the tubercle bacillus. Against *Staphylococcus* and *Streptococcus* it has only slight activity, and against *Escherichia coli* none at all.

The active agent, whatever its nature, is very stable, for it is not completely destroyed even when autoclaved at a pressure of fifteen pounds for fifteen minutes. The filtrates from cultures kept at 28° C. for three months still show activity, and samples of the residue from ether extraction kept at 8° C. for the same length of time lose none of their potency.

Preliminary tests on mice have indicated that the crude extract is relatively non-toxic. Between 6 and 8 mgms can be tolerated by a mouse.

The experiments thus far have shown that there is an additional fungus of the Aspergillus group from the culture filtrate of which a substance can be obtained that definitely inhibits the growth of *M. tuberculosis in vitro*. It seems desirable, before attempting to establish the value of the antibiotic substance in experimental tuberculosis to obtain it in a more pure form. Studies are in progress to this end.

JOSEPH M. KURUNG
NEW YORK STATE HOSPITAL FOR INCIPIENT PULMONARY TUBERCULOSIS,
RAY BROOK, N. Y.

THE EFFECT OF CYSTEINE ON STREPTOMYCIN AND STREPTOTHRICIN

THE recent communication of Cavallito and Bailey[1] describing the complete or partial inactivation of a large number of antibiotics by cysteine prompted us to test the action of the latter on streptothricin and streptomycin concentrates.[2] It was found that streptomycin is inactivated by cysteine, whereas streptothricin is not. Streptomycin is also inactivated by 2-aminoethanethiol but not to any significant extent by thioglycollic acid. The inactivation experiments were carried out by adding neutral solutions of the organic sulfur compounds to known amounts of streptomycin or streptothricin dissolved in neutral phosphate buffer. After storing for several hours, the solutions were tested for antibiotic activity against *Bacillus subtilis* by the Oxford cup method.[3]

TABLE 1

EFFECT OF ORGANIC SULFUR COMPOUNDS ON ACTIVITY OF STREPTOMYCIN AND STREPTOTHRICIN SOLUTIONS

Concentration of organic sulfur compound (mg/ml)	Streptomycin assay (units/ml)	Streptothricin assay (units/ml)
Control (phosphate buffer)	49	52
Cysteine HCl		
0.13	39	..
0.25	29	..
0.50	4	42
1.00	0	..
2.50	..	52
5.00	..	54
2-Aminoethanethiol HCl		
0.50	12	40
2.50	4	57
5.00	0	59
Thioglycollic Acid		
0.50	31	41
2.50	39	40
3.00	26	30

[1] Cavallito and Bailey, SCIENCE, 100: 390, 1944.

[2] The activity of streptomycin concentrates varied from 80 units/mg to 600 units/mg; the activity of the streptothricin was 440 units/mg.

The difference in behavior of streptomycin and streptothricin toward cysteine is of interest and of particular significance in view of the microbiological similarity of the two substances.[4] With the use of cysteine one can not only differentiate the two antibiotics but estimate the relative amounts of each in mixtures of the two (Table 2).

TABLE 2

EFFECT OF CYSTEINE ON MIXTURES OF STREPTOMYCIN AND STREPTOTHRICIN

	Streptomycin added (units/ml)	Streptothricin added (units/ml)	Cysteine hydrochloride added (mg/ml)	Assayed activity (units/ml)
Solution I ...	25	25	0	45
Solution II ..	100	0	2	0
Solution III .	100	8	2	9
Solution IV .	100	15	2	17
Solution V ..	50	50	1.3	45

The cysteine inactivation of streptomycin can be reversed by iodine; presumably cystine is formed during this process. To our knowledge, this is the first recorded instance of reversible cysteine inactivation of an antibiotic. The regeneration of the antibiotic activity of streptomycin solutions containing cysteine was carried out by shaking such solutions with small amounts of a carbon tetrachloride solution of iodine until no further decolorization occurred. The solutions were aerated to remove the organic solvent before assay. The recovery of activity was quantitative.

The observations thus far made indicate that the inactivation of streptomycin is reversible, not a property of the sulfhydryl group alone, nor is it limited to cysteine. A mechanism postulating either a reversible chemical reaction between the two substances or a competitive effect on metabolic processes would be consistent with these observations.

R. DENKELWATER
M. A. COOK
M. TISHLER
RESEARCH LABORATORY,
MERCK AND COMPANY, INC.,
RAHWAY, N. J.

[3] Foster and Woodruff, *J. Bact.*, 45: 408–9 (1943).

[4] Waksman, Bugie and Schatz, *Proc. Staff Meetings Mayo Clinic*, 19: 537–548, 1944.

THE MECHANISM OF PAIN IN TRIGEMINAL NEURALGIA[1]

TRIGEMINAL neuralgia (tic douloureux), an episodic, recurrent, unilateral pain syndrome, occurs for the

most part in persons over fifty years of age who may have vascular disorders such as arteriosclerosis, arterial hypertension, migraine or Meniere's syndrome. Series of attacks may occur during periods of anxiety, fatigue, tension or stress.

