INTERMITTENT ALDOSTERONISM IN PERIODIC PARALYSIS

DEPENDENCE OF ATTACKS ON RETENTION OF SODIUM, AND FAILURE TO INDUCE ATTACKS BY RESTRICTION OF DIETARY SODIUM *

JEROME W. CONN
M.D. Michigan, F.A.C.P.

LAWRENCE H. LOUIS
Sc.D. Michigan

STEFAN S. FAJANS
M.D. Michigan, F.A.C.P.

DAVID H. P. STREETEN †
D. Phil. Oxfd,
M.B. Witw'srand, M.R.C.P.

ROBERT D. JOHNSON
M.D. Michigan

From the Metabolism Research Unit of the Department of Endocrinology and Metabolism, University of Michigan Medical School, Ann Arbor, Michigan

WE have reported that spontaneous attacks of periodic paralysis are preceded by large increases of urinary aldosterone and by intense retention of sodium (Conn et al. 1956). This is followed shortly by sequestration of potassium within the body, both serum and urinary potassium falling abruptly and intensely. Serum-sodium often rises to abnormally high values as serum-potassium reaches its lowest ones. As the attack subsides a great diuresis of sodium occurs together with a less intense increase of urinary potassium. Serum-sodium and serum-potassium return to normal together. By this time urinary aldosterone has returned to base-line values.

We have explored further the rôle of retention of sodium in setting off potassium sequestration—i.e., acute hypokalæmia and hypokaluria. Two young men with the familial type of periodic paralysis were the subjects of this study. One of them, living in our laboratory, submitted cheerfully to 11 months of a rigid metabolic balance régime. The other was studied for 30 days to test in a different person the applicability of the metabolic principles discovered in the first one. The subjects are not related.

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† Howard Hughs Foundation investigator.

The aim of this short communication is to disseminate quickly information which is of immediate practical value to patients with this disorder. Extensive data will be published later. At this time we wish merely to outline some of our results and conclusions.

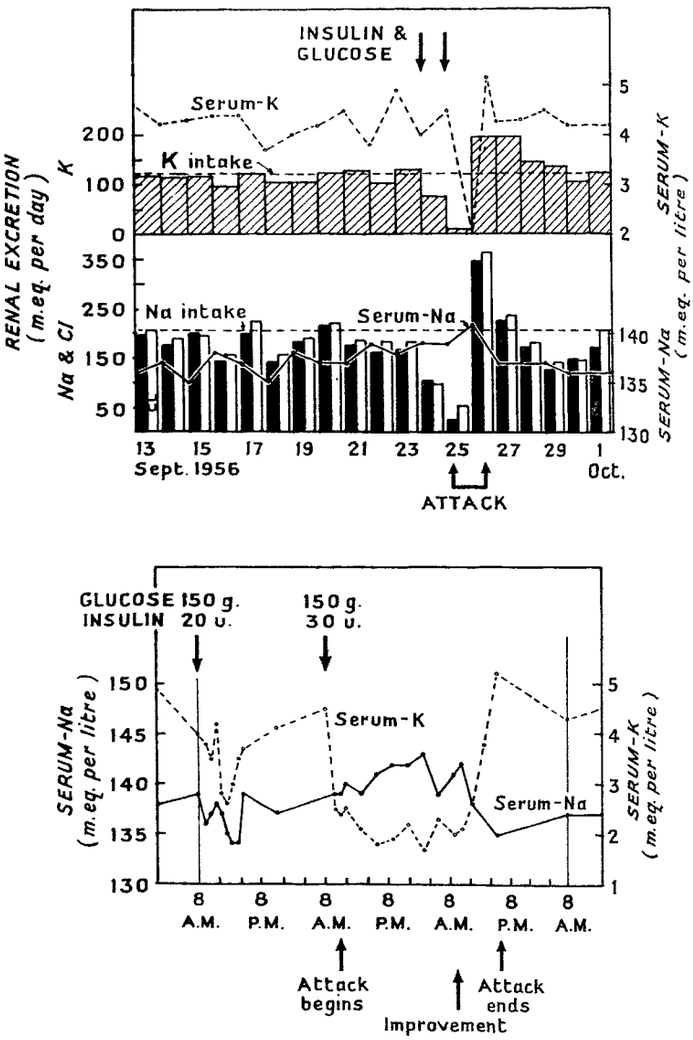

Fig. 2—Changes in electrolyte metabolism during episode of periodic paralysis induced by administration of glucose and insulin.

