Berkseth RO, Kjellstrand CM. Radiologic contrast-induced nephropathy. Med Clin North Am 1984; 68:351-70.
Lang EK, Foreman J, Schlegel JU, Leslie C, List A, McCormick P. The incidence of contrast medium induced acute tubular necrosis following arteriography. Radiology 1981; 138:203-6.
Milman N, Gottlieb P. Renal function after high dose urography in patients with chronic renal insufficiency. Clin Nephrol 1977; 7:250-4.
Cochran ST, Wong WS, Roe DJ. Predicting angiography-induced acute renal function impairment: clinical risk model. AJR 1983; 141:1027-33.
Van Zee BE, Hoy WE, Talley TE, Jaenike JR. Renal injury associated with intravenous pyelography in nondiabetic and diabetic patients. Ann Intern Med 1978; 89:51-4.
Port FK, Wagoner RD, Fulton RE. Acute renal failure after angiography. AJR 1974; 121:544-50.
Martin-Paredero V, Dixon SM, Baker JD, et al. Risk of renal failure after major angiography. Arch Surg 1983; 118:1417-20.
Older RA, Miller JP, Jackson DC, Johnsrude IS, Thompson WM. Angiographically induced renal failure and its radiographic detection. AJR 1976; 126:1039-45.
Byrd L, Sherman RL. Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review. Medicine (Baltimore) 1979; 58:270-9.
Carvallo A, Rakowski TA, Argy WP Jr, Schreiner GE. Acute renal failure following drip infusion pyelography. Am J Med 1978; 65:38-45.
Krumlovsky FA, Simon N, Santhanam S, del Greco F, Roxe D, Pomaranc MM. Acute renal failure: association with administration of radiographic contrast material. JAMA 1978; 239:125-7.
Ansari Z, Baldwin DS. Acute renal failure due to radio-contrast agents. Nephron 1976; 17:28-40.
Weinrauch LA, Healy RW, Leland OS Jr, et al. Coronary angiography and acute renal failure in diabetic azotemic nephropathy. Ann Intern Med 1977; 86:56-9.
Swartz RD, Rubin JE, Leeming BW, Silva P. Renal failure following major angiography. Am J Med 1978; 65:31-7.
Harkonen S, Kjellstrand CM. Exacerbation of diabetic renal failure following intravenous pyelography. Am J Med 1977; 63:939-46.
Knapp MS. Renal failure after contrast radiography. Br Med J 1983; 287:3-4.
Taliercio CP, Vlietstra RE, Fisher LD, Burnett JC. Risks for renal dysfunction with cardiac angiography. Ann Intern Med 1986; 104:501-4.
Cruz C, Hricak H, Samhouri F, Smith RF, Eyler WR, Levin NW. Contrast media for angiography: effect on renal function. Radiology 1986; 158:109-12.
Mason RA, Arbeit LA, Giron F. Renal dysfunction after arteriography. JAMA 1985; 253:1001-4.
Fischer HW, Spataro RF, Rosenberg PM. Medical and economic considerations in using a new contrast medium. Arch Intern Med 1986; 146:1717-21.
Grainger RG. Radiological contrast media. Clin Radiol 1987; 38:3-5.
Schwab SJ, Hlatky M, Morris K, et al. Contrast nephrotoxicity: a prospective randomized trial of ionic versus non-ionic radiographic contrast. Am Soc Nephrol Abstract Book 1988:83A. abstract.
Golman K, Almen T. Contrast media-induced nephrotoxicity: survey and present state. Invest Radiol 1985; 20:Suppl:S92-S97.

CONTRAST NEPHROTOXICITY: A RANDOMIZED CONTROLLED TRIAL OF A NONIONIC AND AN IONIC RADIOGRAPHIC CONTRAST AGENT

STEVE J. SCHWAB, M.D., MARK A. HLATKY, M.D., KAREN S. PIEPER, M.S., CHARLES J. DAVIDSON, M.D., KENNETH G. MORRIS, M.D., THOMAS N. SKELTON, M.D., AND THOMAS M. BASHORE, M.D.

