In all these cases degeneration of the greater superficial petrosal nerve could be shown or reasonably presumed. In Case 1 of this series this nerve has been sectioned and there had been no regeneration of activating fibres along it from the facial nerve—as shown by the persistent dryness of the eye to all normal stimuli. Degeneration of the greater superficial petrosal nerve near the geniculate ganglion might be expected to induce collateral sprouting from the lesser superficial petrosal. All the conditions found provocative by Murray (1959) exist. At the appropriate point just beyond the geniculate ganglion these two nerves lie in extremely close proximity. The communicating twig from lesser to greater petrosal may facilitate the passage of repairing sprouts. The time interval, generally six months or more before crocodile tears follow the nerve injury, is consistent with such reparative process. Salivary secretory fibres are appropriate for lacrimal excitation and a gustatory reflex arc may well become established.

Boyer and Gardner (1949) had found that intracranial section of the glossopharyngeal nerve relieved crocodile tears in their two cases. This fact, with the results obtained in this series by stimulating and by resecting the efferent pathway at a more convenient point, appear to provide conclusive evidence of this hypothesis.

If this be accepted, then tympanic neurectomy would seem the most suitable form of treatment. For the skilled otologist it is a safe operation requiring only two days' hospitalization, and local anaesthesia will often suffice. Normal emotional lacrimation, if it persists, as it may, is preserved. Lacrimal adenectomy or vidian neurectomy (Golding-Wood, 1961) would abolish this. Intracranial glossopharyngeal rhizotomy (Boyer and Gardner, 1949) is unnecessarily hazardous.

Summary and Conclusions

Paroxysmal lacrimation while eating is a well-recognized sequel that may arise six months or more after severe lesion of the facial nerve at or proximal to the geniculate ganglion. It is generally but not necessarily associated with facial synkinesia. It may arise after intracranial section of the greater superficial petrosal nerve without facial palsy.

Hitherto the pathological mechanism of crocodile tears has remained speculative and obscure. From analysis of four cases and relevant literature a new hypothesis is advanced. Degeneration of the greater superficial petrosal nerve excites collateral sprouts from the lesser superficial petrosal, normally subserving salivary secretion; these make functional connexion with the lacrimal glands. Thus a reflex arc provoking lacrimation on chewing food is established and thereafter it will persist indefinitely, to the patient's great embarrassment.

The most convenient point to sever the efferent arc is in the tympanic cavity by resection of the tympanic branch of the glossopharyngeal nerve; with modern otological technique this is a trivial operation for the patient and appears likely to give uniform relief while preserving normal lacrimation if such persists. This operation is offered as the most suitable treatment.

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ETHACRYNIC ACID: A NEW ORAL DIURETIC

BY

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Safe, effective oral diuretics are now available, and the treatment of oedema, although often empirical, is generally satisfactory. There are occasional patients who do not respond adequately to these diuretics, and it was with these "resistant" patients in mind that we investigated the diuretic properties of a new drug, ethacrynic acid (MK-595). MK-595 is an unsaturated ketone derivative of aryloxyacetic acid and is not structurally related to hydrochlorothiazide (Fig. 1) or other diuretics (Schultz *et al.*, 1962).

FIG. 1.—Structural formulae of MK-595 (left) and hydrochlorothiazide.

This drug has been shown to have potent diuretic activity in animals (Baer *et al.*, 1962, 1963), and preliminary observations of the dose-response in oedematous patients have recently been reported (Foltz, 1963). We have compared the action of MK-595 with that of hydrochlorothiazide in normal volunteers and in oedematous patients.

Methods

Dose-response.—The dose of MK-595 which would give maximal diuretic response was determined in three

patients who were free from oedema or any sign of renal disease. They were maintained on a diet containing 50 mEq of sodium and 70 mEq of potassium daily. Single doses of 100, 200, and 300 mg. of MK-595 were given to each patient at intervals of five days. Urine was collected hourly for six hours after the drug had been taken, followed by a six-hour and finally a 12-hour collection period.

