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Treatment of Congestive Heart Failure with Triamterene

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ABSTRACT

Triamterene, a newer oral diuretic, was administered to nine hospitalized patients with congestive heart failure for an average of 15 days, and to 22 ambulatory patients for a period of three to 11 months. The daily dosage of triamterene ranged from 50 to 250 mg., but usually 100-200 mg. was administered daily in two divided doses, with or without the addition of 50 mg. of hydrochlorothiazide daily.

Triamterene is a safe and effective diuretic at doses of 100-200 mg. daily and no drug tolerance develops with long-term therapy. However, when used alone, it is not as effective as hydrochlorothiazide, but in combination with the latter drug the resultant diuresis is unsurpassed by any other oral diuretic therapy that we have used to date.

Triamterene itself does not produce kaliuresis and it blocks thiazide-induced kaliuresis. Serum uric acid levels may rise slightly, but no clinical gout was seen in this study.

SOMMAIRE

On a administré pendant 15 jours en moyenne du triamtérène, diurétique oral très récent, à neuf malades hospitalisés pour insuffisance cardiaque et à 22 malades externes pendant une période allant de trois à 11 mois. La posologie quotidienne de triamtérène était de 50 à 250 mg.; la posologie habituelle variait de 100 et 200 mg. par jour, en deux prises, associés ou non à 50 mg. d'hydrochlorothiazide par jour.

Le triamtérène est un diurétique sûr et efficace à des doses quotidiennes de 100 à 200 mg. et son administration prolongée ne provoque pas d'accoutumance. Cependant, employé seul, il n'est pas aussi actif que l'hydrochlorothiazide; associé à ce dernier produit, il déclenche une diurèse supérieure à celle de tout autre traitement diurétique que nous avons utilisé jusqu'ici.

Le triamtérène ne produit pas de déplétion potassique et il bloque celle qu'entraînent les thiazides. L'uricémie peut s'élever légèrement, mais on n'a pas observé de manifestations cliniques de goutte.

IN 1961 Wiebelhaus *et al.*[1] published the results of the first studies on triamterene (2,4,7-triamino-6-phenylpteridine; SK&F 8542) (Fig. 1). This drug is an orally effective diuretic that belongs to the pteridine class of compounds and is, hence, chemically unrelated to any commercially available diuretic agent. Initially, animal and clinical experiments suggested that triamterene produced diuresis by blocking the sodium-retaining effects of aldosterone and other steroids on the kidney.[1-3]

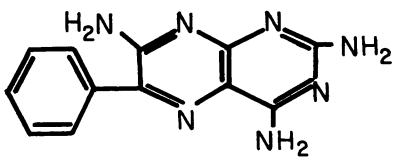

Fig. 1.—2,4,7-Triamino-6-phenyl-pteridine. Chemical structure of triamterene (SK&F 8542).

Additional studies have since confirmed the anti-aldosterone activity of this agent; however, they have also demonstrated that triamterene has a direct diuretic action on the distal convoluted tubule.[4-9]

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Extensive animal and preliminary clinical studies in man have shown that triamterene alone produces a marked natriuresis and chloruresis but little or no kaliuresis.[1-11] When given in combination with the thiazides a more potent diuresis results,[4-11] and it is possible that the potassium-sparing effects of triamterene could offset the kaliuretic effects of the thiazide, thereby maintaining normal body potassium levels.

The following study was undertaken to investigate these effects in patients with congestive heart failure and, more particularly, to evaluate the effects of these drugs in the long-term treatment of ambulatory patients with chronic congestive heart failure.

STUDY GROUP

There were 22 men and nine women, ranging in age from 49 to 84 years, in the study. Twenty-two were seen in the Cardiac Clinic and the rest were seen in the hospital. Twenty-five had arteriosclerotic heart disease, two had rheumatic heart disease, two had hypertensive cardiovascular disease and two had cor pulmonale. In addition, four patients with severe congestive failure, who had shown an increased tolerance to the usual forms of therapy (mercurial injections at repeated inter-

vals, hydrochlorothiazide and potassium chloride), were included in this study and were followed up in the private practice of one of the authors (J.W.). It was not feasible, however, to have routine electrolyte studies carried out on these patients, nor was it possible to see them as often as those patients attending the Clinic.

Patients in Hospital

Nine patients were admitted to hospital with signs and symptoms of severe congestive heart failure. Most also had evidence of marked pulmonary congestion, enlargement of the liver and some degree of edema of the lower extremities. In two, severe ascites was also present.

When possible, a control period of two to three days was allowed before diuretic therapy was started. During this time, however, the patients' daily diets contained 4 to 6 g. sodium chloride and their *ad lib.* fluid intake varied from 1 to 2 l. per day. All patients received digitalis. These treatment methods have been described in detail elsewhere.[12, 13]

The daily dosage of triamterene ranged from 50 to 250 mg. in order to establish a maximum effective therapeutic dose. On the average 100 to 150 mg. was administered daily in two divided doses—one after breakfast and the other after supper. The response to this therapy was compared to that obtained by the use of 50 to 100 mg. hydrochlorothiazide daily and to that obtained with intramuscular injections of meralluride (Mercuhydrin). A combination of triamterene and hydrochlorothiazide was also given for comparison purposes.

The length of time that these patients were studied ranged from eight to 34 days, with an average of 15 days.

Ambulatory Patients

This group included 22 patients who had been treated for chronic congestive heart failure in the Cardiac Clinic for periods ranging from three months to 11 years, with an average of four and one-half years.

Most had previously been treated with hydrochlorothiazide or chlorthalidone (Hygroton), digitalis, ammonium chloride and mercurial injections as required. Their daily diet contained approximately 4 to 6 g. of sodium chloride, and most were fairly well controlled and quite comfortable. There were, however, still some objective signs of congestive failure present (pulmonary congestion, liver engorgement, and leg edema).

Triamterene was given in daily doses of 100 to 200 mg., divided into equal morning and night-time doses. The patients were seen every one to three weeks at the Clinic, at which time they were weighed and blood samples were taken for serum electrolyte and other determinations (sodium, potassium, chloride, blood urea nitrogen (BUN), magnesium, serum glutamic oxaloacetic transaminase (SGOT), and uric acid).

The total period of observation lasted from three to 18 months, averaging eight and one-half months.

BIOCHEMICAL METHODS

The sodium and potassium concentration in both the serum and urine were determined with a direct reading flame photometer (Evans Electroselenium, England). The serum and urine chloride were determined by mercumetric titration.[14] Magnesium levels were determined by a modification of the Titan-yellow procedure.[15] Blood uric acid was determined using the method outlined by Henry, Sobel and Kim,[16] and the BUN value was determined by autoanalyser.*[17, 18] SGOT was determined using the Sigma-Frankel method.†

RESULTS

Table I lists some of the results of therapy in the ambulatory patients seen in the Clinic.

