

Acute Haemodynamic Effects of Frusemide in Patients with Normal and Raised Left Atrial Pressures

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Frusemide is a well-established diuretic (Vorbürger, 1964; McKenzie, Fairley, and Baird, 1966; Kirkendall and Stein, 1968), and a mild hypotensive when given in a dosage of over 120 mg. daily (Davidov, Kakaviatos, and Finnerty, 1967). It is commonly used in the treatment of acute pulmonary oedema with beneficial results (Stason *et al.*, 1966; Peltola, 1965; Biagi and Bapat, 1967). Because of the obvious difficulties, its haemodynamic effects in acute pulmonary oedema have seldom been studied and the stress has been on its diuretic action and clinical improvement after its administration. It appeared to us that a study of the haemodynamic action of the drug on left atrial pressure in selected patients would be helpful in elucidating the mechanism of improvement of the cardiac status.

Though some work has been done on the systemic haemodynamic effects of frusemide (International Furosemide Symposium, Bad Homburg, 1963), little or no information is available on its effect on left atrial pressure and pulmonary haemodynamics in patients either with normal or raised left atrial pressure. It was because of this paucity of information in association with its obvious clinical benefit in patients with acute pulmonary oedema that this study was instituted to investigate its haemodynamic effects in these 2 groups of patients.

PATIENTS AND METHODS

A total of 23 patients was studied, and for convenience the patients were divided into 2 groups. In the first group were 8 patients whose mean left atrial pressure was under 10 mm. Hg. In the second group 15 patients had mitral valve disease with a mean left atrial pressure above 10 mm. Hg, six of them had episodes of paroxysmal nocturnal dyspnoea, and all experienced dyspnoea on exertion.

All patients had right heart catheterization and either

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a brachial artery needle or retrograde aortic catheter inserted. In addition, those with valvular heart disease had left atrial catheterization performed using a modified Brockenbrough needle with a blunt-ended stylette. Cardiac outputs were measured by injecting indocyanine green dye (2.5 mg.) into the pulmonary artery with constant arterial withdrawal through a Gilford densitometer, and the dye curve was recorded on either a Sanborn photographic recorder or an ultraviolet recorder.

Pressures in the pulmonary artery, brachial artery or central aorta, and the left atrium were measured at rest under mild sedation using a Sanborn pressure transducer (Model 267B) coupled to a Sanborn photographic recorder. The reference point for all pressure determinations was 5 cm. below the sternal angle and a simultaneous electrocardiogram was taken with all pressure measurements. One or two control cardiac outputs were determined and their average taken. Frusemide was injected directly into the pulmonary artery through the catheter in a dose of 40 mg. over a two-minute period, and the above parameters were measured 15 minutes and 45 minutes later.

The following values were derived from the results:

$$\begin{aligned} \text{Total pulmonary vascular resistance} \\ (\text{dynes./sec./cm.}^{-5}) \\ &= \frac{\text{Mean pulmonary artery pressure (mm. Hg)}}{\text{Cardiac output (ml./sec.)}} \times 1332 \end{aligned}$$

$$\begin{aligned} \text{Pulmonary vascular resistance} \\ (\text{dynes./sec./cm.}^{-5}) \\ &= \frac{\text{Mean pulmonary artery pressure} - \\ &\quad \text{Mean left atrial pressure (mm. Hg)}}{\text{Cardiac output (ml./sec.)}} \times 1332 \end{aligned}$$

$$\begin{aligned} \text{Total systemic resistance} \\ (\text{dynes./sec./cm.}^{-5}) \\ &= \frac{\text{Mean aortic or brachial artery pressure} \\ &\quad (\text{mm. Hg})}{\text{Cardiac output (ml./sec.)}} \times 1332 \end{aligned}$$

$$\begin{aligned} \text{Central blood volume (ml.)} \\ &= \text{Appearance time of dye (sec.)} \times \text{cardiac output (ml./sec.)} \end{aligned}$$

$$\begin{aligned} \text{Pressure-time index} \\ (\text{mm. Hg sec./min.}) \\ &= \text{Ejection time (sec.)} \times \text{mean ejection pressure (mm. Hg)} \times \text{heart} \\ &\quad \text{rate (beats/min.)} \end{aligned}$$

where mean ejection pressure was taken electronically from a catheter in the ascending aorta and the index was taken as an estimate of left ventricular work.