Normal Volunteers.—MK-595 and hydrochlorothiazide were compared in normal volunteers by the method used by Martz (1962). Six members of the staff of the medical unit were given a diet constant in respect to sodium, potassium, and fluid on three successive Mondays. On Tuesday, breakfast was served in the unit, and at 9 a.m. hourly collections of urine were started. A sodium-load was maintained by the drinking of 300 ml. of 0.14% saline at 9 a.m. and 100 ml. hourly until 5 p.m. At 11 a.m. each subject was given 200 mg. of hydrochlorothiazide, MK-595, or placebo. No lunch was eaten on the day of the test, but dinner at 5 p.m. contained 90 mEq of sodium and 61 mEq of potassium. Six-hour and 12-hour collections of urine were made between 5 and 11 p.m. and between 11 p.m. and 11 a.m. respectively.

Oedematous Patients.—The patients were admitted to the medical unit and kept for the period of the trial on a daily intake constant in respect to sodium (50 mEq) and potassium (70 mEq); fluid was restricted to 1,500 ml. daily. Clinical details of the patients are given in Table II. After a short control period of bed-rest the patients received drug A (MK-595) or drug B (hydrochlorothiazide), each at a dose of 50 mg. thrice daily, according to the schemes A B B A, A B B A or B A A B, B A A B (Gold *et al.*, 1960). The 10 patients were allocated randomly to either of these schemes. All urine was collected in 24-hour periods.

Laboratory Methods.—The volume of each collection of urine was recorded and aliquots were kept at -10°C . for analysis. Sodium and potassium were measured by flame-photometry, using, as standards, solutions with a Na/K ratio similar to that of urine.

Results

Dose-response.—The response to different doses of MK-595 in three patients is given in Fig. 2. A maximum diuresis of water and sodium was achieved with a dose of 200 mg. The maximum effective dose of hydrochlorothiazide is also 200 mg. (Moyer, 1959; Fuchs *et al.*,

FIG. 2.—Dose-response for MK-595 with mean excretion of water, sodium, and potassium in three patients without oedema.

1960), so that for the remainder of the trial the effects of equal doses of MK-595 and hydrochlorothiazide were compared.

Normal Volunteers.—A comparison of the effect of the two diuretics in six normal volunteers is shown in Fig. 3; MK-595 caused a more intense but less prolonged diuresis than did hydrochlorothiazide. In the first six hours MK-595 effected the excretion of a statistically significant greater amount of water, sodium, and

FIG. 3.—Mean excretion of water, sodium, and potassium by six normal volunteers during a 24-hour period after a single 200 mg. dose of MK-595, hydrochlorothiazide, and placebo.

potassium (Table I). By the end of 24 hours the difference between the two drugs with respect to water and potassium excretion was not significant, but sodium excretion was greater with hydrochlorothiazide.

TABLE I.—Effect of MK-595 and Hydrochlorothiazide in Six Normal Subjects

	Period after Single 200-mg. Dose			
	0-6 hours		0-24 hours	
	MK-595	Hydrochlorothiazide	MK-595	Hydrochlorothiazide
Volume (ml.)	1,585	1,382	2,893	2,785
Sodium (mEq)	146	115	228	292
Potassium (mEq)	47	39	96	103

Oedematous Patients.—The results, including the mean values, obtained in the oedematous patients are given in Table II. A gross index of the relative effectiveness of the two drugs is obtained by comparing the sum of the effects on all the days with each drug. Thus days 4, 7, 8, and 11 in patients in group I and days 5, 6, 9, and 10 for those in group II when added give the total diuresis caused by MK-595; an analogous addition gives the diuresis caused by hydrochlorothiazide. The results expressed as average daily excretions are shown in Fig. 4. It is seen that MK-595 caused a greater diuresis of water, sodium, and potassium; this statement is true also for most individual patients (Table II).

Discussion

Although MK-595 and hydrochlorothiazide are not chemically related, the patterns of electrolyte excretion are very similar. In normal volunteers the diuresis induced by MK-595 was more intense but less prolonged; in oedematous patients MK-595 caused a greater diuresis. Nevertheless, the ratio of sodium to potassium in the urine was identical for each drug (1.85 in the oedematous patients).