Triamterene alone produced an effective diuresis with natriuresis but it was not as effective as hydrochlorothiazide alone in initiating a marked diuresis, nor was it as effective in the long-term maintenance of an edema-free state in these patients. The combination of triamterene and hydrochlorothiazide, however, proved to be more effective than either of the drugs used alone.

Hospitalized Patients

Treatment of hospitalized patients with triamterene alone produced a diuresis in some, but this was not always significant. In most patients, there was an accompanying natriuresis. This was not, however, always paralleled by an equal chloruresis, as is normally seen with the use of meralluride or hydrochlorothiazide (Fig. 2). Potassium excretion either remained unaltered or was decreased. Although there was a slight increase in the water and electrolyte response in these patients, it was not always accompanied by an improvement in their clinical condition. This was evident by the lack of change in weight and the persistence of edema and pulmonary rales. It is interesting that, although there was a substantial increase in the sodium and chloride excretion in some patients, their daily output of urine was not always increased; in fact, it remained unchanged in more than one-half of the patients and was only slightly increased in others. (Such variability has been previously observed with the spironolactones.[19]) Crosley *et al.*[7] made a similar observation in their studies and subsequently speculated that this lack of increase in urine volume was associated with an increased loss of fluid through extrarenal sites, e.g. the skin, the lungs or the feces. In our experiments, daily

*Technicon Company, Chauncey, N.Y., U.S.A.
†Sigma Transaminase Kit: Sigma Chemical Co., St. Louis, Mo., U.S.A.

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TABLE I.—CLINICAL DATA ON OUTPATIENTS

Patient, age and sex	Diagnoses and duration of congestive heart failure	Type of previous treatment	Date	Dose of medication		Dose of digitalis (mg.)	Amt. of merc. inj.	Biochemical tests						
				Other (mg.)	SK and F 8542 (mg.)			Na (mEq./l.)	K (mEq./l.)	Cl (mEq./l.)	BUN (mg.%)	Mg (mEq./l.)	SGOT (units)	Uric acid (mg.%)
Mr. E.F. 73—M	ASHD, diabetes, CHF: 8 yrs.	Chlorthalidone, 100 mg.	Dec. 21		50			138.0	3.3	98.0		1.91		
			Jan. 4		50									
			Jan. 11		100									
			Jan. 25		100			142.0	4.7	108.0		1.9		
			Feb. 8		50			140.0	3.8	105.6		2.0		
			Feb. 22		50									
			Mar. 8		100			143.6	4.7	109.0		1.7		
			Mar. 22		100			138.5	4.5	106.0	18	1.8	14	
			Apr. 5		100									
			May 3		100									
			May 17		100	0.2								
			June 14		100									
			July 12		100	0.1		144.0	4.3	106.0	17	1.6	29	
			July 19		100	0.1								
			Aug. 2		100	0.2					15		32	
			Aug. 16		200	0.2		144.0	4.4	105.2	18	1.5	20	
			Aug. 30		200									
			Sept. 13		200			137.0	4.3	103.9	22	2.1	19	
			Sept. 27	50 HCZ	—									
			Oct. 11	50 HCZ	—	0.1								
			Nov. 1	50 HCZ	—	0.1		141.0	3.6	100.4	17			6.1
			Nov. 15	—	100									
			Nov. 29	50 HCZ	—	0.1		141.0	4.5	104.9	22			6.0
			Dec. 13	50 HCZ	—	0.1		143.0	4.4	100.4				
			Dec. 27	50 HCZ	—	0.1								
			Jan. 31	50 HCZ	—	0.1		142.0	3.0	100.4	23	1.6	20	6.5
Mrs. J.F. 63—F	ASHD CHF: 2 yrs.	Hydrochlorothiazide, 100 mg. Mercurial injections (occ.), 2 ml.	July 5		100									