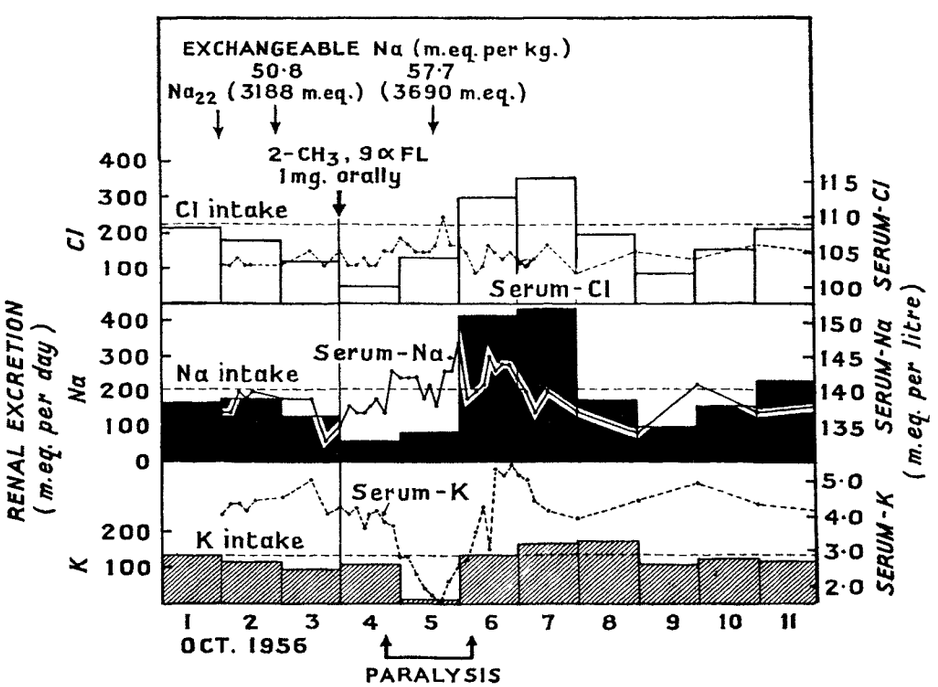

Fig. 1—Induction of episode of periodic paralysis by 2-methyl-9-α-fluorohydrocortisone and high sodium intake.

Method

Two levels of sodium intake were used—8 and 208 m.eq. per day. The composition of the daily ration was otherwise the same, the high sodium régime differing from the low by addition of sodium chloride to the basic diet. Chloride ion, the only other variable, was 27 m.eq. per day on the low, and 229 m.eq. per day on the high, sodium ration. Potassium intake was constant at 132 m.eq. per day.

Results

Under both of these dietary conditions a series of identical experiments were carried out, each designed to induce an episode of periodic paralysis. The following facts were disclosed :

(1) When the diet contained the larger quantity of sodium the administration of glucose and insulin, or of 2-methyl-9-α-fluorohydrocortisone (an extremely potent mineralocorticoid) produced complete (from the neck down) and prolonged (24–48 hours) paralysis (figs. 1 and 2).