Despite this similarity, it would seem that these drugs do not act on renal tubular function by the same

mechanism. There is an additive effect between the two drugs. This is shown in Fig. 5; the days on which a drug was preceded by the same drug (column i) are compared with those which have been preceded by the other drug (column ii). Each of the drugs had a carry-over additive effect which increased the diuretic response on the day after a change in the regime. This additive effect was apparent in the excretion of sodium, potassium, and water.

In the doses given, MK-595 was free of side-effects, except that in one patient it provoked a clinical recurrence of acute gout. In this respect also, MK-595 is similar to hydrochlorothiazide.

MK-595 is a potent diuretic, and the dramatic diuresis induced in some cases could be dangerous. One of our patients (Case 5) excreted 8,590 ml. of urine containing 952 mEq of sodium on the first day of treatment with MK-595. Similar excessive diureses have been observed elsewhere (K. C. Mezey, personal communication, 1963). One patient (Case 6) was resistant to hydrochlorothiazide, but responded to MK-595.

It is too early to define the true status of MK-595. As a diuretic it is, without doubt, potent, but it is not

free of the potassium-wasting which is a feature of the benzothiadiazine diuretics. It may also prove clinically useful in inducing an adequate diuresis in

FIG. 4.—Average of all daily excretions of potassium, sodium, and water by 10 oedematous patients with MK-595 and hydrochlorothiazide.

FIG. 5.—Mean excretion of water, sodium, and potassium by 10 oedematous patients given MK-595 or hydrochlorothiazide. Column (i) is the average for those days in which a drug was preceded by a day on the same drug; column (ii) when preceded by a day on the other drug.

TABLE II.—Urinary Excretion in Oedematous Patients Given MK-595 and Hydrochlorothiazide