Abstract Experimental studies have suggested that nonionic contrast agents are less nephrotoxic than ionic contrast agents. To examine the relative nephrotoxicity of the two types of agents, we randomly assigned 443 patients to receive either iopamidol (nonionic) or diatrizoate (ionic) for cardiac catheterization. The patients were stratified into low-risk (n = 283) or high-risk (n = 160) groups, on the basis of the presence of diabetes mellitus, heart failure, or preexisting renal insufficiency (base-line serum creatinine level, >133 μmol per liter). Serum and urine analyses were performed at base line and 24 and 48 hours after the infusion of contrast material. Nephrotoxicity was defined as an increase in the serum creatinine level within 48 hours of at least 44 μmol per liter.

The median maximal rise in the serum creatinine level was 18 μmol per liter in both the diatrizoate group (n = 235) and the iopamidol group (n = 208) (P not significant; power to detect a difference >9 μmol per liter, >90 percent). Creatinine levels increased by at least 44 μmol per liter (0.5 mg per deciliter) in 10.2 percent of the patients receiving diatrizoate and 8.2 percent of the patients receiving iopamidol (P not significant). Among the high-risk patients, creatinine levels increased by at least 44 μmol per liter in 17 percent of the patients in the diatrizoate group, as compared with 15 percent of the patients in the iopamidol group (P not significant).

We were unable to demonstrate a difference in the incidence of nephrotoxicity between patients receiving a nonionic contrast agent and those receiving an ionic contrast agent. (N Engl J Med 1989; 320:149-53.)

THE administration of radiographic contrast mediums continues to be a common cause of renal injury acquired in the hospital.[1-4] Conventional radiographic contrast agents, as exemplified by sodium diatrizoate (Fig. 1), use iodine (300 mg per milliliter) to absorb x-ray photons in order to achieve radiographic visualization; such agents are highly osmolar (1500 mOsm per liter) and highly charged.[5,6] These characteristics are believed to contribute to both the nephrotoxicity and the allergic reactions associated with these agents. New contrast agents such as iopamidol (Fig. 1) have been developed that have lower osmolarity (796 mOsm per liter) and are nonionic, yet retain sufficient iodine (370 mg per milliliter) to provide satisfactory radiographic visualization.[5-7] The principal disadvantage of the new agents is their cost, which is currently 13 to 25 times that of comparable amounts of ionic contrast material.[8]

Recent studies in laboratory animals suggest that nonionic contrast agents have fewer harmful effects than ionic agents on systemic and renal hemodynamics, as well as a less direct nephrotoxic effect on cells of the proximal renal tubule.[9,10] Nevertheless, studies in humans have shown that nonionic contrast mediums can cause renal injury.[11] This randomized prospective study was undertaken to compare the incidence of

From the Divisions of Nephrology (S.J.S.) and Cardiology (M.A.H., K.S.P., C.J.D., K.G.M., T.N.S., T.M.B.), Duke University Medical Center and the Veterans Administration Medical Center, Durham, N.C. Address reprint requests to Dr. Schwab at the Division of Nephrology, Box 3014, Duke University Medical Center, Durham, NC 27710.

Supported by a grant from Squibb Diagnostics, Princeton, N.J.

nephrotoxicity observed after the use of ionic or nonionic contrast mediums in patients undergoing cardiac catheterization.

Methods

From April 1, 1987, through March 31, 1988, all patients undergoing elective coronary angiography at the Veterans Administration Medical Center in Durham were asked to consider enrollment in this study. The study was approved by the institutional review boards of both Duke University and the Veterans Administration Medical Center. After giving informed consent, patients were randomly assigned to receive either iopamidol or diatrizoate for coronary angiography and left ventriculography. Before randomization, the patients were stratified into either low-risk (n = 283) or high-risk (n = 160) groups on the basis of risk factors reported previously for the development of nephrotoxicity. Patients were placed in the high-risk group if they had diabetes mellitus (treated with either insulin or an oral agent), congestive heart failure (as determined by history or physical examination), or preexisting renal insufficiency (serum creatinine level above 133 μmol per liter [1.5 mg per deciliter]).