			July 12		100			144.0	4.1	102.0	23			
			July 27		100									
			Aug. 9		100			139.0	4.6	102.8	16	1.8	16	
			Aug. 23		100									
			Sept. 13		100			142.0	4.0	101.4	18	2.2	14	
			Oct. 4		200			140.0	4.5	100.9				
			Oct. 18		200			136.0	4.0	101.9	25			4.2
			Nov. 8		200			134.5	4.3	103.9		2.2		7.2
			Nov. 29	50 HCZ	—			139.0	4.4	104.9	36			4.2
			Dec. 20	50 HCZ	—			137.0	3.6	98.0	28			
			Jan. 10	50 HCZ	—			141.0	3.5	104.9	27			5.0
Mr. I.F. 49—M	Cong. card. failure, cor pulmonale CHF: 3 yrs.	Hydrochlorothiazide, 50 mg. Digitalis, 0.25 mg. Mercurial injections (occ.), 2 ml.	Aug. 16		100			140.0	4.6	98.5	21	1.9	27	
			Aug. 30	50 HCZ	100	0.2		135.0	4.4	98.1	23	1.6	27	
			Sept. 13		100	0.25		140.0	4.4	96.5	21	1.9	14	
			Sept. 20		100	0.25		140.0	4.2	104.9	19	1.9	20	
			Sept. 27	50 HCZ	100	0.25		135.0	4.2	103.3	17			6.9
			Oct. 4	50 HCZ	100	0.25		136.5	4.4	95.6				
			Oct. 11		—	0.25		140.0	3.8	97.1				
			Oct. 18		100	0.25		137.5	4.4	99.4	19			7.5
			Nov. 1		100	0.25		136.0	4.4	100.0				9.1
			No.v 8	50 HCZ	100	0.25		136.0	4.5	101.9				7.1
			Nov. 15		100	0.25		139.0	4.4	91.5		1.8		7.3
			Nov. 29	50 HCZ	100	0.25								...
			Dec. 13	50 HCZ	200	0.25		136.0	4.4	96.5				
			Dec. 27	50 HCZ	—	0.25		137.0	3.7	98.0	20		19	
			Jan. 3	50 HCZ	200	0.25								
			Jan. 10	50 HCZ	200	0.25		137.0	4.0	98.0	21			8.1
			Jan. 24	50 HCZ	200	0.25								
			Feb. 7	50 HCZ	200	0.25		138.0	3.4	100.4		1.5	15	6.2
			Feb. 28	50 HCZ	200	0.25								
			Mar. 28	100 HCZ 600 KCl	—	0.25								
			Apr. 11	100 HCZ 600 KCl	—	0.25								
			Apr. 25	100 HCZ	—	0.2		138.0	2.7	100.4				
			May 9	100 HCZ	200	—	2 c.c.							
			May 16	100 HCZ	200	—		140.0	3.9	97.6				
Mrs. A.S. 53—F	ASHD CHF: 11 mos.	Chlorthalidone, 150 mg.	Sept. 13		100	0.1		138.0	3.0	95.5	21	1.7	25	
			Sept. 20		100	—		142.0	3.4	100.4	17	1.68		6.4
			Sept. 27		200	0.1		136.5	3.9	99.5				
			Oct. 4		200	0.1		140.0	3.7	103.3				
			Oct. 18		150	0.1		142.0	4.2	103.8	22			5.4
			Nov. 1		100	0.1								
			Nov. 8		100	0.1		137.0	4.4	103.9				5.2
			Dec. 6	50 HCZ	—	0.1		137.5	3.8	105.1				
			Dec. 27	50 HCZ	—	0.1		138.0	3.6	101.9	17		16	6.5
			April 24											
Mrs. U. 68—F	Congestive ht. failure, myocard. infarc., diabetes ASHD, hypertension	Chlorothiazide, 250 mg. (t.i.d.) KCl (occ.)	July 19	250 CHO	100	0.2		141.0	3.9	100.0	17		27	
			Aug. 2		100	0.2					38	1.82	34	
			Aug. 9		—	0.2		129.0	4.5	95.0	30			
			Aug. 16		100			133.0	4.9	102.0	27	1.6	23	
			Aug. 23		100			130.0	4.5	98.0	28	1.9	15	
			Aug. 30		100			138.0	4.4	103.0	25	1.8	16	
			Sept. 6		100			137.0	4.7	102.0	24	1.9	14	
			Sept. 20		200			137.5	4.2	110.0	22	1.8	17	
			Oct. 4		200			138.0	4.6	108.0				
			Oct. 11		200			140.0	4.5	103.0				
			Oct. 18		200			138.0	4.4	106.0	32			6.95
			Nov. 1		200	0.25		135.0	4.2	110.0				7.00
			Nov. 15		200	0.25		144.0	4.9	105.0		2.1		7.8
			Nov. 29	50 HCZ	200	0.25		138.0	4.7	104.0	30			6.3
			Dec. 13		200	0.25		136.0	4.4	103.0				
			Dec. 27		—	0.25		135.5	4.2	97.5	46		25	
			Jan. 10		—	0.25								
			Jan. 24		—	0.25								
			Feb. 7		—	0.25		137.0	3.0	99.0	24		15	7.4
Mr. I.OE. 69—M	ASHD CHF: 2 yrs.	Hydrochlorothiazide	Nov. 23		100	0.25		140.0	4.4	99.0	1	1.99		
			Dec. 7		50	0.25								
			Dec. 21		100	0.25								
			Jan. 4		150	0.25								
			Jan. 18		150	0.25		142.0	6.0	104.0		1.90		
			Feb. 1	50 HCZ	—	0.25								
			Feb. 8	50 HCZ	—	0.25		140.0	5.3	102.0		2.08		