RESULTS

Patients with Mean Left Atrial Pressures < 10 mm. Hg

Pulmonary Artery, Left Atrial, and Systemic Arterial Pressures. There were no significant changes in these parameters either 15 or 45 minutes after intravenous frusemide (Table I).

Cardiac Output. There was an average fall of 13.6 per cent after 15 minutes and 24.6 per cent after 45 minutes (Table I).

Calculated Resistances. Though the frusemide caused no change in total pulmonary or pulmonary vascular resistance, there was an average rise of 26.6 per cent and 32.6 per cent in total systemic resistance 15 and 45 minutes after frusemide (Table I).

Patients with Mean Left Atrial Pressures > 10 mm. Hg

Pulmonary Artery. The reduction in mean pulmonary artery pressure was only significant 45 minutes after frusemide (mean = -9.0 mm. Hg, S.E. = ± 1.5) (Table II).

Left Atrium. Though the average fall in left atrial pressure was small 15 and 45 minutes after frusemide (mean = -3.0 and -4.5 mm. Hg, respectively), these changes were significantly different from control though not from one another (Table II).

Cardiac Output. Fifteen minutes after frusemide the changes in cardiac output were variable (mean = +0.8%, S.E. ± 3.2) and not significant, while after 45 minutes cardiac output was reduced by 17.4 per cent which was highly significantly different from both the control and 15-minute cardiac output measurements (Table II).

Total Systemic Resistance. Though there was no change in mean systemic arterial pressure produced by frusemide, after 45 minutes there was an increase of 20.8 per cent (S.E. ± 5.3%) in total systemic resistance which is significantly different from control ($0.01 < p < 0.001$) and the 15-minute measurement ($0.05 < p < 0.02$) (Table II).

Pulmonary Resistance. There was a significant fall in total pulmonary resistance after 15 minutes (mean = -14.0%) and 45 minutes after the intravenous frusemide (mean = -16.4%) though the 45-minute fall was not greater than the 15-minute fall ($p > 0.05$), but there were no significant changes in pulmonary vascular resistance (Table II).

TABLE I
HAEMODYNAMIC DATA FROM PATIENTS WITH

Case No., sex, and age (yr.)	Rhythm	Clinical diagnosis	Observation	Mean pulmonary artery pressure (mm. Hg)	Mean systemic artery pressure (mm. Hg)
1 M 53	Sinus	Chronic bronchitis	Control	13	—
			After 15 min.	16	—
			After 45 min.	15	111
2 F 45	„	Chronic bronchitis	Control	14	82
			After 15 min.	14	84
			After 45 min.	11	80
3 M 17	„	“Innocent systolic murmur”	Control	11	104
			After 15 min.	—	114
			After 45 min.	16	104
4 F 39	„	Mild mitral incompetence	Control	15	85
			After 15 min.	14	98
			After 45 min.	12	81
5 F 25	„	Mild aortic stenosis	Control	—	79
			After 15 min.	—	65
			After 45 min.	—	63
6 F 43	„	Mild mitral stenosis	Control	15	66
			After 15 min.	14	65
			After 45 min.	13	63
7 F 23	„	Mild mitral stenosis	Control	18	78
			After 15 min.	14	85
			After 45 min.	9	70
8 F 44	„	Mild mitral stenosis	Control	13	67
			After 15 min.	10	73
			After 45 min.	8	69

Table III summarizes the significance of the above results.

In addition to the above measurements the following data were obtained.

Central Blood Volume. In 3 patients (Cases 13, 22, and 23) changes in central blood volume were calculated and after 15 minutes the average fall was 10.0 per cent, and 17.2 per cent 45 minutes after the frusemide had been given.

Pressure-time Index (Table IV). In a few patients the pressure-time was calculated and used as a measure of left ventricular function. While there was no change after 15 minutes, there was an average fall of 16.4 per cent 45 minutes after frusemide.