Patients were given intravenous fluids before angiography, consisting of 1 to 1.5 liters of 5 percent dextrose in half-normal saline, as a routine clinical precaution to minimize nephrotoxicity. This fluid challenge was administered overnight before cardiac catheterization and was continued at a rate of 125 ml per hour for four hours afterward. Diuretic agents and nonsteroidal antiinflammatory drugs were withheld before catheterization according to the protocol, unless they were specifically needed, and no nephrotoxic antibiotics were administered before the study. Patients with a history of allergic reaction to contrast mediums (anaphylaxis or urticaria) received methylprednisolone and cimetidine as prophylaxis. Iopamidol (Isovue 370, Squibb, Princeton, N.J.) and sodium diatrizoate (Renografin, Squibb, or Hypaque, Winthrop–Breon, New York) were used exclusively as the contrast agents. The average dose of contrast material (±SEM) was 171±53.7 ml (range, 30 to 500). A history was taken, and a physical examination and base-line laboratory tests were performed by the study coordinators before catheterization. During catheterization, a technician or nurse kept a detailed account of the procedure. The study coordinators reviewed hospital records and interviewed each patient about potential complications within 24 hours of the procedure.

Blood and urine samples were obtained immediately before cardiac catheterization and 24 and 48 hours afterward. All samples were analyzed in duplicate with a Beckman 700 AutoAnalyzer (Beckman Instruments, Somerset, N.J.). The serum and urine specimens were analyzed for levels of creatinine, sodium, and uric acid. Levels of urinary protein were measured with use of a urine dipstick (Miles Laboratories, Elkhart, Ind.). All urine specimens were analyzed microscopically by a physician or medical technologist. Fractional excretion of sodium and ratios of urinary uric acid to creatinine were calculated with use of standard formulas.[12]

Contrast nephrotoxicity was defined as an increase in the serum creatinine level of at least 44 μmol per liter (0.5 mg per deciliter) above the base-line value within 48 hours of exposure to a contrast agent. Uric acid excretion was considered elevated if the ratio of uric acid to creatinine in urine exceeded 0.8. Hyperuricemia was considered to be present if the base-line serum uric acid level was 0.47 mmol per liter (8 mg per deciliter) or higher. Statistical comparisons between the groups of patients who received ionic and nonionic contrast material were performed with use of the Wilcoxon rank-sum test for continuous data and the chi-square test for categorical data. All P values reported are two-tailed.

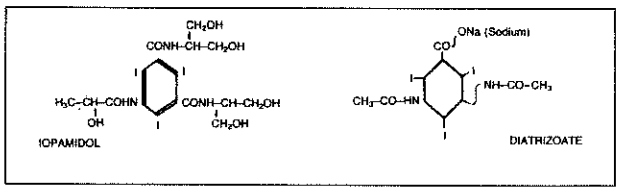

Figure 1. Chemical Structure of Iopamidol and Diatrizoate.

Table 1. Clinical Characteristics of 443 Patients Receiving Radiographic Contrast Agents for Cardiac Catheterization.

Characteristic	Treatment Group	
	Diatrizoate (N = 235)	Iopamidol (N = 208)
Mean age	59.4	59.4
	number (percent)	
Age >60 yr	119 (51)	106 (51)
History		
Diabetes mellitus	49 (21)	41 (20)
Congestive heart failure	38 (16)	28 (13)
Laboratory data		
Mean base-line serum creatinine	100*	97*
Base-line serum creatinine >133 μmol/liter	14 (6)	14 (7)
Blood uric acid >0.47 mmol/liter	61 (26)	37 (18)
Proteinuria >2+	1 (0.4)	2 (1)

*Values are micromoles per liter.