(2) When glucose and insulin induce an episode of periodic paralysis the great

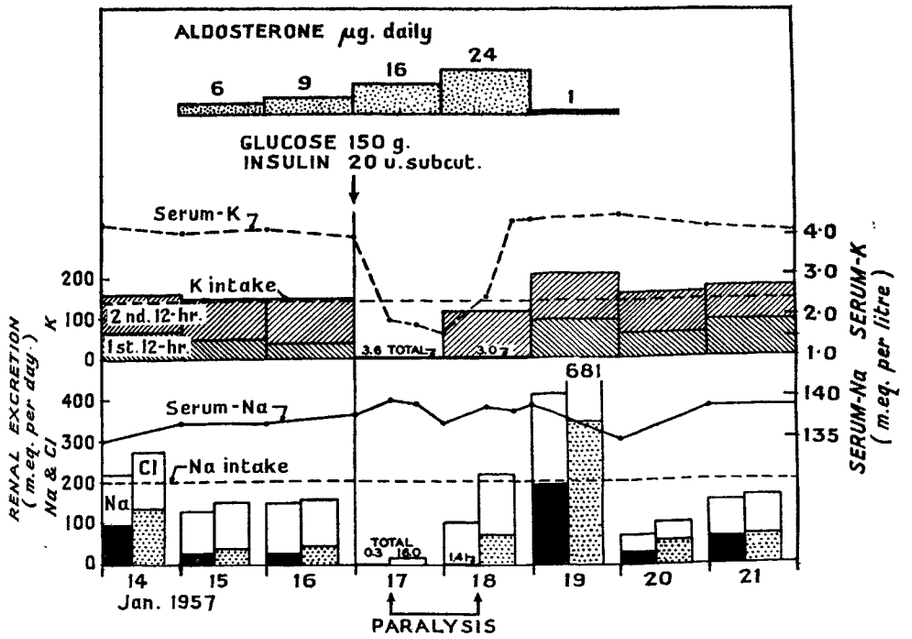

Fig. 3—Changes in electrolyte metabolism and urinary excretion of aldosterone during episode of paralysis induced by glucose and insulin. Lower part of histogram: first 12 hours; upper part, second 12 hours. Aldosterone estimated by method of Neher and Wettstein (1956).

retention of sodium which precedes the actual attack is accompanied by a sharp rise of urinary aldosterone (fig. 3). During the intense diuresis of sodium which follows an attack urinary aldosterone falls below normal. By what means increased utilisation of carbohydrate produces increased secretion of aldosterone in this disease is now under investigation.

(3) In all of these paralytic episodes urinary and serum K fell sharply but the sequestration of K was always preceded and then accompanied by intense retention of sodium.

(4) The very earliest return of muscle function is related temporally to increasing amounts of urinary sodium; and in some attacks it can be demonstrated that serum-potassium is still near its minimal value at the time that the ability to move muscles is returning. This is then followed by a rapid increase of urinary and serum potassium.

(5) Total body exchangeable sodium (Na^{22}) was found to be elevated before induction of attacks and this increased considerably during induction of an attack (fig. 1).

(6) When retention of sodium was prevented by provision of the diet very low in sodium, *attacks of paralysis could not be produced* by the procedures which had provoked the severe ones previously mentioned; and sequestration of potassium did not occur (fig. 4). This has been demonstrated in both of our cases of periodic paralysis.

(7) As in normal individuals, these subjects when taking the low-sodium diet exhibited persistently raised levels of urinary aldosterone, yet there were no attacks. Thus, the sudden sequestration of potassium which accompanies an attack of periodic paralysis is not due per se to the presence of aldosterone. Sodium must be available and must be retained in the body before potassium begins to move to its site or sites of sequestration.

(8) Whereas 2-methyl-9-α-fluorohydrocortisone produced prolonged retention of sodium and diuresis of potassium in normal men (fig. 5), it produced sodium retention followed by sequestration of potassium in both patients

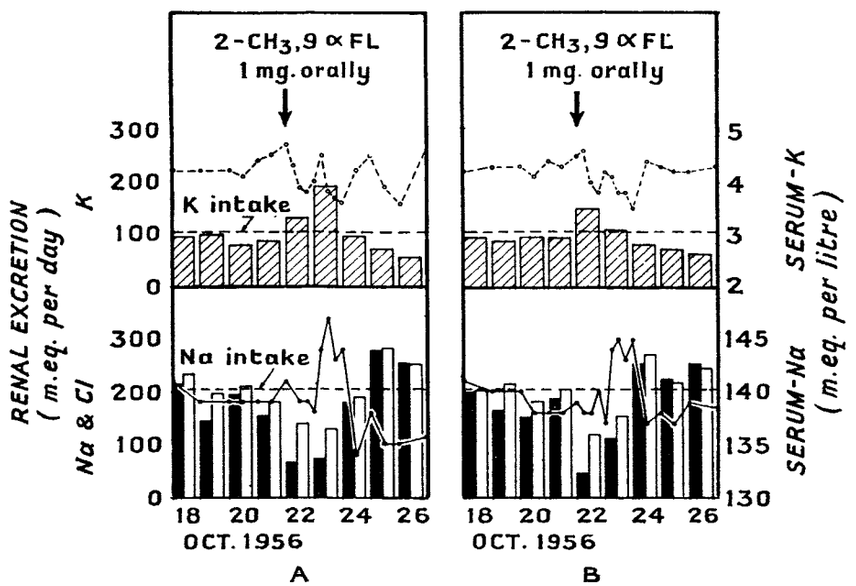

Fig. 5—Effects of 2-methyl-9-α-fluorohydrocortisone on electrolyte metabolism in two healthy young men aged 21 (A) and 19 (B).