DISCUSSION

In patients with mean left atrial pressures less than 10 mm. Hg the essential haemodynamic change produced by intravenous frusemide was a conspicuous reduction in cardiac output. This reduction in cardiac output was accompanied by an increase in total systemic resistance which maintained mean systemic arterial pressure, presumably due to the activity of baroreceptor reflexes. This reduction in cardiac output was due to a reduced stroke volume and the underlying mechanism responsible for this is probably a reduction in plasma volume (Wolfer

and Schneider, 1963), though measurements of this were not performed in the above study.

Many of the patients with mitral valve disease where the left atrial mean pressure exceeded 10 mm. Hg had experienced paroxysmal nocturnal dyspnoea which, like other forms of pulmonary oedema, probably occurs when the mean left atrial pressure exceeds a value of about 30 mm. Hg. This is consistent with Starling's law of capillaries and has been noted at cardiac catheterization in patients with mitral stenosis (personal observations). All patients with raised left atrial pressures and mitral stenosis had experienced progressive dyspnoea on exertion. It was because of these facts that they were considered suitable alternatives to patients with acute pulmonary oedema, and the effect of a powerful diuretic on their haemodynamics should reflect the changes expected when the beneficial action of frusemide is noted in patients with acute pulmonary oedema (Peltola, 1965; Stason *et al.*, 1966).

When the mean left atrial pressure was above 10 mm. Hg, intravenous frusemide reduced the cardiac output 45 minutes later and the total systemic arterial resistance increased, just as in the case of the other group of patients with normal mean left atrial pressure. In addition, however, the former group reduced their mean left atrial and mean pulmonary arterial pressures, so that the strain on

MEAN LEFT ATRIAL PRESSURES <10 mm. Hg

Mean left atrial pressure (mm. Hg)	Mean gradient across pulmonary vascular tree (mm. Hg)	Cardiac output (l./min.)	Total pulmonary vascular resistance (dynes/sec./cm. ⁻⁵)	Pulmonary vascular resistance (dynes/sec./cm. ⁻⁵)	Total systemic vascular resistance (dynes/sec./cm. ⁻⁵)
4	9	3.24	321	222	—
4	12	3.68	347	260	—
4	11	3.23	371	272	2744
—	—	2.86	392	—	2295
—	—	2.35	476	—	2850
—	—	2.19	402	—	2922
5	6	6.15	143	65	1351
7	—	5.81	—	—	1569
5	11	4.18	306	211	1990
7	8	3.69	326	174	1841
6	8	2.73	410	234	2869
3	9	2.74	350	263	2363
9	—	4.92	—	—	1283
4	—	3.15	—	—	1647
3	—	2.56	—	—	1969
10	5	5.19	231	77	1016
9	5	4.14	270	96	1254
7	6	3.77	276	127	1336
10	8	5.21	276	123	1197
9	5	4.64	241	86	1463
5	4	3.97	181	81	1409
3	10	7.92	131	101	676
4	6	7.45	107	64	784
5	3	6.65	96	36	830

TABLE II
HAEMODYNAMIC DATA IN PATIENTS WITH

Case No., sex, and age (yr.)	Rhythm	Clinical diagnosis	Observation	Mean pulmonary artery pressure (mm. Hg)	Mean systemic artery pressure (mm. Hg)
9 F 32	Sinus	Mitral stenosis	Control After 15 min. After 45 min.	20 15 11	52 50 50
10 F 38	„	Mitral stenosis	Control After 15 min.	20 20	101 103
11 F 52	Atrial fibrillation	Mitral stenosis	Control After 15 min. After 45 min.	30 22 24	— 59 63
12 F 61	„ „	Mitral stenosis	Control After 15 min.	32 28	124 151
13 F 57	Sinus	Mitral stenosis	Control After 15 min. After 45 min.	25 23 19	85 85 80
14 F 49	Atrial fibrillation	Mitral stenosis + aortic stenosis	Control After 15 min. After 45 min.	37 40 35	74 73 74
15 F 32	Sinus	Mitral stenosis	Control After 15 min. After 45 min.	35 26 18	78 97 75
16 F 37	Atrial fibrillation	Mitral stenosis	Control After 15 min.	42 45	77 78
17 F 55	Sinus	Mitral stenosis	Control After 15 min. After 45 min.	33 27 27	65 65 84
18 F 30	„	Mitral stenosis	Control After 15 min. After 45 min.	36 24 23	83 75 76
19 F 39	„	Mitral stenosis + aortic insufficiency	Control After 15 min. After 45 min.	69 70 66	65 73 78
20 F 51	Atrial fibrillation	Mitral stenosis + aortic insufficiency	Control After 15 min. After 45 min.	37 25 23	80 64 71
21 M 44	„ „	Mitral stenosis	Control After 15 min.	51 51	83 81
22 F 41	Sinus	Mitral stenosis + aortic insufficiency	Control After 15 min. After 45 min.	27 20 12	80 76 56
23 M 43	Atrial fibrillation	Mitral stenosis + mitral insufficiency	Control After 15 min. After 45 min.	36 36 28	67 72 73