Results

Four hundred forty-three consecutive patients were randomly assigned to groups before cardiac catheterization. Eleven patients were excluded from the study because they had been catheterized on an emergency basis and could not be evaluated beforehand or randomized. Twenty-six patients were excluded for logistic reasons, and three refused to be randomized. The characteristics of the randomized patient population are detailed in Table 1. Two hundred thirty-five patients were randomly assigned to receive diatrizoate, whereas 208 were randomly assigned to receive iopamidol. The mean age of the total patient population was 59 years, and 225 patients (51 percent) were over 60 years of age. All but three patients were men. Base-line serum creatinine measurements ranged from 35 to 539 μmol per liter (0.5 to 6.1 mg per deciliter). One hundred sixty patients (36 percent) fell into one of the high-risk groups as previously defined, with 81 receiving diatrizoate and 79 receiving iopamidol (Table 2). Ninety patients had diabetes mellitus (20 percent), 66 had congestive heart failure (15 percent), and 28 (7 percent) had preexisting renal impairment (serum creatinine level above 133 μmol per liter). The number of patients with several risk factors was similar in both groups. Four patients had three risk factors, whereas 30 patients had two. The base-line serum creatinine levels and the numbers of patients with serum creatinine levels higher than 133 μmol per liter (1.5 mg per deciliter) were also similar in both groups (Table 1). Hyperuricemia and proteinuria of more than 2+ were present in equal numbers of patients in both groups. As expected with randomization, there were no significant differences in any characteristics between the patients in the diatrizoate group and those in the iopamidol group (Table 1).

Table 2. Changes in Serum Creatinine Levels after the Administration of Contrast Agents.*

	DIATRIZOATE		IOPAMIDOL	
	MEDIAN	MEAN (95% CI)	MEDIAN	MEAN (95% CI)
	(N = 235)		(N = 208)	
	micromoles per liter			
All patients				
Base-line measurement	97	100 (95–105)	88	97 (93–101)
Peak increase	18	23 (19–28)	18	20 (17–23)
High-risk patients	(N = 81)		(N = 79)	
Base-line measurement	97	110 (99–122)	97	108 (99–116)
Peak increase	18	31 (20–41)	18	24 (18–31)
Low-risk patients	(N = 154)		(N = 129)	
Base-line measurement	97	94 (91–98)	90	91 (88–94)
Peak increase	18	19 (16–22)	18	17 (15–20)

*The percentages of patients with an increase in the serum creatinine level of 44 μmol per liter or more within 48 hours were as follows — in all patients: diatrizoate group, 10.2; iopamidol group, 8.2; in high-risk patients: diatrizoate, 17.0; iopamidol, 15.0; in low-risk patients: diatrizoate, 7.0; iopamidol, 5.0. CI denotes confidence interval.

The changes in serum creatinine concentrations after the administration of contrast material are described in Table 2 and shown in Figure 2. The serum creatinine levels rose a median of 18 μmol per liter (0.2 mg per deciliter) above the base line in patients receiving either contrast agent (Table 2). The number of patients with an increase in the serum creatinine level of more than 44 μmol per liter (10.2 percent receiving diatrizoate and 8.2 percent receiving iopamidol) did not differ in either contrast group (P not significant). The maximal increases in serum creatinine were 345 μmol per liter (3.9 mg per deciliter) in the diatrizoate group and 212 μmol per liter (2.4 mg per deciliter) in the iopamidol group. No patients in this study had nephrotoxicity or acute oliguria requiring dialysis as a result of the administration of contrast material.

The numbers of patients designated as being at high risk of renal injury from contrast material were not significantly different in the two groups (81 vs. 79), and their base-line serum creatinine levels were similar (Table 2). The mean and median peak increases in serum creatinine above the base line did not differ in either the high-risk group or the low-risk group when the two types of contrast material were compared (Table 2). Analysis of the risk factors determined prospectively revealed that the high-risk group had a greater incidence of nephrotoxicity (Table 2), but that only base-line serum creatinine levels above 133 μmol per liter correlated with the increments in serum creatinine mediated by contrast material. Figure 2 shows the distribution of increases in serum creatinine above the base-line values after the administration of the two types of contrast material. Increments in serum creatinine above the base-line level were distributed equally in both groups. There were no differences between the iopamidol and the diatrizoate groups in the percentage of patients with increases at any level of increment above base-line values.