TABLE I.—CLINICAL DATA ON OUTPATIENTS—*Continued*

Patient, age and sex	Diagnoses and duration of congestive heart failure	Type of previous treatment	Date	Dose of medication: Other (mg.)	Dose of medication: SK and F 8542 (mg.)	Dose of digitalis (mg.)	Amt. of merc. inj.	Biochemical tests: Na (mEq./l.)	K (mEq./l.)	Cl (mEq./l.)	BUN (mg.%)	Mg (mEq./l.)	SGOT (units)	Uric acid (mg.%)
Mr. I.OE.—*continued*			Mar. 1	50 HCZ	—	0.25								
			Mar. 22	—	100	0.25								
			April 5	50 HCZ	100	—		138.0	4.5	96.0	44	1.98	17	
			May 3		100	0.25								
			May 31		—	0.25		140.0	5.3	101.0	34			
			June 21		100	0.25								
			July 12		—	0.25								
			July 27		100	0.25		142.0	5.8	103.0	42	2.12		
			Aug. 9		200	0.25								
			Aug. 23		200	0.25		140.0	5.1	101.0	45	1.84	20	
			Sept. 6		200	0.25		139.0	5.7	101.0	38	2.02	16	
			Sept. 20		200	0.25		138.0	5.4	100.0	37	2.06	16	
			Oct. 4		200	0.25		137.0	5.1	98.0				
			Oct. 25		200			143.0	5.0	102.0				6.6
			Nov. 8		200	0.25		140.0	5.2	101.0				
			Nov. 22		200	0.25								
			Dec. 6	50 HCZ	—	0.25		136.0	5.3	102.0				
			Dec. 20	50 HCZ	—	0.25		140.0	4.1	97.0			20	
			Jan. 3	50 HCZ	—	0.25		143.0	4.2	99.0	38			
			Jan. 31	50 HCZ	—	0.25		137.0	4.1	97.0	30	1.8	14	6.5
Mr. G. 77—M	Cong. card. failure, ASHD, diabetes, myocard. infarc. CHF: 3 mos.	Hydrochlorothiazide, Digitalis	July 5		100	0.25		143.0	3.1	99.0	28			
			July 19		100	0.25		143.0	4.6	101.0	25		25	
			Aug. 2		100	0.25					30		36	
			Aug. 16		200			141.0	5.3	100.0	28	1.8	42	
			Aug. 30		200									
			Sept. 13		200	0.2		137.0	5.6	100.0	35	2.2	20	
			Sept. 27		200	0.2								
			Oct. 4		200	0.2		139.0	5.3	98.0				5.2
			Oct. 18		100	0.2								
			Nov. 1		100	0.2		138.0	5.0	100.0			42	5.5
			Nov. 22		100	0.2								
			Dec. 6	50 HCZ	—	—		140.0	5.1	99.0				
			Dec. 20	50 HCZ	—	0.2		138.5	5.0	101.0				
			Jan. 31	50 HCZ	—	0.2		135.5	3.7	91.0	39			
			Feb. 4					140.0	4.7	99.0	28	1.58	27	4.1
Mr. I.M. 76—M	Cong. ht. failure, HCVD CHF: 5 yrs.	Chlorthalidone, Ammonium chloride, Digitalis	Dec. 21	NH_4 Cl	100	0.2		137.0	4.7	105.0		1.8		
			Jan. 18	NH_4 Cl	100	0.2								
			Jan. 25	NH_4 Cl	100	0.2								
			Feb. 8	NH_4 Cl	100	0.2		140.0	4.7	104.0		1.7		
			July 5	NH_4 Cl	150	0.2								
			Oct. 25	NH_4 Cl	200	0.2		137.0	6.5	103.0				4.0
			Nov. 8	NH_4 Cl	200	0.2		138.0	4.7	103.0		1.8		5.0
			Nov. 29	50 HCZ	—	0.2		141.0	4.6	104.0	16			4.4
Mr. A.A. 70—M	ASHD CHF: 8 yrs.	Chlorthalidone, 100 mg. Mercurial injections (occ.), 2 ml.	Nov. 23	NH_4 Cl	100			128.0	3.6	91.0		2.1		
			Dec. 7	NH_4 Cl	100									
			Dec. 21		100	0.2		133.0	4.0	98.0		2.1		
			Jan. 4	50 HCZ	100	0.2								
			Jan. 25	50 HCZ	100	0.2								
			Feb. 8	50 HCZ	100			128.0	4.0	95.0		2.5		
			Mar. 1	50 HCZ	100	0.2								
			Mar. 15	50 HCZ	200	0.2		130.0	4.5	96.0	23			
			Mar. 29		100	—								
			April 12		100	0.1								
			May 3		100	0.1								
			May 24		100	0.1								
			June 14		100	0.1								
			July 5		100	0.1		136.0	3.9	98.0	23		20	
			July 19		200	0.2								
			July 26		200	—		137.0	4.3	102.0	25		17	
			Aug. 9		200	0.2		136.0	5.0	104.0	21	2.3	15	
			Sept. 6		200	—		137.0	5.2	102.0	27	2.4	16	
			Sept. 20		200	0.1								
			Oct. 4		200	0.1		135.0	4.3	100.0				
			Oct. 11		200	0.1		137.0	4.2	102.0				
			Oct. 25		200	0.1		136.0	4.0	101.0				5.7
			Nov. 8		200	0.1		135.5	4.1	104.8				5.2
			Nov. 22		200	0.1		139.0	4.2	106.0				5.5
			Dec. 6	50 HCZ	—	0.1		135.0	3.6	106.0				
			Dec. 20	50 HCZ	—	0.1		137.0	3.5	99.0	22		14	
			Jan. 3	50 HCZ	—	—								
			Jan. 10	50 HCZ	—	—								
			Jan. 24	50 HCZ	—	0.1		136.0	3.5	94.1				
			Feb. 7			—								
Mr. P. 68—M	HCVD CHF: 5 yrs.	Hydrochlorothiazide, Digitalis	Jan. 11		100	0.25		136.0	3.6	93.0		1.6		
			Jan. 25		100	0.25								
			Feb. 15		100	0.25								
			Mar. 15		100	0.25		133.0	4.7	98.0	25			
			Mar. 29		100	0.25								
Mr. G.B. 68—M	ASHD CHF: 11 yrs.	Meralluride, Hydrochlorothiazide Mercurial injections	Nov. 23	50 HCZ	100		2 c.c.	137.0	5.6	100.0		2.0		
			Nov. 30	50 HCZ	—	0.2								
			Dec. 14		100	0.2								
			Dec. 21		100	0.2								
			Dec. 28		100	0.2		137.0	5.6	102.0		2.05		
			Jan. 4		100	0.2								
			Jan. 18		100	0.2	2 c.c.							
			Jan. 25	50 HCZ	—	0.1								
			Feb. 1	50 HCZ		0.1								
Mr. J.B. 67—M	ASHD CHF: 10 yrs.	Hydrochlorothiazide, Digitalis	Jan. 4	50 HCZ	100	0.1		138.0	5.6	115.0		1.6		
			Jan. 11	50 HCZ	100	0.1		140.0	6.9	117.0		1.4		
			Jan. 25	50 HCZ	100	0.1								
			Feb. 1	50 HCZ										
			Feb. 8	50 HCZ		0.1		135.0	5.6	113.0		1.5		
			Feb. 15	100 HCZ										
			Feb. 22	50 HCZ		0.4								
			Mar. 1	50 HCZ		0.4								
			Mar. 8	50 HCZ		0.4								
			Mar. 15	50 HCZ		0.4		133.0	5.4	108.0	36	1.5		
			Mar. 22	—	100									
			Mar. 29		100									

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TABLE I.—CLINICAL DATA ON OUTPATIENTS—*Continued*

