹⁴ 15 minutes after initiation of the session.

In conclusion, the generation of C3a and C5a anaphylatoxins may directly cause pulmonary sequestration of leukocytes and neutropenia during hemodialysis with cuprophane membranes. As suggested by Hakim et al.,¹ it appears, however, that lipoxygenase products released by activated neutrophils and platelets may also be involved either by a complement-neutrophil-platelet interaction or by a membrane-cell interaction. The close temporal relation of complement activation, neutrophil stimulation, and enhanced HETE production certainly supports the former mechanism but does not exclude the latter.

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Table 1. Substances Stimulated by Neutrophils and Platelets during Hemodialysis.*

TIME	NEUTROPHILS			PLATELETS	
	ANTIBODY BINDING TO Fc RECEPTOR	ANTIBODY BINDING TO C3b RECEPTOR	SUPEROXIDE ANION PRODUCTION	5-HETE PRODUCTION	12-HETE PRODUCTION
	pg/10 ⁶ cells		nmol/15 min/10 ⁶ cells	cpm/10 ⁷ cells/hr	cpm/10 ⁷ cells/hr
0 min	7206 ± 630	2540 ± 320	12.9 ± 2.8	462 ± 71	329 ± 58
15 min	2210 ± 180	1170 ± 240	64.1 ± 7.1	2358 ± 242	2944 ± 314
60 min	12,310 ± 1450	5310 ± 410	25.9 ± 5.8	718 ± 125	640 ± 110

*Results are the means (± S.E.M.) of triplicate determinations performed on neutrophils and platelets from five patients. The differences observed between the values obtained after 15 minutes of dialysis and those measured at time zero or after 60 minutes are all statistically significant (P < 0.01). The amount of anti-Fc-receptor or of anti-C3b-receptor antibody bound to the neutrophils is also significantly higher 60 minutes after initiation of hemodialysis than at time zero (P < 0.01).

The first part of the book is devoted to a general history of the United States from its discovery to the present time.

The second part is devoted to a detailed history of the United States from the discovery to the present time.

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The sixteenth part is devoted to a detailed history of the United States from the discovery to the present time.

The seventeenth part is devoted to a detailed history of the United States from the discovery to the present time.

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To the Editor: Hakim et al. discuss hypersensitivity reactions to dialyzer membranes and associated changes in complement activation. They describe the "first-use syndrome" and state that this reaction is usually not seen if a membrane is reused. We have recently observed a patient who repeatedly had typical symptoms of first use when she underwent dialysis with reused but not with unused membranes.

A 67-year-old woman in whom granulomatous interstitial nephritis was diagnosed in 1977 began receiving hemodialysis later that year. She did relatively well until January 1984, when within three to four minutes of initiation of dialyses with reused membranes, she repeatedly reported respiratory distress. Her symptoms included malaise, a "warm feeling," gradually increasing shortness of breath, chest tightness, itching, nausea, dyspnea, rales, and wheezing. Table 1 shows the observed sequence of events.

In our unit, as in those in the Hakim study, all dialyzers, including new ones, are prepacked in 2 per cent formaldehyde, preproc-

Table 1. Occurrence of Symptoms of Respiratory Distress during Dialyses with Unused and Reused Membranes.

DATE	MEMBRANE	USE	SYMPTOMS
1/3	HPF200 (cuprophane)	#2	+
1/3	CD4000 (cellulose acetate)	#1	0
1/5	CD4000	#2	+
1/7	GAMBRO 11.5 (cuprophane)	#1	0
1/10	CD4000	#3	+
1/12	CD4000	#1	0
1/14	CD4000	#1	0
1/24	CD4000	#2	+
1/26	CD4000	#1	0
1/28	CD4000	#1	0
1/31	CD4000	#1	0
2/2	CD4000	#1	0

essed in an identical fashion with dialysate and flushing with sterile saline, and checked for residual formaldehyde by means of Schiff's reagent. To test the possibility that our patient was reacting to formaldehyde used before dialyzer reuse (despite a negative Schiff test), we measured levels of formic acid before and during treatment with the reused dialyzers and found the levels to be unchanged. Serum levels of C3 and C4 before and after the treatments associated with reactions were little changed, but C3a or C5a were not measured. White-cell nadirs were comparable on days of reaction and those of nonreaction. Since our formaldehyde-prepacked dialyzers did not elicit a symptomatic response on initial use, it is unlikely that formaldehyde was the agent responsible for the reaction. To support this hypothesis, we varied the volume of saline flush from 500 to 2500 ml, to maximize formaldehyde removal, and again noted little effect with this maneuver. We have no reason to implicate the membrane material since no reaction was elicited after initial use of cuprophane or cellulose acetate.