Table 3 shows determinations of urine chemistries after angiography in patients with and without an increase in the level of serum creatinine. Control urine chemistries before angiography did not differ when groups were compared according to contrast agent or risk status. Specifically, the median urinary sodium measurements before catheterization were 64.7 and 64.2 mmol per liter (P not significant) in the ionic and nonionic contrast groups, respectively, and 65.6 and 51.6 mmol per liter (P not significant) in the patients in whom contrast nephrotoxicity developed and those in whom it did not. Urinary sodium levels and fractional excretion of sodium after exposure to contrast material did not differ in patients with nephrotoxicity and those without it (Table 3). Ratios of uric acid in urine to that in plasma also had no value in predicting contrast nephrotoxicity (Table 3). No significant differences in the degree of crystalluria were found in patients who had increases in serum creatinine as compared with those who did not. In addition, there were no differences in urinary indexes when these groups were divided according to type of contrast material (Table 3). Despite intravenous hydration, the fractional excretion of sodium was low in patients in both contrast groups after the administration of contrast material, independently of any change in serum creatinine levels (Table 3).

Discussion

Nephrotoxicity due to the administration of contrast material is reported to be one of the most common causes of acute renal failure acquired in the hospital.[1-4,13-15] Hou and associates found that the likelihood of acute renal failure due to contrast material exceeded the likelihood of acute renal failure mediated by aminoglycoside antibiotic agents.[2] In recent studies, the incidence of nephrotoxicity of contrast agents has shown wide variability.[1-4,13-15] A variety of underlying conditions have been suggested as being associated with an increased likelihood of renal toxicity after the use of ionic contrast material. These include age, renal impairment, diabetes mellitus, proteinuria, congestive heart failure, and hyperuricemia.[1-4,13-17] Other investigators have attempted to reduce the likelihood of contrast nephropathy by pretreatment with volume expansion or diuresis.[3,4,18]

Several investigators have proposed that nonionic

Table 3. Urine Chemistries after Angiography in Patients with an Increase in the Serum Creatinine Level and Those with No Increase.*

	INCREASE*		NO INCREASE	
	DIATRIZOATE	IOPAMIDOL	DIATRIZOATE	IOPAMIDOL
Median fractional excretion of sodium (%)	0.7	0.3	0.5	0.4
Median ratio of uric acid in urine to that in plasma	0.20	0.19	0.27	0.25
Crystalluria†(%)	4	0	4	5

*An increase in the serum creatinine level was defined as an increase of 44 μmol per liter or more within 48 hours.

†Crystalluria was defined as the presence in spun urine of more than five crystals per high-power field.

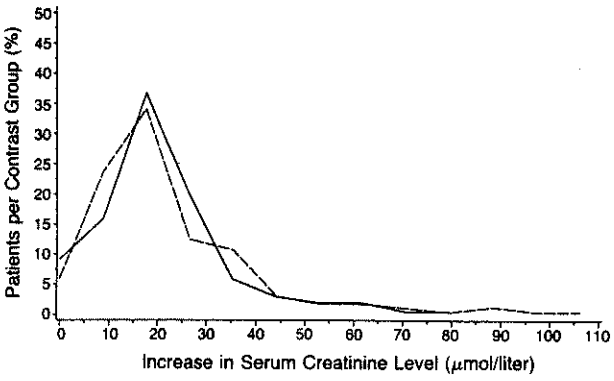

Figure 2. Peak Increases in Serum Creatinine Levels after the Administration of Contrast Agents.