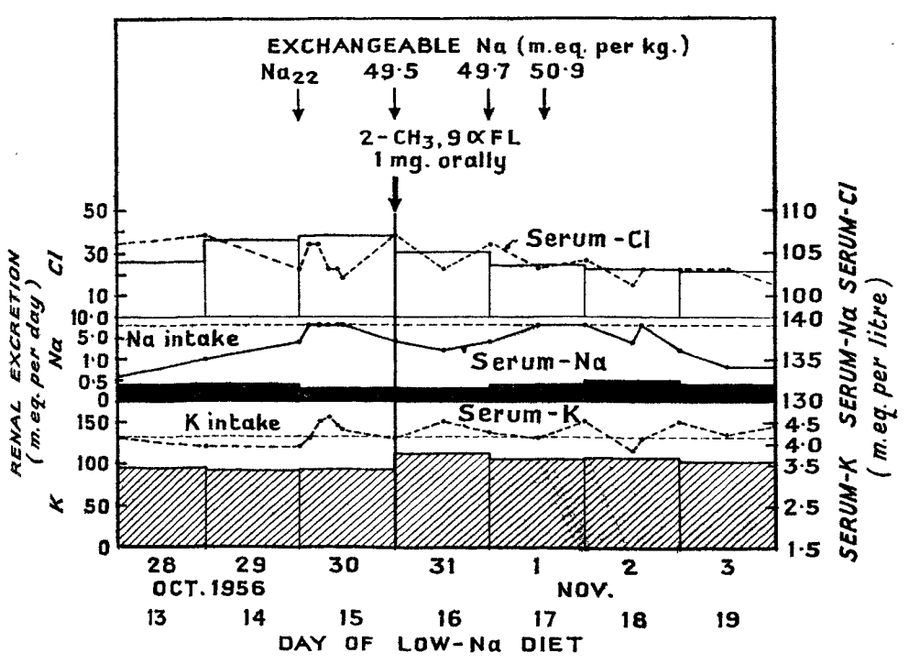

Fig. 4—Data indicating failure of 2-methyl-9-α-fluorohydrocortisone to induce attack when sodium retention is prevented by low-sodium diet.

with periodic paralysis (fig. 1). This would appear to rule out the possibility of production of an abnormal potassium-retaining adrenal steroid in this disease. Instead it appears that when a sodium-retaining corticoid is actively causing sodium retention in periodic paralysis the potassium response is a paradoxical one. This conclusion is strengthened by the fact that we have clearly identified as aldosterone the urinary sodium-retaining corticoid found in excess in this disorder.

(9) Skeletal muscle obtained during the period of high-sodium intake contains much too much sodium and a normal or slightly subnormal concentration of potassium (see accompanying table). Microscopically, the lesion characteristic of this disease is observed—namely, numerous large and small glistening vacuoles within muscle-fibres. The vacuoles do not stain as fat or glycogen (fig. 6).

(10) In skeletal muscle obtained after 44 days on the low-sodium diet this vacuolar change in the muscle-fibres has disappeared (fig. 6b). The accompanying table shows the values for concentration of Na and K in muscle at this time.