Patient, age and sex	Diagnoses and duration of congestive heart failure	Type of previous treatment	Date	Dose of medication: Other (mg.)	Dose of medication: SK and F 8542 (mg.)	Dose of digitalis (mg.)	Amt. of merc. inj.	Biochemical tests: Na (mEq./l.)	K (mEq./l.)	Cl (mEq./l.)	BUN (mg.%)	Mg (mEq./l.)	SGOT (units)	Uric acid (mg.%)
Mr. J.P. 59—M	HCVD, hypothyroidism. CHF: 18 mos.	Hydrochlorothiazide, Digitalis Potassium chloride	Dec. 21		100	0.2		138.0	4.2	100.0		2.0		
			Dec. 28		100	0.2								
			Jan. 4		100	0.2								
			Jan. 11		100	0.2		138.0	4.3	101.0		1.99		
			Jan. 18		100	0.2								
			Jan. 25		100	0.2								
			Feb. 1	50 HCZ	—									
			Feb. 15		—									
Mrs. E.L. 63—F	ASHD CHF: 9 yrs.	Hydrochlorothiazide, 50 mg. Meralluride, 2 ml.	July 12		100			141.0	3.5	105.0	21	1.7		
			Aug. 2		100						22		25	
			Aug. 16		100			140.0	4.8	101.0	22	1.6	22	
			Sept. 6		100			137.0	4.5	103.0	20	1.9	22	
			Oct. 4		100			137.0	4.3	105.0				
			Jan. 10	50 HCZ	—			139.0	4.3	108.0	24			5.0
			Jan. 31	50 HCZ	—			141.0	3.4	100.0	22	1.8	20	5.2
Mr. A.M. 71—M	ASHD CHF: 5 yrs.	Chlorthalidone, 100 mg., b.i.d. Digitalis, Mercurial injections, Ammonium chloride	Dec. 21	100 CHL	100	0.25		137.0	3.8	100.0		1.79		
			Jan. 11	100 CHL	100	0.25								
			Jan. 25	100 CHL	100	0.25								
			Feb. 8	100 CHL	100	0.25		140.0	3.4	98.0		1.64		
			Feb. 22	100 CHL	100	0.25								
			Mar. 8	100 CHL	100	0.25		140.0	3.8	100.0		1.96		
			Mar. 29	—	100	0.25	2 c.c.							
			April 5	—	100	0.25								
			May 24	50 HCZ and KCl	—	0.25								
			June 14	50 HCZ and KCl	—	0.25								
			June 28	50 HCZ and KCl	—		2 c.c.							
			July 26		100		2 c.c.	136.0	3.0	100.0	13		14	
			Aug. 9		100			138.0	3.2	98.0	20	1.64	20	
			Aug. 23		100			134.5	3.0	—	19	1.5		
			Sept. 6	50 HCZ		0.25	2 c.c.	136.0	3.2	96.0	21	1.6	22	
			Sept. 13	50 HCZ		0.25	2 c.c.							
			Sept. 20	50 HCZ and KCl	100	0.25	2 c.c.	137.0	3.6	100.0	26	1.5	25	
			Sept. 27	50 HCZ and KCl	100	0.25	2 c.c.	134.0	3.8	99.0	21		24	
			Oct. 4	50 HCZ and KCl	200	0.25	2 c.c.							
			Oct. 11	50 HCZ and KCl	200	0.25	2 c.c.	139.0	4.0	98.0				
			Oct. 18	100 HCZ	—	0.25	2 c.c.	143.0	4.8	—	35			9.7
			Oct. 25	100 HCZ	—	0.25	2 c.c.							
			Nov. 1	50 HCZ	—	0.25	—	138.0	3.0	100.0	17			5.9
			Nov. 8	50 HCZ	200	0.25	2 c.c.	140.0	3.8	101.0		1.6		7.0
			Nov. 15	50 HCZ	200	0.25	2 c.c.							
			Nov. 22	50 HCZ	200	0.25	2 c.c.							
			Nov. 29	50 HCZ	200	0.25	2 c.c.	139.0	3.8	98.0	17	1.6		7.6
			Dec. 6	100 HCZ	—	0.25	2 c.c.							
			Dec. 13	100 HCZ	—	0.25	2 c.c.	140.0	3.4	97.0				
			Dec. 20	50 HCZ	200	0.25	2 c.c.	137.0	3.2	98.0	19		17	
			Dec. 27	50 HCZ	100	—	2 c.c.							
			Jan. 3	50 HCZ	100	—	2 c.c.							
			Jan. 10	—	200	0.25	—	135.0	3.4	96.0	22			6.9
			Jan. 17	10g KCl	200	0.25	2 c.c.							
			Jan. 24	10g KCl	200	0.25	2 c.c.							
			Jan. 31		200	0.25	2 c.c.	137.0	4.0	99.0	21		22	6.1
Mrs. H.M. 54—F	Cong. card. failure RHD CHF: 2 yrs.	Hydrochlorothiazide, 100 mg. Digitalis	Aug. 9		100	0.2		141.0	3.9	98.0	20	1.8	52	
			Aug. 23		100	0.2		140.0	3.8	99.0	21	1.8	48	
			Aug. 30		100	—		143.0	4.8	98.0	27	1.9	41	
			Sept. 6		100	—								
			Sept. 13		100	0.2		141.0	5.5	102.0	22	2.2	73	
			Sept. 20		150	0.2		136.0	5.0	102.0	19	2.2	62	
			Sept. 27		150	0.2		138.0	5.3	101.0	19		70	9.3
			Oct. 4		150	0.2								
			Oct. 18		—	0.2		141.0	4.8	101.0	17			9.8
			Oct. 25		—	—		143.0	5.1	104.0				9.3
			Nov. 1		150	0.2		141.0	4.8	103.0				9.5
			Nov. 8		150	0.2		144.0	5.0	104.1				8.7
			Nov. 15		150	0.2								
			Nov. 29	50 HCZ	—	0.25		141.0	4.8	102.0	17			9.5
			Dec. 13	100 HCZ and KCl	—	0.25		140.0	4.8	95.0				
			Dec. 27	100 HCZ and KCl	—	0.25		136.0	3.6	96.0	18		45	
			Jan. 24	100 HCZ and KCl	—	0.25								
			Feb. 7	100 HCZ and KCl	—	0.25		138.0	3.0	94.0	21		46	5.9
Mr. I.S. 75—M	Cong. card. failure ASHD CHF: 2 yrs.	Digitalis	Aug. 9		100	0.2		137.0	4.3	99.0	17	1.7	17	
			Aug. 23		100	0.2		139.0	4.4	99.0	23	1.9	15	
			Sept. 6		200			136.0	4.2	96.0	20	2.0	19	
			Sept. 20		200			136.0	4.8	100.0	20	2.1	17	
			Oct. 11		200			140.0	3.8	100.0				
			Nov. 1		200	0.25		137.0	4.6	103.0	28			8.2
			No.v 8		200	0.25		142.0	4.3	103.0				5.3
			Nov. 22		200	0.25		137.0	4.3	104.0				
			Dec. 6	50 HCZ	—	0.25		136.0	4.2	102.0				
			Jan. 3	50 HCZ	—	0.25		133.5	3.3	93.0	27	1.98		
			Jan. 31	50 HCZ	—	0.25		135.0	3.5	94.0	26		14	5.2
Mr. M.S. 79—M	ASHD CHF: 5 yrs.	Chlorthalidone	Mar. 22		100	0.2		140.0	5.1	100.0	26		19	
			April 5		100	0.2								
			May 3		100	0.2								
			June 28		100	0.2		139.0	5.0	105.0	31			
			July 5		100									
			Aug. 2		200									
			Aug. 16		200			137.0	4.9	105.0	25	1.64	22	
			Sept. 6		200			135.0	4.5	101.0	33	2.0	20	