the right ventricle was smaller and the back pressure on the lung vessels was reduced. It is possible that the latter would reduce the work of ventilation, and in the few patients studied there was in fact a fall in central blood volume, which probably accounts for the reduced dyspnoea to be seen in patients with high left atrial pressures after frusemide therapy (Peltola, 1965; Stason *et al.*, 1966). This is consistent with the work of McCredie (1967) who measured pulmonary extravascular fluid volume using a double isotope technique and showed that this volume was increased when the mean left atrial pressure exceeded 12 mm. Hg. Reduction of left atrial mean pressure by frusemide would diminish this fluid volume, reduce the work of

ventilation, and hence diminish the degree of dyspnoea.

Beside the reduction in the work of the right ventricle due to a lowered mean pulmonary artery pressure, the work of the left ventricle was reduced as measured by the fall in the pressure-time index. Hence, cardiac work, both left and right ventricular, is reduced after intravenous frusemide, and this is in agreement with the work of Rowe *et al.* (1962) using intravenous chlorothiazide in hypertensive patients. Undoubtedly this is a cause of the clinical improvement seen in patients on diuretic therapy.

Though there was a reduction in pulmonary artery pressure and cardiac output which led to a fall in total pulmonary resistance in patients with

MEAN LEFT ATRIAL PRESSURE >10 mm. Hg

Mean left atrial pressure (mm. Hg)	Mean gradient across pulmonary vascular tree (mm. Hg)	Cardiac output (l./min.)	Total pulmonary vascular resistance (dynes/sec./cm. ⁻⁵)	Pulmonary vascular resistance (dynes/sec./cm. ⁻⁵)	Total systemic vascular resistance (dynes/sec./cm. ⁻⁵)
12	8	5.99	267	107	694
9	6	5.31	226	90	753
6	5	4.38	201	91	912
12	8	2.30	695	278	3510
11	9	2.25	710	320	3659
16	14	4.96	483	225	—
12	10	4.71	373	176	1001
11	13	3.73	514	278	1349
18	15	2.30	1112	487	4309
18	10	2.58	867	310	4677
13	12	3.44	581	279	1976
11	12	3.42	537	280	1985
8	11	2.93	518	300	2181
15	22	—	—	—	—
21	19	—	—	—	—
22	13	—	—	—	—
21	14	3.88	721	288	1606
15	11	3.73	577	236	2077
11	7	2.75	523	204	2181
22	20	3.51	956	455	1793
21	24	3.99	901	481	1562
23	10	4.08	646	196	1273
18	9	3.99	541	180	1302
17	10	3.67	588	218	1828
24	12	5.57	517	172	1191
17	7	4.86	395	115	1233
14	9	4.53	406	159	1341
26	43	4.51	1222	762	1151
30	40	5.53	1011	578	1055
29	37	4.43	1191	668	1408
27	10	—	—	—	—
18	7	—	—	—	—
16	7	—	—	—	—
32	19	—	—	—	—
27	24	—	—	—	—
17	10	4.06	531	197	1574
14	6	3.57	448	224	1701
6	6	2.79	344	172	1603
22	14	2.51	1148	446	2136
13	23	2.68	1076	687	2151
15	13	2.52	888	412	2316