Various conceptions of this disorder have been presented.[2,3] Recent observations indicate a relation between tic douloureux and defects in cranial circulation. Thus, surgical procedures designed to induce cranial vasodilatation have in two instances eliminated tic douloureux for an indefinite period.[4,5] The administration of vasodilator agents has reduced both the frequency and intensity of attacks of tic.[6] Beta methylcholine chloride was effective in one patient.[6] Also, attacks of tic pain have been temporarily abolished by the inhalation of amyl nitrite, and the continued administration of nicotinic acid by mouth had longer lasting effect in seven patients.[7] On the other hand, attacks of pain have been precipitated in patients with trigeminal neuralgia by vasoconstrictor agents, *i.e.*, by the administration of benzedrine sulphate and subcutaneous epinephrine.[7]

It has been demonstrated that during the initial phases of anoxia, nerve cells and axones may have their thresholds lowered or may discharge spontaneously.[8] Furthermore, high intensity pain may result from pressure ischemia of the Gasserian ganglion and adjacent sensory root and nerves.[9] These data, demonstrating that cranial vasodilatation can eliminate pain and that impaired circulation and vasoconstriction about the head can precipitate pain, suggested that this apparent relation of the cranial circulation to tic douloureux should be further investigated.

MATERIAL AND METHODS

Only those patients were used for investigation who had "trigger areas" which, when experimentally stimulated, predictably produced pain. These patients, for varying periods of years, had had paroxysmal attacks of moderate or high intensity, burning and aching pain, lasting from one to sixty seconds, occurring singly or in series, spontaneously and after stimulation of "trigger areas" and precipitated by chewing, talking, laughing, swallowing, shaving or drinking cold water. The pain was limited to an area of the face innervated by one or more divisions of the fifth cranial nerve.

The seven patients so selected were instructed to indicate, on stimulation of the "trigger area," the moment of onset, the duration and the intensity of each attack. Before the action of any agent was studied a suitable "control" was established by experimentally inducing attacks of pain at three-minute intervals for twenty-one to thirty minutes. A vasodilator agent was then administered for varying periods, the patient meanwhile being stimulated at two- or three-minute intervals on the "trigger area," which during the control period had predictably elicited pain. When an agent was repeatedly administered during a period of two weeks, the "trigger area" was stimulated at stated intervals each day. The effects of such stimulation were recorded in terms of occurrence, duration and intensity of pain. The action of four vasodilator agents, known also to have an effect on intracranial vessels, histamine,[10] amyl nitrite,[11] ten per cent. carbon dioxide[12] and nicotinic acid[13,14] was investigated. In these experiments blood pressure changes never exceeded 20 mm of mercury above or below its initial level.

RESULTS

In all the patients both spontaneous and experimentally induced attacks of pain were diminished in intensity and duration, or eliminated by at least one of the vasodilator agents used. In most patients each of the four vasodilator agents was effective in modifying or eliminating attacks of pain during administration and for a short time thereafter. The additive effect of two agents, *i.e.*, nicotinic acid and amyl nitrite, could be demonstrated. Placebo procedures and agents did not have a similar effect. The vasodilator agents induced their effects usually some minutes after administration, either intravenous or by inhalation. Four minutes after nicotinic acid was given intravenously, attacks could no longer be induced for a thirty-minute period. There was occasionally a time interval of as long as sixty minutes between the beginning of administration and the onset of a major effect on tic. In several instances during the repeated administration of nicotinic acid (200 mg orally every four hours for two weeks) recurrence

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[1] From the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College, New York, N. Y.

[2] W. E. Dandy, *Am. Jour. Surg.*, 24: 447, 1934.

[3] F. H. Lewy and F. C. Grant, *Arch. Neur. and Psychiat.*, 40: 1126, 1938.

[4] P. G. Flothow, *Northwest Medicine*, 29: 69, 1930.

[5] R. E. McKechnie, *Canadian Med. Asn. Jour.*, 28: 41, 1933.

[6] M. J. Cooper, *Am. Jour. Med. Sci.*, 195: 83, 1938.

[7] W. E. Adams and W. Robinson, *Lancet*, 2: 555, 1941.

[8] Detlev W. Bronk, *Proc. Asn. Nerv. and Ment. Dis.*, 18: 298, 1937.

[9] Harvey Cushing, *Am. Jour. Med. Sci.*, 160: 157, 1920.

[10] H. S. Forbes, H. G. Wolff and S. Cobb, *Am. Jour. Physiol.*, 89: 266, 1929.

[11] H. G. Wolff, *Arch. Neurol. and Psychiat.*, 22: 686, 1929.