The percentage of patients is plotted against the maximal increase in creatinine level from base-line values. The solid line represents 208 patients receiving iopamidol, the dashed line 235 patients receiving diatrizoate.

contrast agents may have little or no nephrotoxic potential.[5,7,9,10] In this regard, we recently evaluated the incidence of nephrotoxicity in 1444 patients undergoing cardiac catheterization with nonionic contrast material.[11] Serum creatinine levels increased by 44 μmol per liter (0.5 mg per deciliter) or more in 6 percent of the patients who received nonionic contrast material for cardiac catheterization.[11] The risk of nephrotoxicity increased exponentially when patients with serum creatinine levels higher than 107 μmol per liter (1.2 mg per deciliter) received nonionic contrast material. In addition, elevated base-line serum creatinine levels were the only risk factor that correlated with the development of contrast nephrotoxicity.

We designed this study to compare the renal effects of an ionic and a nonionic contrast agent. Using a population carefully randomized and matched for putative risk factors for contrast nephrotoxicity, we could not show any difference in nephrotoxicity between two contrast agents. As is shown in Figure 2, there were no significant differences in increments in serum creatinine levels between the patients who received the ionic contrast agent and those who received the nonionic agent. When the median maximal increases in serum creatinine levels were examined, there were no differences in increments in serum creatinine after exposure to the contrast agents (Table 2). This study was designed to detect a difference in the serum creatinine level of 9 μmol per liter (0.1 mg per deciliter) between the two contrast groups. The statistical power to detect this difference was well over 90 percent. Thus, it is very unlikely that an important difference in nephrotoxic potential was missed because of a Type II statistical error.[19]

Since less than 5 percent of the patients had serum creatinine levels higher than 265 μmol per liter (3 mg per deciliter), we could not assess the effect of these contrast agents in patients with advanced renal impairment. In accordance with our earlier observations, we found the incidence of nephrotoxicity to be in the range of 8 to 10 percent with either contrast agent. Clinically serious renal impairment was uncommon in our study, regardless of the contrast agent used. The interpretation of these favorable findings requires a cautionary note, however. All the patients in this study were well hydrated both before and after angiography, and none had had a recent renal injury that would predispose them to injury from contrast material. In common clinical practice, the incidence of clinically serious renal injury may be greater than that observed here.

We were unable to define any factors other than preexisting renal impairment that would allow us to predict which patients would have acute renal injury after the injection of contrast material. Fang and associates suggested that low fractional excretion of sodium after such exposure was associated with a high likelihood of nephrotoxicity.[20,21] In our study, we could not document a significant difference in the fractional excretion of sodium between patients who had an increase in serum creatinine level of more than 44 μmol per liter and patients who did not. It is noteworthy, however, that fractional excretion of sodium was low (less than 1 percent) in most patients after angiography, regardless of nephrotoxicity or type of contrast material used (Table 3). A biphasic response of early renal vasodilation followed by vasoconstriction has been described.[22-24] It is interesting to speculate whether the activation of intrarenal vasoconstrictors mediated by contrast agents may lead to this avid reabsorption of sodium, as has been proposed.[22] Vari et al. showed that in combination with sodium restriction, use of the prostaglandin inhibitor indomethacin uniformly led to contrast nephrotoxicity in rabbits.[23] The ratio of uric acid concentrations in urine to those in plasma was not shown to correlate in either group with the likelihood of increases in serum creatinine levels. We were also unable to find any significant change in the degree of crystalluria in these same groups.

The cost of nonionic radiographic contrast material continues to be a serious impediment to its wider use. Although we did not detect any differences in nephrotoxic potential between the two contrast agents, we and other investigators have shown marked decrements in other side effects when nonionic radiographic agents are used, as compared with ionic agents.[25-29] Significant reductions in cardiovascular complications such as bradyarrhythmias, tachyarrhythmias, and hypotension have been reported in patients undergoing coronary arteriography with nonionic contrast material.[25-29] Whether these advantages outweigh the cost considerations remains to be decided.[8]

In conclusion, in this large prospective, randomized, controlled clinical trial, a nonionic radiographic contrast agent (iopamidol) had no significant advantage in preventing contrast nephrotoxicity when compared with a conventional ionic contrast agent (diatrizoate). Elevated serum creatinine levels appeared to be the only risk factor for the development of renal injury induced with the use of either ionic or nonionic contrast material. Since less than 5 percent of the pa-

tients in this study had advanced renal impairment, the applicability of our findings cannot necessarily be extended to this patient group. In the majority of patients, there appears to be no advantage to using a nonionic contrast agent to prevent renal injury mediated by contrast material.