This sequence of events suggests possible "reuse-iation of the dialyzer membrane and perhaps should "second-use" or "reuse" syndrome. As dialyzer reuse prevalent, we can expect to see further reports of suc

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The above letters were referred to the authors of the article and the editorial in question, who offer the following replies:

To the Editor: Dr. Duarte makes some very interesting comments and describes an important factor in the hemodynamic instability of dialysis patients. Our work addressed the relation between the first-use syndrome and complement activation, which we believe to play an additive and perhaps synergistic part in the adverse symptoms that dialysis patients may experience. We believe that one clue to the difference between first use and effects of acetate is that clinically, adverse symptoms due to complement activation usually occur early, whereas the effects of dialysate containing acetate tend to become manifest late in the course of dialysis.

Dr. Malaise and co-workers describe another aspect of the complex blood-membrane interaction that occurs during dialysis. We have indeed shown in previous work¹ the relation of complement activation and increased expression of C3b receptors on neutrophils and have also documented platelet activation² during hemodialysis. Whether these are separate or interrelated events awaits further work.

Stein et al. describe a patient with symptoms suggestive of first-use syndrome but occurring with reused membranes. Many of these symptoms occurred with reused cellulose acetate membranes. We have shown that these membranes (unlike cuprophane membranes) retain their ability to activate complement during reuse.³ If the reuse involves the use of sodium hypochlorite, then complement activation can also occur when cuprophane membranes are reused, since this agent quickly oxidizes and dissolves any autologous protein layer that may be present inside the hollow fibers after use.

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To the Editor: Duarte quite appropriately brings up the possible detrimental effects of acetate in dialysate on the hemodynamic stability of patients receiving maintenance hemodialysis. Space constraints in my editorial¹ prevented meaningful commentary on the peripheral-vasodilatory and cardiac-depressant properties of acetate that have been postulated to contribute to the hypotension and cardiovascular instability observed during hemodialysis with an acetate dialysate. In support of this hypothesis, a number of clinical studies have shown a reduced incidence of hypotension in some patients when bicarbonate was substituted for acetate in the dialysate.²⁻⁴ However, other studies have been unable to document a cardiodepressant effect of acetate or have shown a clear-cut adverse effect of acetate dialysate on peripheral resistance.⁵⁻⁹ These apparently conflicting results may be due to a number of variables other than acetate in the various reports published to date.

In one of the more recent and carefully designed studies of the issue, Dr. Velez and his co-workers¹⁰ demonstrated that in patients with stable cardiac function, bicarbonate afforded no greater hemo-

THE STATE OF TEXAS,
COUNTY OF []

I, the undersigned, a Notary Public in and for the State of Texas, do hereby certify that the within and foregoing instrument, to-wit: a certain deed of conveyance, bearing date the [] day of [] 19[] A.D., and recorded in my office on the [] day of [] 19[] A.D., in Book [] of Deeds, page [], is a true and correct copy of the original instrument as the same appears from the records of my office.

Given under my hand and seal of office, at the City of [], this [] day of [] 19[] A.D.

[Signature]
Notary Public in and for the State of Texas

My commission expires on the [] day of [] 19[] A.D.

This deed was acknowledged before me on the [] day of [] 19[] A.D., by [] and [] who are known to me to be the persons whose names are subscribed to the foregoing instrument, and they declared to me that they executed the same for the purposes and consideration therein expressed.

Notary Public in and for the State of Texas

I, the undersigned, a Notary Public in and for the State of Texas, do hereby certify that the within and foregoing instrument, to-wit: a certain deed of conveyance, bearing date the [] day of [] 19[] A.D., and recorded in my office on the [] day of [] 19[] A.D., in Book [] of Deeds, page [], is a true and correct copy of the original instrument as the same appears from the records of my office.

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dynamic stability than did acetate if the sodium concentration of the dialysate was 141 mmol per liter. When sodium concentrations in the dialysate were lower, bicarbonate did appear to decrease orthostatic symptoms and signs moderately. The authors concluded that in patients who are unable to tolerate dialysates with high sodium concentrations (because of excessive thirst, hypertension, or heart failure), the use of bicarbonate in the dialysate might reduce adverse symptoms. Whether acetate dialysate, independent of sodium concentration, is detrimental in patients with compromised cardiac function remains to be documented. More important, whether variables other than the sodium concentration in the dialysate will emerge as responsible for the current controversy on the acute detrimental effects of acetate dialysate in some patients remains to be examined.