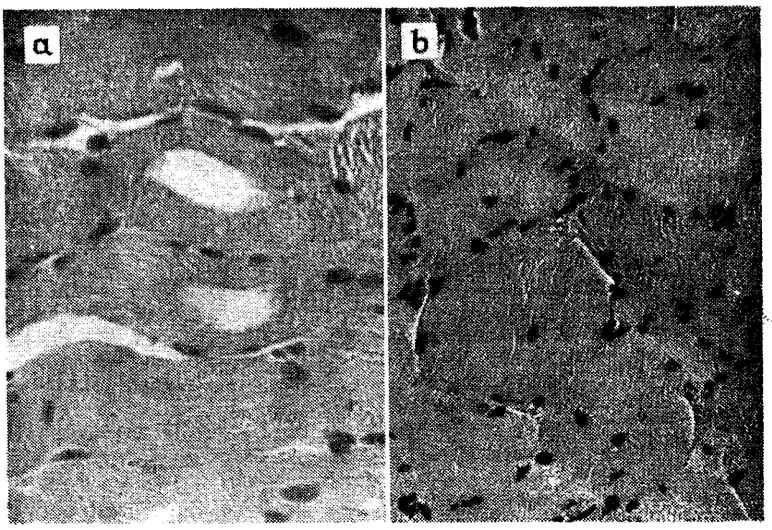

Fig. 6—Skeletal muscle from patient with periodic paralysis: (a) during high-sodium intake, showing vacuoles; (b) during low-sodium intake, showing no vacuoles.

Discussion

The dramatic decrease in the level of serum-potassium at the beginning of a paralytic episode in the "familial type" of periodic paralysis has resulted in extensive studies of potassium metabolism in this disease. Current therapy consists in administration of potassium salts daily by mouth as prophylaxis, and of potassium chloride intravenously for established attacks. We are impressed with the facts that, although an incipient attack can be aborted or a severe one sometimes ended by administration of potassium, they still occur even when 10–12 g. of potassium chloride is ingested daily.

Studies of sodium metabolism in this disease are meagre. In two studies sodium balance was found to be positive before and negative after the attack (Ferrebee et al. 1940, Danowski et al. 1948), but the significance of this finding was not appreciated. It is clear from the present data that the sudden and profound sequestration of potassium is always preceded by an intense positive balance for sodium. In normal individuals on very low levels of dietary sodium, urinary excretion of potassium is not increased by administration of 2-methyl-9-α-fluorohydrocortisone (J. W. Conn, unpublished). Thus, it appears that even in normal people the effects of mineralocorticoids upon potassium metabolism are secondary to retention of the sodium ion.

SODIUM AND POTASSIUM CONTENT OF MUSCLE AND SERUM IN PERIODIC PARALYSIS, HEALTH, AND PRIMARY ALDOSTERONISM

—	Date	Weakness	Paralysis	Muscle: Sodium (m.eq. per kg.*)	Muscle: Potassium (m.eq. per kg.*)	Serum: Sodium (m.eq. per kg.)	Serum: Potassium (m.eq. per kg.)
Periodic paralysis:							
Case 1† ..	Oct. 31, 1955	+	−	48	82	137	4·0
,, ,, ..	Jan. 14, 1956	+	+	52	85	116	3·0
,, ,, ..	Mar. 10, 1956	−	−	46	75	139	4·5
,, ,, ..	Nov. 29, 1956§	−	−	34	74	135	4·1
,, ,, ..	Feb. 19, 1957§	+	+	46	81	137	3·7
Case 2‡ ..	Feb. 8, 1957	+	+	47	82	137	1·3
Healthy people:							
Shohl 1939				31	93	..	..
Farago et al. 1951				21	106	..	..
Baldwin et al. 1952				..	95	..	..
van Buchem et al. 1956				26–36	91–107	..	..
Primary aldosteronism:							
Conn 1955 (preop.)				49	62	144	3·1
Conn et al. (unpubl.) (18 mos. postop.) ..				32	76	141	4·1
van Buchem et al. 1956 (preop.) ..				52	68	..	..

* Expressed in terms of fresh wet weight.
† Male, aged 19.
‡ Male, aged 24.
§ After 44 days on low sodium intake plus initial desalting with acetazolamide ('Diamox') and mercaptomerin ('Thiomerin'). After 38 days on high sodium intake.

With respect to the *clinical* entity of periodic paralysis we call attention to several well-recognised discrepancies which make it difficult to correlate attacks of paralysis solely with an abnormality of potassium metabolism:

(1) Attacks of total paralysis may occur at levels of serum-potassium which when found in other conditions are not low enough to result in muscular paralysis (Darrow 1946, Danowski et al. 1949, Elkinton et al. 1951).

(2) The severity of different attacks in the same individual is not correlated closely with the degree of hypokalæmia.