We are indebted to Susan Allen, Paul Owens, and Robin Sykes for technical assistance, to Dr. Vincent W. Dennis for review of the manuscript, and to Mrs. Sue Younkin for assistance in the preparation of the manuscript.

References

1. D'Elia JA, Gleason RE, Alday M, et al. Nephrotoxicity from angiographic contrast material: a prospective study. Am J Med 1982; 72:719-25.
2. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med 1983; 74:243-8.
3. Byrd L, Sherman RL. Radiocontrast-induced acute renal failure: a clinical and pathophysiologic review. Medicine (Baltimore) 1979; 58:270-9.
4. Abraham P, Harkonen S, Kjellstrand C. Contrast nephropathy. In: Massry SG, Glassock RJ, eds. Textbook of nephrology. Vol. 1. Baltimore: Williams & Wilkins, 1983:6.205-6.210.
5. Evens RG. Low osmolarity contrast media: choice and challenge for the 80's. Diagn Imaging 1987; 9:Suppl:1-30.
6. Evans JR, Cutler RE, Pettis JL. Low-osmolar radiocontrast agents and nephrotoxicity. Dialysis Transplant 1987; 16:504-6, 508.
7. Bettmann MA, Higgins CB. Comparison of an ionic with a nonionic contrast agent for cardiac angiography: results of a multicenter trial. Invest Radiol 1985; 20:Suppl:S70-S74.
8. Fischer HW, Spataro RF, Rosenberg PM. Medical and economic considerations in using a new contrast medium. Arch Intern Med 1986; 146:1717-21.
9. Katzberg RW, Morris TW, Lasser EC, et al. Acute systemic and renal hemodynamic effects of meglumine/sodium diatrizoate 76% and iopamidol in euvolemic and dehydrated dogs. Invest Radiol 1986; 21:793-7.
10. Humes HD, Creslinski DA, Messana JM. Pathogenesis of radiocontrast-induced renal failure: comparative nephrotoxicity of diatrizoate and iopamidol. Diagn Imaging 1987; 9:Suppl:12-8.
11. Davidson CJ, Hlatky M, Schwab SJ, Morris K, Skelton T, Bashore T. Nephrotoxicity and nephrotic risk factors: a prospective trial of nonionic contrast media. Ann Intern Med (in press).
12. Schwab SJ. Renal diseases. In: Orland MJ, Saltman RJ, eds. Manual of medical therapeutics. 25th ed. Boston: Little, Brown, 1986:177-95.
13. Krumlovsky FA, Simon N, Santhanam S, del Greco F, Roxe D, Pomaranc MM. Acute renal failure: association with administration of radiographic contrast material. JAMA 1978; 239:125-7.
14. Cochran ST, Wong WS, Roe DJ. Predicting angiography-induced acute renal function impairment: clinical risk model. AJR 1983; 141:1027-33.
15. Coggins CH, Fang LS-T. Acute renal failure associated with antibiotics, anesthetic agents, and radiographic contrast agents. In: Brenner BM, Lazarus JM, eds. Acute renal failure. Philadelphia: W.B. Saunders, 1983:283-320.
16. Gelman ML, Rowe JW, Coggins CH, Athanasoulis C. Effects of an angiographic contrast agent on renal function. Cardiovasc Med 1979; 4:313-5, 320.
17. Weinrauch LA, Healy RW, Leland OS Jr, et al. Coronary angiography and acute renal failure in diabetic azotemic nephropathy. Ann Intern Med 1977; 86:56-9.
18. Snyder HE, Killen DA, Foster JH. The influence of mannitol on toxic reactions to contrast angiography. Surgery 1968; 64:640-2.
19. Freiman JA, Chalmers TC, Smith H Jr, Kuebler RR. The importance of beta, the Type II error and sample size in the design and interpretation of the randomized control trial: survey of 71 "negative" trials. N Engl J Med 1978; 299:690-4.
20. Fang LST, Sirota RA, Ebert TH, Lichtenstein NS. Low fractional excretion of sodium with contrast media-induced acute renal failure. Arch Intern Med 1980; 140:531-3.
21. VanZee BE, Hoy WE, Talley TE, Jaenike JR. Renal injury associated with intravenous pyelography in nondiabetic and diabetic patients. Ann Intern Med 1978; 89:51-4.
22. Workman RJ, Schaff MI, Jackson RV, Diggs J, Frazer MG, Briscoe C. Relationship of renal hemodynamic and functional changes following intravascular contrast to the renin–angiotensin system and renal prostacyclin in the dog. Invest Radiol 1983; 18:160-6.
23. Vari RC, Natarajan LA, Whitescarver SA, Jackson BA, Ott CE. Induction, prevention and mechanisms of contrast media-induced acute renal failure. Kidney Int 1988; 33:699-707.
24. Katzberg RW, Pabico RC, Morris TW, et al. Effects of contrast media on renal function and subcellular morphology in the dog. Invest Radiol 1986; 21:64-70.
25. Ciuffo AA, Fuchs RM, Guzman PA, et al. Benefits of nonionic contrast in coronary arteriography: preliminary results of a randomized double-blind trial comparing iopamidol with Renografin-76. Invest Radiol 1984; 19:Suppl:S197-S202.
26. Bashore TM, Davidson CJ, Mark DB, Kisslo K, Hlatky M, Skelton TN. Iopamidol use in the cardiac catheterization laboratory: a retrospective analysis of 3312 patients. Cardio 1988; 5:4-10.
27. Bettmann MA, Bourdillon PD, Barry WH, Brush KA, Levin DC. Contrast agents for cardiac angiography: effects of a nonionic agent *vs.* a standard ionic agent. Radiology 1984; 153:583-7.
28. Sullivan ID, Wainwright RJ, Reidy JF, Sowton E. Comparative trial of iohexol 350, a non-ionic contrast medium, with diatrizoate (Urografin 370) in left ventriculography and coronary arteriography. Br Heart J 1984; 51: 643-7.
29. Wolf GL, Mulry CS, Kilzer K, Laski PA. New angiographic agents with less fibrillatory propensity. Invest Radiol 1981; 16:320-3.