TABLE I.—CLINICAL DATA ON OUTPATIENTS—*Continued*

Patient, age and sex	*Diagnoses and duration of congestive heart failure*	*Type of previous treatment*	*Date*	*Dose of medication*		*Dose of digitalis (mg.)*	*Amt. of merc. inj.*	*Biochemical tests*						
				Other (mg.)	*SK and F 8542 (mg.)*			*Na (mEq./l.)*	*K (mEq./l.)*	*Cl (mEq./l.)*	*BUN (mg.%)*	*Mg (mEq./l.)*	*SGOT (units)*	*Uric acid (mg.%)*
Mr. M.S.—*Continued*			Sept. 20		200			133.0	6.0	102.0	30		29	6.0
			Oct. 18		200			141.0	4.2	102.0	33			6.4
			Oct. 25		200			137.0	4.7	106.0				6.7
			Nov. 1	50 HCZ	200			137.0	4.7	106.0	36			7.0
			Nov. 29	—	200			138.0	4.2	102.0	32			
			Dec. 13	50 HCZ	—									
Mr. B.S. 68—M	ASHD cong. card. failure, rheum. arthritis, CHF: 2 yrs.	Chlorothiazide, 500 mg. Digitalis	Jan. 4	500 CHO KCl	100	0.2		137.0	3.8	95.0		2.0		
			Jan. 25	500 CHO	100	0.2								
			Feb. 8	50 HCZ	100	0.2		137.0	4.6	100.0		1.98		
			Mar. 8	50 HCZ	100	0.2								
			May 17	50 HCZ	—	0.2								
			June 14	50 HCZ	—	0.2								
			June 21	50 HCZ	—	0.2								
			Sept. 6	50 HCZ	—	0.2								
			Sept. 13		100	0.25		141.0	3.4	95.0	24	2.2	20	
			Sept. 27		100	0.25								
			Oct. 4		200	0.25		141.5	4.2	100.0				
			Oct. 18		100	0.25		145.0	4.0	101.0	23			6.1
			Nov. 8	50 HCZ	100	0.25								
			Nov. 15	50 HCZ	100	0.25		135.0	4.1	100.0				5.5
			Nov. 29	50 HCZ	—	0.25								
			Jan. 3	50 HCZ	—	0.25		140.0	4.4	101.0	19			5.0
Mrs. T.A. 84—F	ASHD, diabetes CHF: 3+ yrs	Hydrochlorothiazide, 50 mg. Digitalis, 0.25 mg. Mercurial injections	Jan. 25	50 HCZ	100	0.25								
			Feb. 8	50 HCZ	100	0.25	2 c.c.	128.0	4.5	95.0		1.6		
			Feb. 22	—	100	0.25								
			Mar. 15	50 HCZ NH_4 Cl	100	—		126.5	6.1	98.0	30	1.5		
			Mar. 29		100	0.25								
			April 12		100									
			May 10		100									
			June 8		100			133.0	5.7	92.0	21			
			July 5		100			140.0	4.1	101.0	21		8	
			Aug. 9		100			134.0	4.8	98.0	20	1.7	17	
			Aug. 23		100			133.0	4.2	98.0	20	1.7	13	
			Sept. 20		100			131.0	4.1	96.0	15	1.9	7	
			Oct. 25		100			136.0	4.5	97.1				
			Nov. 15		100			135.5	5.0	97.0		2.0		
			Dec. 6	50 HCZ	—			133.0	4.5	101.0				
			Jan. 3	50 HCZ	—									
			Jan. 31	50 HCZ	—			135.0	3.5	94.0	22	1.6	8	4.6
Mr. I.E. 79—M	ASHD, RHD, nephrotic syndrome CHF: 8 yrs.	Chlorthalidone, 100 mg. KCl Digitalis Meralluride	Jan. 11	50 HCZ	100	0.2		142.0	3.0	90.0		2.2		
			Jan. 18	50 HCZ and KCl	100	0.1								
			Jan. 25	50 HCZ and KCl	100	0.1								
			Feb. 15	50 HCZ	—	0.1								
			Mar. 15	50 HCZ	100	0.1		133.0	4.0	97.0	33			
			Mar. 29	KCl	100	0.1								
			April 5	KCl	100	0.1								
			May 3	KCl	100	0.1								
			May 24	50 HCZ and KCl	100	0.1		141.0	3.3	100.0	20			
			June 14	50 HCZ and KCl	100	0.1								
			July 12		100	0.1		142.0	3.9	100.0	32		22	
			July 27		100	—		147.0	3.9	100.0	32		22	
			Aug. 2	50 HCZ and KCl	—	0.1								
			Sept. 6	50 HCZ and KCl	—	0.1								
			Nov. 1	50 HCZ and KCl	100			143.0	3.8	102.0				4.8
			Nov. 15	50 HCZ and KCl	—	0.1								
			Dec. 27	50 HCZ and KCl	—	0.1								
			Jan. 17	50 HCZ and KCl	—	0.1								

ABBREVIATIONS:—ASHD—arteriosclerotic heart disease; HCVD—hypertensive cardiovascular disease; RHD—rheumatic heart disease; HCZ—hydrochlorothiazide; CHL—chlorthalidone; CHO—chlorothiazide; KCl—potassium chloride; NH_4 Cl—ammonium chloride.
DRUGS:—chlorthalidone (Hygroton); hydrochlorothiazide (Hydrodiuril); digitalis (digitoxin); chlorothiazide (Diuril); meralluride (Mercuhydrin).
LABORATORY NORMALS:—BUN: 8-23 mg.%; uric acid: 4.5-7.0 mg.%; SGOT: 10-40 units.

weights were not always recorded, so it is difficult to form an opinion on this matter.

In contrast to the relative lack of response with the use of triamterene alone, the use of the combination of triamterene and hydrochlorothiazide produced a good diuretic response, and a clinical improvement was shown by the lessening of edema and the disappearance of pulmonary rales in several of the patients. Furthermore, although triamterene alone seemed less potent than either hydrochlorothiazide or parenteral meralluride, the potency of the combination appeared to approach that of the meralluride. It should be pointed out, however, that in some instances the concomitant administration of 2 c.c. of meralluride resulted in a massive diuresis (Fig. 3) which greatly exceeded the response to the combination or either of the components used alone. Once again, we were able to notice the potassium-sparing effects of the triamterene component of the combination, even though there was a substantial increase in the output of sodium and chloride (Fig. 3).

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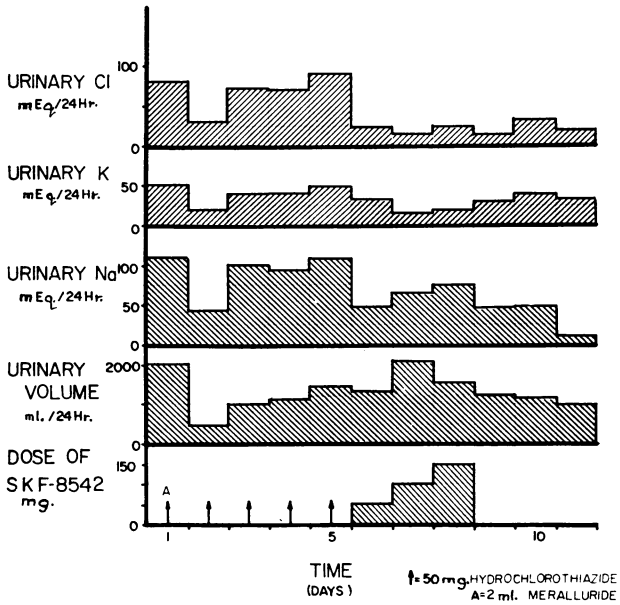

Fig. 2.—This case (A.R.) illustrates the decrease in urinary excretion of potassium and chloride when triamterene is given.