(3) When the serum-potassium has been estimated frequently throughout attacks, we have often observed that muscular function begins to return while serum-potassium values are close to the lowest value observed during the attack.

(4) Sporadic cases (Watson 1946, Bull et al. 1953) and families (Tyler et al. 1951, McArdle 1956) exhibit the typical clinical syndrome without *any* decrease of serum-potassium during attacks. It seems very significant that in such cases Tyler et al. (1951) have found the vacuolar myopathy (a lesion characteristic of familial periodic paralysis [Goldflam 1897, Schmidt 1919, Zabriskie and Franz 1932, Allott and McArdle 1938]) which is demonstrated in fig. 6a and shown in fig. 6b to have disappeared with reduction of intracellular sodium toward normal.

All of these considerations viewed in the light of the experimental data described here, suggest that the common denominator is an excessive quantity of intracellular sodium. This by no means excludes hypokalæmia, when it occurs, as a contributory factor; nor does it mean that a sudden increase of intracellular potassium does not influence the onset of a paralytic attack. It does indicate, however, that retention of sodium is the primary factor which sets into motion the characteristic chain of events in an episode of periodic paralysis; and it provides a much more direct approach to the prevention of paralytic episodes.

Comparison of the sodium and potassium content of muscle in periodic paralysis and in primary aldosteronism (see table) suggests that when intracellular sodium is too high the muscle cell must be able to extrude potassium if paralysis is to be avoided. The sum of the intracellular cations may be a critical factor in the muscular paralysis. The mechanism by which in most of these cases retention of sodium under the influence of aldosterone sets off the potassium-sequestration phenomenon requires further study. Similarly, the mechanism by which intermittent aldosteronism exists in this disease is not yet clear.

It seems likely, then, that an abnormally high concentration of sodium within the muscle cell is partly responsible for the disturbance of muscle function in periodic paralysis. The histological lesion of this disease—i.e., hydropic vacuolisation within the muscle-fibre—is related to the high concentration of intracellular sodium, although total cationic concentration may be important. Since the same pathological lesion has been observed in patients who, although suffering from typical periodic paralysis, exhibit no hypokalæmia or hypokaluria during attacks (Tyler et al. 1951), it is probable that retention of abnormal amounts of sodium is the common factor in the various subgroups of periodic paralysis. Balance studies for sodium are needed in such cases.

From a practical point of view these studies indicate that a diet low in sodium prevents attacks of periodic paralysis. A period of "desalting" with mercurial diuretics and/or carbonic-anhydrase inhibitors, associated with a low-sodium diet, may be required as an initial step.

Apparently the stimulus for excessive secretion of aldosterone in periodic paralysis is extra-adrenal in origin. Although adrenalectomy would remove the source of aldosterone, we believe that this procedure is not indi-

cated because: (1) episodes of paralysis become less frequent and finally disappear as the patient grows older; and (2) replacement therapy, unless grossly sub-optimal, would probably be associated with periodic retention of sodium, especially under conditions of stress (Ingle 1952).

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THE EFFECT OF TOLAZOLINE HYDROCHLORIDE ON TIC DOULOUREUX

E. W. POOLE
M.B. N.Z., M.R.C.P.E.
LATE NUFFIELD DOMINIONS TRUST ASSISTANT AND GOODGER SCHOLAR, DEPARTMENT OF NEUROLOGY, UNITED OXFORD HOSPITALS

IT has long been recognised that attacks of tic douloureux may be suppressed by vasomotor agents such as choline derivatives, nicotinic acid, histamine, and amyl nitrite (Cooper 1938, Adams and Robinson 1941, Karl et al. 1945, Wolff 1948). Such effects, even if temporary, provide a line of therapeutic investigation and are of interest in the study both of the disease and of the pharmacology of the agent used. In this field the action of more recent and possibly more effective vasodilator agents appears little explored, and this report presents some experiences with tolazoline hydrochloride. The aim has been to determine the existence and characteristics of any effects rather than to establish an optimal therapeutic régime.