Case No.	Age	Sex	Diagnosis	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
				Drug*	—	—	—	M	H	H	M	M	H	H	M	—	—	M
Group I																		
1	59	F	Ischaemic heart failure	Volume (ml.)	—	1,500	1,850	1,660	2,700	2,300	2,960	2,220	2,280	2,105	2,045	940	1,160	1,700
				Sodium (mEq)	—	44	59	53	190	118	147	85	96	69	73	22	12	13
				Potassium (mEq)	—	44	48	62	118	100	90	74	80	62	74	29	40	51
2	56	F	Portal cirrhosis	Volume (ml.)	—	1,480	1,380	1,870	1,630	1,260	2,145	2,145	1,200	1,083	2,175	1,140	1,225	1,540
				Sodium (mEq)	—	53	32	66	71	43	120	112	39	26	100	34	24	48
				Potassium (mEq)	—	43	36	52	64	50	81	64	41	31	56	31	35	38
3	78	M	Pulmonary heart disease	Volume (ml.)	—	—	340	1,020	820	780	1,740	1,740	920	880	1,180	870	700	1,240
				Sodium (mEq)	—	—	19	89	92	90	214	185	72	109	100	81	51	130
				Potassium (mEq)	—	—	17	36	28	27	44	35	21	22	32	18	17	24
4	53	F	Nephrotic syndrome	Volume (ml.)	1,180	1,040	1,750	1,620	2,164	2,790	2,230	2,490	2,515	1,980	1,780	1,720	1,570	1,490
				Sodium (mEq)	35	36	71	86	208	205	198	195	202	167	130	77	51	40
				Potassium (mEq)	37	37	50	51	61	64	55	57	59	57	60	68	62	68
5	58	M	Ischaemic heart disease	Volume (ml.)	—	1,160	1,500	8,590	3,190	2,980	5,250	2,520	2,330	1,825	3,164	2,290	2,048	2,410
				Sodium (mEq)	—	19	47	952	422	414	506	92	87	69	175	39	14	48
				Potassium (mEq)	—	41	42	149	82	64	141	108	90	78	95	61	52	78
Mean				Volume (ml.)	1,180	1,295	1,364	2,952	2,100	2,022	2,865	2,223	1,849	1,574	2,069	1,392	1,341	1,676
				Sodium (mEq)	35	38	46	249	196	174	237	134	99	88	115	51	31	56
				Potassium (mEq)	37	41	38	70	71	61	82	68	58	50	63	41	41	51
Group II																		
				Drug*	—	—	—	H	M	M	H	H	M	M	H	—	—	H
6	29	F	Portal cirrhosis	Volume (ml.)	500	460	470	485	2,305	1,500	1,090	850	2,155	1,605	800	765	660	660
				Sodium (mEq)	3.4	1.4	0.9	2.1	28	6.4	5.4	2.1	45	41	3.3	3.3	1.6	2.4
				Potassium (mEq)	12	13	13	23	148	69	50	36	142	84	35	25	16	28
7	76	M	Nephrotic syndrome	Volume (ml.)	—	710	770	1,585	1,880	1,860	1,790	1,170	1,500	1,740	1,390	1,440	1,025	1,220
				Sodium (mEq)	—	16	22	133	148	144	138	80	111	130	109	102	72	67
				Potassium (mEq)	—	42	35	76	77	74	77	58	56	63	47	52	37	48
8	48	F	Nephrotic syndrome	Volume (ml.)	1,540	1,420	1,450	2,420	3,305	2,480	3,350	2,220	2,430	2,005	2,350	1,600	1,760	1,740
				Sodium (mEq)	27	28	18	162	197	127	321	191	141	82	180	76	41	82
				Potassium (mEq)	67	67	64	76	71	54	82	83	78	60	80	75	57	86
9	63	M	Pulmonary heart disease	Volume (ml.)	—	1,780	1,400	2,115	2,950	2,100	2,410	2,040	2,190	2,460	2,230	1,850	1,625	1,540
				Sodium (mEq)	—	13	5.2	104	195	145	176	137	119	115	128	118	71	103
				Potassium (mEq)	—	23	11	29	47	33	45	38	41	48	57	53	37	35
10	65	M	Nephrotic syndrome	Volume (ml.)	—	—	1,140	1,620	2,000	1,430	1,820	1,580	1,900	2,080	1,710	1,440	985	1,740
				Sodium (mEq)	—	—	4.2	24	38	8.3	13	25	24	24	29	17	7.1	65
				Potassium (mEq)	—	—	76	155	135	94	127	105	111	95	93	72	48	64
Mean				Volume (ml.)	1,020	1,092	1,046	1,645	2,488	1,875	2,092	1,572	2,035	1,978	1,696	1,419	1,211	1,380
				Sodium (mEq)	15	15	10	85	121	86	136	87	88	76	90	63	37	63
				Potassium (mEq)	40	36	40	72	95	65	76	64	86	70	62	55	39	52

* M = MK-595 150 mg. daily.

H = Hydrochlorothiazide 150 mg. daily.

those patients who have not responded to other diuretics.

Summary

A new diuretic drug, ethacrynic acid (MK-595), has been compared with hydrochlorothiazide in normal volunteers and oedematous patients. Structurally the two drugs are not related. Ethacrynic acid is a potent diuretic causing an excretion pattern similar to that caused by hydrochlorothiazide. It produced in oedematous patients a greater diuresis than hydrochlorothiazide, each at a dose of 50 mg. thrice daily, but the potassium loss was correspondingly greater. One patient who was resistant to hydrochlorothiazide had an adequate diuresis with ethacrynic acid. Acute gout was induced by ethacrynic acid in one patient; no other side-effects were noted.

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Preliminary Communications

Liver Damage after Halothane Anaesthesia

Halothane is regarded as a powerful and safe inhalant anaesthetic agent, and since 1956 it has been used millions of times. A recent post-operative death from toxic hepatitis led to a search into the background, when 11 deaths following halothane anaesthesia were found reported in the literature (Burnap *et al.*, 1958; Virtue and Payne, 1958; Vourc'h *et al.*, 1960; Temple *et al.*, 1962; Brody and Sweet, 1963; Lindenbaum and Leifer, 1963; Bunker and Blumenfeld, 1963). It is difficult to assess scattered reports, and so this case is presented to add to the collective series, in the hope that when other such misfortunes occur they may be reported. Perhaps then the damage done to the liver by this commonly used drug may be better evaluated.