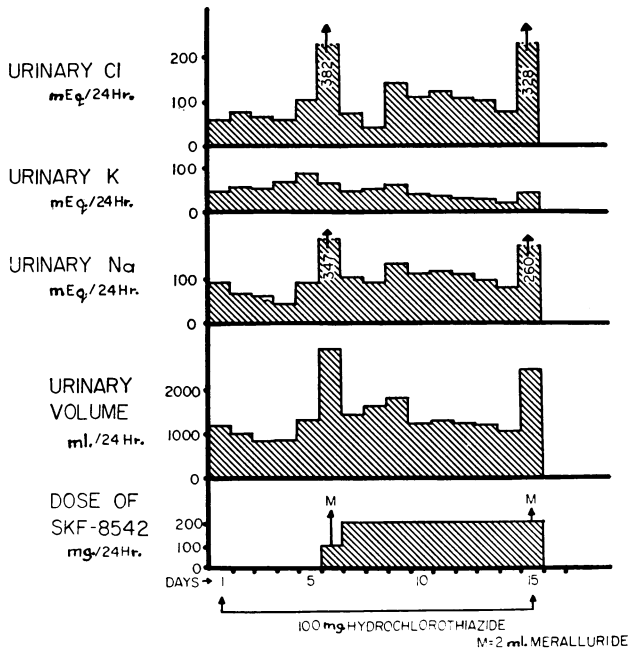

Fig. 3.—This case (J.S.) illustrates that combined therapy is more effective than hydrochlorothiazide alone. Note the diminution in urinary excretion of potassium when triamterene is added to the regimen. This case also illustrates that in certain instances the intramuscular injection of meralluride may give a superadded effect.

Ambulatory Patients Attending the Cardiac Clinic

Those patients in this group who could be classified as having mild or minimal congestive heart failure and who were easily controlled, prior to the study, with 50 mg. of hydrochlorothiazide or 100 mg. of chlorthalidone daily, could easily be controlled with 100 to 150 mg. of triamterene daily. However, in the more severe cases of congestive failure, which previously had required 50 to 100 mg. of hydrochlorothiazide and occasional mercurial injections in some, the administration of triamterene alone in doses up to 250 mg. daily could not maintain the patients in an edema-free state. But when the combination of triamterene and hydrochlorothiazide was used, a prompt diuresis was noticed, along with a weight loss and an increase in the patient's well-being. Only two of the patients with very severe congestive failure could not be maintained in an edema-free state by the use of the combination alone; they occasionally required concomitant injections of meralluride during the period of observation. The optimum dose of triamterene with or without the addition of hydrochlorothiazide, depending on the degree of congestive failure, was between 100 and 200 mg. daily in two divided doses. The prolonged use of triamterene at this dosage level did not lead to any drug tolerance.

In the four patients with severe congestive heart failure who were followed up in the private practice of one of the authors (J.W.), the addition of triamterene to their regimen of thiazide and frequent injections of meralluride proved to be very effective in initiating further diuresis and maintaining an edema-free state. Not only was it possible to induce a further diuresis, but three of these patients no longer required their periodic mercurial injections. The degree and duration of the heart failure in these four patients was much more severe than that of the patients listed in Table I and yet it was in these cases that the most gratifying results were observed.

Effect on Electrolytes

Throughout the study of patients in the Cardiac Clinic, the most important observation was that the addition of triamterene always corrected any hypokalemia which may have been present when hydrochlorothiazide was given alone without a generous potassium supplement. This was verified many times by substituting a thiazide for triamterene in the patients' therapy and a prompt fall in serum potassium levels was noted. When triamterene was again given and the thiazide was stopped, the serum potassium levels quickly returned to normal (Table I).

The use of the combination of triamterene and hydrochlorothiazide rarely led to a lowered serum potassium level, indicating that the decreased excretion associated with triamterene was sufficient to overcome the increased excretion promoted by hydrochlorothiazide. A serum potassium level above normal values was seen only twice, but this was only when triamterene alone was given in doses of 200 to 300 mg. daily.

In two instances, when triamterene alone was given in doses of 200 mg. daily, the serum chloride levels rose to 114-115 mEq. and we felt that the drug should be stopped. When the combination tablet was given these levels quickly returned to normal and, in fact, hyperchloremia was never seen with combination therapy.

Blood urea levels were determined regularly and were at times elevated, but never to any degree of clinical significance.

Uric acid levels were raised in many of the patients; however, no clinical evidence of gout was seen at any time.

Serum magnesium and SGOT levels always remained within normal limits.

SIDE EFFECTS

In keeping with our experience with chlorothiazide[12] and hydrochlorothiazide,[13] we found that prolonged daily administration of the triamterene was well tolerated by all patients and in no instance was it necessary to discontinue therapy with the drug because of gastrointestinal disturbances. Only in two cases was drug therapy discontinued, as mentioned above, because serum chloride levels became slightly elevated.

DISCUSSION

The foregoing data clearly indicate that triamterene is an effective oral diuretic and that it is useful clinically when it is used alone for maintenance of an edema-free state in patients with mild congestive heart failure. In many instances the use of triamterene alone was not as effective as the use of hydrochlorothiazide alone in patients with moderate to severe congestive heart failure; but, generally, the combination of the two drugs proved to be a more effective diuretic in the initiation and maintenance of an edema-free state than either drug when used alone. These studies therefore support the results obtained by others.[4-11]

As would be expected, the degree of the diuretic response was more pronounced in those patients with the most peripheral edema, and was much less marked when the patient was already in an edema-free state.

A maximum clinical effect appeared to be achieved at a dose of 100 to 200 mg. daily in two divided doses and additional increases in dose never resulted in further significant clinical improvement. No drug tolerance developed.

It should be pointed out that during our observations of the nine hospitalized patients, it seemed that although triamterene increased the excretion of water and electrolytes, the patients' clinical state was not significantly altered. It was only when the combination of triamterene and hydrochlorothiazide was used, resulting in a more marked excretion of electrolytes, that a significant clinical improvement was noted.

The greatest advantage to be derived from the use of triamterene is its marked capacity to conserve potassium. Not only is it able to do this when used alone, but it is able to overcome thiazide-induced kaliuresis when it is used in combination with hydrochlorothiazide. Treatment of patients with this combination therefore results in a massive diuresis without any danger of depleting the body potassium. Moreover, the slight rise in potassium levels sometimes seen with the use of triamterene alone is completely eliminated with the use of the combination. By the proper use of these drugs we were able to maintain normal serum potassium levels throughout the period of observation, without the addition of potassium supplements.

Contrary to the observations of some other investigators,[9] we found that triamterene was associated with an increase in serum uric acid, although clinical evidence of gout was never observed.

The rise in blood urea may be explained by a reduced glomerular filtration rate.[7, 11] Furthermore, Rowe *et al.*[20] demonstrated a decrease in cardiac output, suggesting that the mechanism might be hemodynamic in nature and perhaps similar in both cause and effect to the alterations which occur in these functions following ingestion of chlorothiazide.