Material and Methods

Observations were made in 9 patients with tic, 2 of whom had disseminated sclerosis and 1 an acoustic neuroma. 3 had had alcohol injection years previously. Only unequivocal cases of tic were accepted. Patients with frequent daily pains and active trigger areas but without severe cardiovascular disease were selected. Most of them were awaiting surgical treatment, which was delayed only in some instances where the response seemed especially promising. Tolazoline hydrochloride ('Priscol,' Ciba) was usually given first orally (12·5 mg.) as a test for idiosyncrasy, and in 1 case this route alone was used. However, graduated intravenous administration (up to 50 mg. in 10–15 minutes) was preferred so that observations could be made over a short period, thereby minimising errors from fluctuations in clinical state. Peripheral vascular responses were assessed by subjective flushing and by objective changes—e.g., conjunctival suffusion and changes in skin colour and temperature (measured with Marks skin thermometers on the extremities). The patient was kept resting flat during intravenous tests, and the blood-pressure and pulse-rate were noted at intervals.

The effects on the tic were judged by the number of attacks and their ease of provocation, both with ordinary activity (talking, eating, &c.) and with deliberate stimulation of the trigger area (touching, rubbing) before, during, and after administration of the drug. It was, however, considered unjustifiable to activate deliberately trigger areas repeatedly during the course of an injection to determine the precise temporal relationship between the peripheral vascular effects and relief of pain; so this was not closely defined.

Results

8 patients were given tolazoline intravenously, and in 6 there was a dramatic cessation of attacks and inactivation of trigger areas, persisting for some hours; but in 2 there was little definite change. In 5 of these patients (3 responding and 2 resistant) further intravenous tests were possible (after at least 48 hours' interval) and gave similar results. Of the 2 showing no remission with intravenous therapy one was subsequently found to have an acoustic neuroma and the other showed smaller peripheral vascular responses than usual. The final case in the series was treated only orally and went into a remission for 4 months.

Illustrative Case-reports

Case 1.—A woman, aged 66, with tic affecting the second and third divisions of the right trigeminal nerve for 18 months. She had had numerous increasingly severe attacks daily for many weeks when first seen, most of them coming on spontaneously, trigger areas being inconstantly active. Her blood-pressure was 190/90 mm. Hg. Oral tolazoline 25 mg. t.d.s. produced subjective flushing and immediate reduction in the number and severity of her attacks, and at higher dosage (50 mg. t.d.s.) the attacks ceased entirely in 2 days, the patient remaining pain-free under this régime for nearly a week. At this point inert tablets were substituted, and the pains promptly recurred, though not to their usual extent before therapy. Restoration of oral tolazoline did not control these pains as completely as before (nor was the flushing response so definite); but a single 50-mg. intravenous dose produced marked vascular responses and immediate complete freedom lasting 3 days. Over the next 2 weeks limited pains reappeared on three occasions, and on each 50 mg. intravenously produced immediate relief lasting some days without further therapy. The pains did not return after the final injection, and the patient has remained pain-free for more than 2 years without further treatment.

Case 2.—A woman, aged 52, with tic affecting the second and third divisions of her right trigeminal nerve for 16 years, treated 14 years previously by alcohol injection. She had had, for 3 weeks, numerous severe attacks daily, triggered consistently from gum and lip. Blood-pressure 140/80 mm. Hg. Intravenous tolazoline 25 mg. produced flushing and dramatic relief of both spontaneous and provoked pains. Within 10 minutes food could be chewed on that side and dentures inserted for the first time in 3 weeks, the trigger areas being entirely inactive. However, 3 hours later slight tingling and soreness could be provoked from the trigger areas, and within 12 hours the pains had returned to some extent. Surgical intervention prevented further observations.

Case 3.—A woman, aged 51, with tic affecting the third division of her right trigeminal nerve for 8 years, treated on three occasions by alcohol injection. Numerous severe attacks had been occurring daily for 3 weeks, and oral trigger areas were acutely active. Blood-pressure 105/85 mm. Hg. An oral test dose of tolazoline 12·5 mg. was given, but the pains were so distressing that an intravenous injection was started without awaiting the oral response. 10 mg. intravenously unfortunately produced "bumping" in the chest, shivering, and numerous extra systoles, along with warming of the extremities. However, the attacks ceased, and within 25 minutes of the injection the trigger areas became inactive, and the face could be rubbed and food taken without incident for the first time in 2 weeks. The cardiac abnormalities subsided within 2 hours of the injection. Apart from one spon-