CASE REPORT

A married woman aged 55 attended in December, 1962, with post-menopausal bleeding. She had undergone no previous operations and there were no episodes of jaundice in her or her family's past history. Examination showed an obese patient with hypertension (190/110). No other abnormalities were detected, and beyond a cervical polyp the pelvic organs were normal.

On January 1, 1963, a curettage was performed under general anaesthesia which lasted 15 minutes (premedication with pethidine 100 mg. and hyoscine 0.4 mg., induction with methohexitone 80 mg., and continued with suxamethonium

80 mg. and endotracheal nitrous oxide, oxygen, and halothane). The polyp was removed, and uterine curettings later showed the presence of a papillary adenocarcinoma.

On January 8 the patient underwent a second operation. Anaesthesia was as detailed above, using intermittent suxamethonium for relaxation, and a total hysterectomy with bilateral salpingo-oophorectomy was performed without difficulty. The operation lasted 90 minutes and the blood loss was estimated at 400 ml. The specimen showed a well-localized area of carcinoma at the fundus of the uterus, without evidence of invasion of the myometrium.

Post-operatively she made a good recovery, there being no episodes of anoxia and her blood-pressure being steady. There was a transient urinary infection by *Escherichia coli* which responded well to five days' treatment with sulphadimidine 1 g. six-hourly. Ten days after operation a spike of pyrexia occurred to 102° F. (38.9° C.), and the next day the patient was slightly jaundiced. This was a new symptom. There was no abdominal pain or nausea, or any vomiting. On examination no enlarged liver or spleen could be felt, nor was there any tenderness. The urine was dark and the stools were light brown. It was thought that the patient had an atypical form of infectious hepatitis, and she was therefore isolated and treated with a high-glucose, fluid diet.

At this time the blood examination showed: Hb 15 g./100 ml., P.C.V. 49%, M.C.H.C. 32%, W.B.C. 11,300/c.mm. (polymorphs 78%, lymphocytes 18%, eosinophils 4%). Icteric index 35 units. Plasma proteins 5.8 g. (albumin 3.6 g., globulin 2.2 g.). Serum alkaline phosphatase 18 units. Thymol turbidity 3 units. Zinc sulphate 3 units. Serum glutamic oxaloacetic transaminase 555 units. Serum glutamic pyruvic transaminase 468 units. It was thought that the above results were consistent with a toxic hepatitis, and a careful investigation of the patient was made in connexion with hepatotoxic drugs taken in the past. She was insistent that prior to admission no such drugs could have been taken.

She slowly became more jaundiced, and by the 17th post-operative day the bilirubin had risen to 21.3 mg./100 ml. (direct 7.9 mg.). On this day she deteriorated clinically, starting to vomit and becoming drowsy. Examination showed a "hepatic flap" but no spider naevi. There was still no liver enlargement or tenderness. An intravenous drip of 10% dextrose was started, with neomycin 500 mg. three-hourly, given by mouth. The liver-function tests were unchanged except that the prothrombin time was now 51 seconds (normal control 12 seconds), and the S.G.O.T. and S.G.P.T. were both over 800 units. The serum electrolytes were normal and the red and white cell counts were unchanged.

Despite treatment the patient died the next day in deepening coma. At necropsy, two days after death, no gross abnormalities were seen in the heart or lungs; the liver was of moderate size; being soft and congested, while the gall-bladder and bile-passages were normal. No abnormalities were seen in the abdomen and the operation site was healthy, with no evidence of any residual growth. Histological examination of the liver showed a total necrosis of cells in all areas of the lobules.

DISCUSSION

When a large number of variable pharmacological factors exist it is hard to prove a cause-and-effect relationship with one drug. However, the association of obvious liver damage coming 12 days after the second halothane anaesthesia fits well with a group of nine such cases recently reported (Lindenbaum and Leifer, 1963). In this series it was shown that the patient's age and previous history were not relevant. All the cases had a pyrexia, and, while jaundice appeared in most, hepatic tenderness was present in only a few. Abnormal white-cell counts occurred in the majority, and eosinophilia was present in three. No relation