To date there is no definite explanation for the ability of triamterene to produce a natriuresis without an accompanying significant or appropriate diuresis in many patients, although such a phenomenon has been noted with antimineralocorticoids.[19]

The ability of triamterene to suppress the excretion of potassium or to maintain the patient in a state of positive potassium balance must somehow be related to its effect on the distal tubules, although its exact mechanism is still unknown.

The occasional lack of parallelism between the natriuretic and the chloruretic responses observed in our series has previously been observed by Crosley *et al.*,[7] but the response remains unexplained and cannot be answered by our own observations.

ADDITIONAL STUDY

After completion of the above-described work, 12 of the outpatients (Table I) were given a tablet form of triamterene (100 mg. each) in order to compare their response to that obtained with encapsulated triamterene. Similar concomitant medications were also given. No differences could be seen in either their clinical or their biochemical response. We conclude therefore that a 100-mg. triamterene tablet is therapeutically equivalent to two 50-mg. triamterene capsules.

SUMMARY

The effects of triamterene, administered to 35 patients with congestive heart failure, were studied. Those with mild congestive failure were easily controlled with triamterene alone. Others with moderate to severe failure were better controlled with hydrochlorothiazide; however, this response could not match the excellent diuresis produced by using triamterene in combination with hydrochlorothiazide.

Triamterene itself does not produce kaliuresis and it blocks thiazide-induced kaliuresis. The tendency for a slight rise in potassium levels in some patients while receiving triamterene alone is offset by the addition of hydrochlorothiazide.

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Contrary to the reports of other investigators we found that uric acid levels tended to rise when triamterene was given; however, no clinical evidence of gout was observed in this study.

Two patients had to discontinue triamterene therapy because of a rise in the serum chloride level. This was not seen when triamterene was used in combination with hydrochlorothiazide. There were no other untoward effects.

The drug was most effective at doses of 100 to 200 mg. daily, and no drug tolerance developed after long-term therapy.

Triamterene, in either 50-mg. capsules or 100-mg. tablets, appears safe and effective for use as a diuretic in patients with congestive heart failure and when used in combination with hydrochlorothiazide the resultant diuresis is unsurpassed by any other oral diuretic therapy that we have used to date.

We are deeply grateful to Mrs. Violet Foldes, B.Sc., for her excellent technical assistance throughout this study.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

BLOOD AS A THERAPEUTIC AGENT

A review of the literature of blood transfusion since the operation was made practical through the experimental work of Crile and Carrel reveals the fact that only within the last two years has it received attention as a therapeutic agent in the management of the various conditions in infancy. Recent clinical experience confirms in many instances the enormous value of the introduction of whole blood into the circulation, and furthermore, it has emphasized its limitations.

The broad indications for transfusion are based on the fact that transfused blood is a perfect substitute for blood lost in acute hæmorrhage. In certain pathological hæmorrhages the blood has definite hæmostatic properties and in some secondary anæmias it acts as a powerful stimulant to tide over a crisis in the disease. Another type of case that up to the present time has received less attention from the standpoint of the possibilities of transfusion is that showing purulent foci such as severe suppurative or infective conditions, as for example, empyema and pneumonia, both of which tax severely the blood elements and hæmatopoietic organs, producing a secondary anæmia according to the intensity of the process, in this manner lowering the infant's resistance sufficiently to jeopardize life. By transfusion one introduces whole blood and pure complement which carry with them resistance unobtainable in any other form of procedure. In certain pathological hæmorrhages transfused blood has a remarkable hæmostatic effect. The bleeding in these cases is supposed to be due to the lack of certain elements, thrombin and prothrombin, in the patient's blood. Transfusion corrects this deficiency and at the same time restores the blood already lost by the hæmorrhage. In this latter effect transfusion has a distinct advantage over the injection of serum subcutaneously, which has also proved to be valuable in these pathological hæmorrhages. In exsanguinated patients simply to check the bleeding may not be sufficient, transfusion is required to restore the cellular elements of the blood.

In hæmorrhagic disease of the newborn, a disease formerly credited with a mortality of from 50 per cent to 75 per cent, transfusion stops the bleeding, restores the lost blood and transforms a sick, and often dying, infant into a normal healthy child. Welch, Schloss and Commisky and others have reported excellent results with the subcutaneous injection of blood serum and whole blood in hæmorrhagic disease, but as is frequently the case, the patient is beyond serum treatment, and in such instances transfusion has been conclusively proven effective.

Infants are susceptible to the effects of hæmorrhage. A baby of eight pounds is estimated to have a total quantity of a little more than six ounces. Since a dog cannot always survive a loss of one half the total quantity of blood, it is fair to assume that the loss of an exsanguinated infant is about one half its total quantity. Thus in dealing with hæmorrhagic disease of the newborn, it is not safe to temporize too long with measures which may check the bleeding after a time, but cannot relieve the anæmia. This advantage of transfusion over serum injections applies with equal force to any case of hæmorrhage in which we have an exsanguinated patient.

Transfusion is less clearly indicated in the secondary anæmias which are not due to the loss of red corpuscles from the body, as in leukemia. The cause of the anæmia is too often a pathological condition which is incurable or not altered by the transfusion of blood. In simple secondary anæmia due to sepsis, and in certain cases of decomposition, the beneficial effect of the transfusion is obtained by increasing the patient's resistance and augmenting the natural forces which combat the progress of the disease. In purpuric conditions of obscure etiology, transfusion is not indicated by the results which have been secured up to the present time. It may prove to have a place in the treatment of purpura when we have a better understanding of the diseases in which purpuric hæmorrhages occur. In many acute infections, general tuberculosis and malignant disease, the negative results are sufficiently definite to show transfusion to be of only temporary benefit.

Embolism, sepsis, the transmission of disease, and even hæmolysis, are of much less frequent occurrence than was formerly supposed. The danger of hæmolysis has been exaggerated by most writers. Crile says that "kinship between donor and recipient is apparently of no special advantage, and the laboratory test may show hæmolysis, and yet the same blood be entirely safe in transfusion." He performed transfusion in eighteen tuberculous cases and in most of these the donor's blood hæmolyzed the recipient's blood in the test tube, but not in the patient. In our twenty-one cases we have seen but one case of hæmolysis after transfusion; this exhibited itself in the form of a slight icterus twenty-four hours after operation, otherwise recovery was complete.

Properly safeguarded transfusion is not a dangerous operation. The withdrawal of too much blood from the donor and the dilatation of the recipient's heart are usually avoidable mishaps. The introduction of air bubbles both large and small, contrary to the general opinion, have caused absolutely no harm.—L. B. Robertson and A. Brown, *Canad. Med. Ass. J.*, 5: 298, 1915.