[12] H. G. Wolff and W. G. Lennox, *Arch. Neurol. and Psychiat.*, 23: 1097, 1930.

[13] C. D. Aring, H. D. Ryder, E. Roseman, M. Rosenbaum and E. B. Ferris, *Arch. Neurol. and Psychiat.*, 46: 649, 1941.

[14] M. T. Moore, *Arch. Int. Med.*, 65: 1, 1940.

of mild attacks of pain occurred when the patients were startled or when they were markedly anxious. In every patient sustained sensations of burning and aching were experienced over one or more divisions of the fifth nerve on the side of the tic for the first two to six days of nicotinic acid administration. Thereafter, in all but one patient, pain was eliminated during the short period of observation. It would appear that the paresthesias were due to partial ischemia because they were eliminated by inhaling amyl nitrite. In three patients nicotinic acid was effective in reducing the frequency and intensity of attacks for the first two days of administration, but then for two to three days spontaneous attacks occurred more frequently and were more intense, and attacks could be more readily induced experimentally. Thereafter, attacks of pain were eliminated. Cessation of administration of nicotinic acid was followed by a return of the attacks of pain, both the spontaneous and the experimentally induced. In some of these patients the recurrence of tic douloureux was first noted during episodes of anxiety or sudden physical activity.

In one patient an attack of tic douloureux was initiated at the peak of the pressor response when an extremity was immersed in ice water.

None of the vasodilator agents used raised the pain threshold.

CONCEPT OF MECHANISM

It is inferred from these observations that tic douloureux is the result of paroxysmal ischemia of trigeminal structures. The site of the ischemia may be central or peripheral. However, it is difficult to conceive of a central defect so circumscribed as to affect the function of only the trigeminal cells without involving adjacent nuclei and tracts. Also, such a defect must be so discrete as to produce pain limited to one or another division of the fifth cranial nerve. A peripheral ischemia involving Gasserian ganglion sensory root and nerves, however, could result in such a circumscribed disturbance. It is of interest that the vascular bed of the Gasserian ganglion is relatively poor.[15, 16] It is therefore postulated that afferent stimuli (touch, pressure, cold, muscle, etc.) arising from the "trigger area" evoke reflex vasoconstriction either widespread or local, but involving the trigeminal structures. Such reflex vasoconstriction alone, or more commonly when superimposed upon structurally narrowed vessels, results in a sudden and critical increase in ischemia and pain. This postulate is compatible with the observation that blocking such efferents by procaine or alcohol minimizes or eliminates tic douloureux for shorter or longer periods.

The short paroxysm of pain (from one to sixty seconds) can be understood as the effect of periodic vasoconstriction. In patients who are spontaneously having a series of attacks an episode of vasoconstriction may be followed by a short interval of improved blood supply, when the next of a series of vasoconstrictor episodes may induce another attack. Such phases may follow each other for one or more hours.

The time lapse between the administration of a vasodilator agent and reduction of the pain may be explained by assuming a cumulative effect of prolonged meager blood supply to nerve or a refractive state of the local blood vessels. The hyperalgesia of the skin over the painful area that occasionally occurs after a paroxysm of pain is compatible with a state of lowered pain threshold accompanying nerve ischemia.[8, 17]

In those patients who, when startled, apprehensive or subjected to immersion of an extremity in ice water, experience spontaneous attacks of pain, vasoconstriction within the trigeminal structures may be part of a widespread vasoconstrictor reflex or a response to a blood-borne pressor substance. In those patients in whom vasodilator agents modify the syndrome only slightly, structural changes in the blood vessels may be sufficiently advanced to prevent adequate vasodilatation. Because of individual variations in temperament, in the degree and rate of structural vascular changes and in tolerance to vasodilator agents, inferences about long term therapy are not justified. This study is focussed on the mechanism of pain in trigeminal neuralgia.

RICHARD C. KARL
GEORGE E. PEABODY
HAROLD G. WOLFF

SCIENTIFIC APPARATUS AND LABORATORY METHODS

SYNTHETIC LATEX AS INJECTION MASS FOR CLOSED VESSELS

THE use of natural latex as injection mass has been adequately discussed,[1, 2, 3, 4] but to our knowledge nothing has been published concerning synthetic latexes, although at present these are more available.

Two synthetic latex compounds have been used in the present work for vascular injection of cadavers. Present findings are based upon results of injection

[15] H. S. Dunning and H. G. Wolff, *Jour. Comp. Neur.*, 67: 433, 1937.

[16] H. G. Wolff, *Proc. Assn. Res. Nerv. and Ment. Dis.*, 18: 29, 1937 (see p. 52).

[17] N. Bigelow, I. Harrison, H. Goodell and H. G. Wolff, *Jour. Clin. Invest.*, in press, July, 1945.

[1] L. Petrovits and Z. Szabó, *Anat. Anz.*, Bd. 89, pp. 34–45, 1939.