TABLE III
SUMMARY OF HAEMODYNAMIC CHANGES PRODUCED BY INTRAVENOUS FRUSEMIDE

	Left atrial pressure (< 10 mm. Hg)		Raised left atrial pressure (> 10 mm. Hg)	
	After 15 min.	After 45 min.	After 15 min.	After 45 min.
Mean pulmonary artery pressure (Δ)	-1.0	-2.1	-3.6	-9.0*
Mean left atrial pressure (Δ)	-0.7	-2.3	-3.0*	-4.5*
Mean systemic arterial pressure (Δ)	+3.3	-4.4	+2.1	-1.5
Cardiac output ($\Delta\%$)	-13.6*	-24.6*	+0.8	-17.4*
Total pulmonary resistance ($\Delta\%$)	+6.9	+14.0	-14.0*	-16.4*
Pulmonary vascular resistance ($\Delta\%$)	+1.9	+44.1	-6.2	-4.7
Total systemic resistance ($\Delta\%$)	+26.6*	+32.6*	+6.2	+20.8*

Δ and $\Delta\%$ are, respectively, the absolute and percentage changes from control values.
* p value < 0.05.

TABLE IV
PRESSURE-TIME INDEX

Case No.	Age (yr.)	Diagnosis	Left atrial pressure (mm. Hg)			Mean central aortic pressure (mm. Hg)			Pressure-time index (mm. Hg sec./min.)		
			*Control	15	45	Control	15	45	Control	15	45
4	39	Mild mitral incompetence	7	6	3	85	98	81	1824	2058	1685
13	57	Mitral stenosis	13	11	8	85	85	80	2111	2066	1851
22	41	Mitral stenosis + aortic insufficiency	17	14	6	80	76	56	2125	2052	1505
10	38	Mitral stenosis	12	11	—	101	103	—	2234	2253	—
† 17	55	Mitral stenosis	23	18	17	65	65	84	1474	1602	2095
† 24	56	? Cardiomyopathy	5	5	4	70	65	65	1053	1017	1015

* Control = control value before frusemide 40 mg. intravenously. 15 = 15 min. after frusemide injection; 45 = 45 min. after frusemide injection.

† On daily oral frusemide.

raised left atrial pressures, there was no change in the true resistance of the pulmonary vascular bed (pulmonary vascular resistance), which was not unexpected as this vascular bed is resistant to most pharmacological agents (Harris and Heath, 1962).

Recently, Stampfer *et al.* (1968) have studied the action of diuretics on exercise tolerance in patients with impaired cardiac function. They noted a fall in mean left atrial and mean pulmonary artery pressures after a diuresis with a fall in cardiac output and ventricular stroke work. In the two studies mentioned above (Rowe *et al.*, 1962; Stampfer *et al.*, 1968) and the results in this paper there was a reduction in cardiac output with diuretic therapy. However, Rader *et al.* (1964) calculated that there was an increase in cardiac output in patients with congestive heart failure treated with a mercurial diuretic though there was some variability in their results. The above data in patients with raised mean left atrial pressures support strongly the hypothesis that symptoms of impaired cardiac function are due to circulatory congestion and reduction of this relieves the symptoms. Rader *et al.* (1964) also point out that this impairment occurs whether "cardiac function is improved towards the normal or not", i.e. cardiac output may or may not increase with clinical improvement in congestive heart failure.

Effective therapy either by intravenous digoxin or venesection improved cardiac function in congestive failure by reducing right atrial pressure to cause an increase in cardiac output (McMichael and Sharpey-Schafer, 1944; Howarth, McMichael, and Sharpey-Schafer, 1946). The main conclusion from this work was that cardiac output increased in response to treatment of heart failure. Others usually noted an increase in cardiac output with venesection in patients with congestive heart failure, though this was not consistent (Judson *et al.*, 1955). The emphasis in previous work on the treatment of heart failure has been on an increase in cardiac out-

put as congestive heart failure is treated, and the explanation given was that the patient's myocardium was functioning on the descending limb of the Starling curve.

However, the results of our investigations, together with those of Stampfer *et al.* (1968), are at variance with this hypothesis for there is a decrease in cardiac output, not an increase, with diuretic therapy in heart disease. The increased exercise tolerance seen after treatment in patients with significant mitral stenosis, or other causes of impaired cardiac function (Stampfer *et al.*, 1968) is due, not to an increase in resting cardiac output produced by diuretic therapy, but rather to a reduction in the burden imposed on the right and left ventricles and also on the work load of ventilation.