MEDICAL PROGRESS

DIAGNOSIS OF GENETIC DISORDERS AT THE DNA LEVEL

Stylianos E. Antonarakis, M.D.

EXTRAORDINARY progress in the understanding of the structure and function of human genes has been made in the past 25 years. Techniques have been developed for the manipulation and study of genes in both normal and abnormal states. Many of these achievements have been extremely important to medicine, and they have led to the diagnosis of basic defects at the DNA level and the understanding of the biochemical mechanisms of several diseases.

Most of the progress has related to disorders due to a defect in a single gene. In this category of genetic diseases, there is clear Mendelian inheritance of a characteristic phenotype. All known autosomal dominant, autosomal recessive, and X-linked disorders belong to this category.[1,2] The genes responsible for some of these disorders have been cloned (isolated and propagated in large amounts in bacteria) and characterized (Table 1). There are several ways to clone such genes.[61] The protein that some of the genes encode is known. With information derived from the amino acid sequence in the protein, from antibodies against the defective protein, or from a functional assay of protein activity, the gene can be cloned and characterized. For disorders in which the defective protein is unknown, the gene can be cloned with the use of information

From the Department of Pediatrics, Genetics Unit, Johns Hopkins University School of Medicine, CMSC 1003, Baltimore, MD 21205, where reprint requests should be addressed to Dr. Antonarakis.

Supported by institutional grants from the National Institutes of Health, the March of Dimes, and Johns Hopkins University.