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THE CASE OF THE FITTING FLYER

To the Editor: In November and December of 1984, a single man presented at three general hospitals successively in southern Vermont and New Hampshire, with a similar history. Claiming to be 33 or 34, this white man of medium build with sandy-blond, curly hair sought the attention of a family practitioner in each town for new-onset seizures threatening his career as a pilot (airline, oil-rig helicopter ferry, or corporation). This precipitated urgent neurologic consultation in each case. He convincingly reported right-sided focal motor seizures with secondary generalization preceded on each occasion by classic scintillating scotomata in both visual fields. He had suffered a fall from an aircraft wing in Los Angeles three years earlier, acquiring a hairline fracture over the left temporal region. A CT scan at the time was remarkable for "swelling," for which he received two weeks of treatment with steroids before returning to flying duties.

Examination by two neurologists failed to confirm convincing signs of central nervous system dysfunction. Hospitalization (in Rutland, Vt.) without anticonvulsants failed to document the two to three seizures per day he reported, and a CT scan and electroencephalogram were normal. Subsequently, it was learned that after discharge he had left the area with one of the hospital's nurse's aides, who was abandoned after her funds had been expended by the "patient." The second (Brattleboro, Vt.) and third (Keene, N.H.) consultants treated him with phenytoin (Dilantin) and arranged for outpatient testing appointments, which were never kept. At no point did he ever admit to prior evaluation or produce his pilot's license. It was later learned that he had been evaluated for syncope one year earlier in Burlington, Vermont.

Apparently, this man uses a history of new seizures to gain admission to a hospital with the intention of taking advantage of unsuspecting health care providers. Allegations of physical abuse of one victim have not been confirmed. Emergency room physicians, family practitioners, and neurologists should be aware of this man's behavior.

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OVERHEAD ON NIH GRANTS

To the Editor: In his thorough review of the fiscal 1985 National Institutes of Health (NIH) appropriation, Iglehart (Oct. 25 issue)¹ points out that "overhead rates have risen to an estimated 31 per cent in fiscal 1985." This statement has been the source of some confusion at this institution and should be clarified. Indirect cost (overhead) expressed as a proportion of total cost is a different measure from an institution's "overhead rate." Overhead rates refer to the calculation of federally reimbursable indirect costs expressed as a percentage of an agreed-on base, such as institutional research salaries and wages or modified total direct costs. In fiscal 1982, the average institutional indirect cost rate at the top 20 research universities supported by the NIH was 47 per cent of modified total direct costs.²

The calculation and expression of indirect cost rates, tailored to specific institutional needs and governed by regulations of the Office of Management and Budget, should be distinguished from the calculation of indirect costs expressed as a proportion of total costs. The latter is no doubt the calculation to which Mr. Iglehart refers, since the NIH has reported that 30.9 per cent of its total research funds were provided for indirect costs in fiscal 1983.³

Many of us in the research administration community endorse the efforts of the NIH and the Office of Science and Technology Policy to control the growth of indirect costs. The extension of prior approval authorities to grantee institutions is one step in this process with which our organization is familiar as a site for pilot testing. We advocate and will support more such steps in the direction of reduced paper work and the elimination of redundant levels of approval.

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- Iglehart J. The NIH appropriation. *N Engl J Med* 1984; 311:1132-6.
- Selby SE. Indirect cost rate composition and myths. *J Soc Res Admin* 1984; 15 (Winter):29-37.
- National Institutes of Health. Statistics and Analysis Branch, Division of Research Grants. Extramural trends. FY 1972-1983. Washington, D.C.: Government Printing Office, 1984:54-5. (Informal chart book.)

BOOK REVIEWS

STANLEY COBB: A BUILDER OF THE MODERN NEUROSCIENCES

By Benjamin V. White. 445 pp., illustrated. Boston, The Francis & Taylor Library of Medicine, 1984. \$29.50. (Distributed by the University Press of Virginia, Charlottesville.)

Stanley Cobb (1887-1968) had a key role in the development of neurology, psychiatry, and the basic neurosciences. His career was spent at the Harvard Medical School from 1919 to 1954, a period that was critical for the future of each of these disciplines.

It was during this period that the Flexners and the Rockefeller Foundation, working with a small number of medical-school deans, were instrumental in disseminating the concept of academic medi-