SUMMARY

The haemodynamic actions of frusemide (40 mg.) were studied 15 and 45 minutes after intravenous injection in patients with normal or raised left atrial pressures. Where the mean left atrial pressure was less than 10 mm. Hg, the major haemodynamic change was a conspicuous fall in cardiac output due to a reduction in stroke volume with a compensatory increase in calculated systemic resistance considered to be due to baroreceptor reflexes.

When the mean left atrial pressure was increased, the cardiac output was again reduced 45 minutes after intravenous frusemide and total systemic vascular resistance increased. In addition, there was a significant reduction in mean left atrial and mean pulmonary artery pressures such that total pulmonary vascular resistance decreased, though there was no change in the resistance across the pulmonary vascular tree. In addition, a decrease in central blood volume occurred in the 4 patients studied.

Reduction in cardiac output and pulmonary artery pressure in the patients with increased left atrial pressure would reduce the work of the right ven-

tricle. There was a decrease in left ventricular work (as measured by a pressure-time index), and the reduction in central blood volume would be expected to diminish the work of ventilation.

It is considered that improvement in symptoms in patients with raised left atrial pressure which follows frusemide therapy is due to a reduction in myocardial work load and the work of ventilation, and there is strong evidence against a previous hypothesis that improvement in heart failure is accompanied by an increase in cardiac output because the patient's myocardium had previously been working on the descending limb of a Starling curve.

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REFERENCES

- Biagi, R. W., and Bapat, B. N. (1967). Frusemide in acute pulmonary oedema. *Lancet*, **1**, 849.
- Davidov, M., Kakaviatos, N., and Finnerty, F. A. (1967). Anti-hypertensive properties of furosemide. *Circulation*, **36**, 125.
- Harris, P., and Heath, D. (1962). The effect of drugs. In *The Human Pulmonary Circulation*, pp. 113-126. E. & S. Livingstone, Edinburgh.
- Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1946). Effects of venesection in low output heart failure. *Clin. Sci.*, **6**, 41.
- International Furosemide Symposium, Bad Homburg (1963). Farbwerke Hoechst A.G., Frankfurt.
- Judson, W. E., Hollander, W., Hatcher, J. D., Halperin, M. H., and Friedman, I. H. (1955). The cardio-hemodynamic effects of venous congestion of the legs or of phlebotomy in patients with and without congestive heart failure. *J. clin. Invest.*, **34**, 614.
- Kirkendall, W. M., and Stein, J. H. (1968). Clinical pharmacology of furosemide and ethacrynic acid. *Amer. J. Cardiol.*, **22**, 162.
- McCredie, M. (1967). Measurement of pulmonary edema in valvular heart disease. *Circulation*, **36**, 381.
- McKenzie, I. F. C., Fairley, K. F., and Baird, C. W. (1966). A clinical trial of frusemide ("Lasix"). *Med. J. Aust.*, **1**, 879.
- McMichael, J., and Sharpey-Schafer, E. P. (1944). The action of intravenous digoxin in man. *Quart. J. Med.*, n.s., **13**, 123.
- Peltola, P. (1965). Furosemide (Lasix) as a diuretic. *Acta med. scand.*, **177**, 777.
- Rader, B., Smith, W. W., Berger, A. R., and Eichna, L. W. (1964). Comparison of the hemodynamic effects of mercurial diuretics and digitalis in congestive heart failure. *Circulation*, **29**, 328.
- Rowe, G. G., Castillo, C. A., Crosley, A. P., Maxwell, G. M., and Crumpton, C. W. (1962). Acute systemic and coronary hemodynamic effects of chlorothiazide in subjects with systemic arterial hypertension. *Amer. J. Cardiol.*, **10**, 183.
- Stampfer, M., Epstein, S. E., Beiser, G. D., and Braunwald, E. (1968). Hemodynamic effects of diuresis at rest and during intense upright exercise in patients with impaired cardiac function. *Circulation*, **37**, 900.
- Stason, W. B., Cannon, P. J., Heinemann, H. O., and Laragh, J. H. (1966). Furosemide. A clinical evaluation of its diuretic action. *Circulation*, **34**, 910.
- Vorburger, C. (1964). Un nouveau diurétique, le Fursemid. *Rev. méd. Suisse rom.*, **84**, 277.
- Wolfer, H. J., and Schneider, W. (1963). In *International Furosemide Symposium*. Farbwerke Hoechst A.G., Frankfurt.