

ANTITUSSIVE MEDICATION
IN ASTHMA, EMPHYSEMA AND CHRONIC
BRONCHITIS

By

NATHAN E. SILBERT
U.S.A.

Cough, failure to raise inspissated mucus, wheezing and the general symptom syndrome associated with chronic bronchitis, pollen bronchitis, pollen asthma, chronic bronchial asthma, emphysema, and bronchiectasis have long been a vexing problem to the practitioner in all fields of medicine. The search for an effective antitussive medication which would not abolish the normal activity of the ciliary lining of the bronchial tree and yet afford the necessary free flow of secretion and the release of the heavier inspissated mucus has been the subject of cooperative study. Therapeutic agents which will minimize, if not completely relieve, the aggravating chronicity of coughs in the above-mentioned bronchial conditions has been under study for the past fifteen months.

The unique advantage of ion exchange resin complexes for prolonging the activity of various medications and for reducing their toxicity has been adequately demonstrated in previously published data. *Sensenbach* and *Hays* (1) have shown that the combination of a variety of therapeutically useful drugs with certain ion exchange resins to form resin complexes is capable of producing a drug having a predictable rate of release in the gastro-intestinal tract through the mechanism of ion exchange. *Becker* and *Swift* (2) showed that such resin complexes have a substantially lower toxicity than correspond-

ing soluble salts of the same drugs. *Deeb* and *Becker* (3) showed that such resin complexes produce sustained blood levels in experimental animals. *Chan* and *Hays* (4) applied these principles to the antitussive field and, in addition, showed in human subjects that the antitussive potency of dihydrocodeinone resin complex could be synergized by the addition of phenyltoloxamine resin complex. Their data were confirmed by *Townsend* (5) and by *Cass* and *Frederik* (6, 7). In previous studies (8, 9) this author delineated the clinical value of chlorpheniramine alone and with antitussive medications. This current study demonstrates the antitussive potency derived when combining and synergizing the resin complexes phenyltoloxamine, ephedrine, chlorpheniramine, and codeine.

The therapeutic use of resin complexes, especially dihydrocodeinone and phenyltoloxamine, has found wide acceptance among internists, pediatricians, allergists and general practitioners for the control of severe cough. This combination, however, was felt to be inadequate in controlling the more severe cough observed in bronchial asthma, chronic severe bronchitis and emphysema. Therefore, at the suggestion of the author, additional agents were added to enhance their individual and combined therapeutic values. This new formulation found good patient acceptance as well as producing a relatively high therapeutic index of usefulness.

Since the symptoms of cough, bronchospasm and wheezing are prime criteria in establishing a diagnosis of bronchial asthma, it may be of pertinent interest to briefly review some of the histopathologic findings in this clinical entity. "Narrowing of the bronchial lumen, shortening and contraction of the bronchi, and the accumulation of the inflammatory exudate is believed to produce the wheezing heard on expiration. This sound is one of the cardinal symptoms in bronchial asthma. However, foreign bodies—tuberculosis, cancer, and other types of bronchial obstruction—can also produce wheezing. Macroscopically the lungs are clear and distended and they fill the thoracic cage. They are usually pale and not easily collapsed. The bronchi, on the other hand are usually dilated,

filled with plugs of mucus, and inflammatory exudate. The wall is thickened and the mucus, as a rule, is inspissated, tenacious, and stringy. Curschmann's spirals, Charcot-Leyden crystals, eosinophils and pus cells may be present. There is inter- and intracellular edema of the mucosa, and the epithelium is infiltrated with eosinophils. The basement membrane and ciliated epithelium are thickened and hyaline can be observed. The bronchial glands are increased in size and filled with mucin; there are inflammatory changes, infiltration of eosinophils, hyperplasia and sacculatation (9).

Not since the studies of *Chen* and *Schmidt* (10) in 1925 when the ancient Chinese drug, Ma Huang, was introduced, has ephedrine in any form provided more sustained relief or controlled bronchospasm more effectively than has its resin complex. The utilization and clinical effectiveness of the sustained release modality is capable of delivering the medication in a predetermined controlled rate of release from the gastrointestinal tract into the circulatory system with good patient acceptance.

In a recent paper by *Friedlaender*, *Friedlaender* and *Hays* (11) it was reported: "Until recently little was known about the disposition and metabolism of ephedrine, and it was thought that the drug was excreted in the urine almost entirely unchanged. This was ascribed to the failure of monoamine oxidase to attack this compound (12). More recently, investigations of *Axelrod* (13) have shown that the fate of ephedrine varies considerably from one species to another. In the dog, which closely resembles man in the biotransformation of ephedrine, the drug is rapidly demethylated to norephedrine, which is a stable potent pressor agent, and it is likely that the activity of ephedrine is mediated to a considerable extent through this metabolite. Nor-ephedrine is relatively stable and is excreted in the urine unchanged. A minor route of metabolism is by hydroxylation of nor-ephedrine to yield the para-hydroxy derivative. In the rat, contrary to man, demethylation takes place slowly, and considerable amounts are excreted unchanged, or possibly as the hydroxylated derivative."

METHODS AND MATERIALS

This study reports the subjective benefits derived as well as the Lung Volume and Ventilation changes in 10 of the 103 patients studied. In the early phase of the work a variety of agents in resin form were evaluated and either eliminated or retained in the final formulation. During this phase of study the double-blind method was employed. Neither the author nor the patient knew the contents of the various formulations. Additions, deletions or retention of agents was determined on the basis of patient's subjective affirmation or denial of the medication. When side effects were observed to any disturbing degree in an appreciable number of patients using any given formulation, then that particular experimentally numbered preparation was reported to the compounding chemists and new additions or deletions were made in the laboratory without knowledge of the observing clinician. When a combination finally produced the most noticeable effective relief with the minimum of side effects, the formulation was made available to the clinician and the final study was commenced. In only one instance was the clinician aware of formulation prior to study and this was in the case of determining which resin should be used with regard to the codeine derivative. Final determination clinically substantiated that the resin complex of 10 mg. of codeine per 5 ml. dose was equally as effective as 1.6 mg. of the resin complex of dihydrocodeinone.

TABLE 1
Distribution of patients by age and sex.

Age Groups	Males	Females	Totals
Children, mean average age of 7 years, 9 months	19	13	32
Adults, mean average age of 41 years, 2 months	49	22	71
Totals	68	35	103

Therefore, the final formulation for the study upon which this report is based consisted of:

Codeine	10 mg.
Phenyltoloxamine	5 mg.
Ephedrine	25 mg.
Chlorpheniramine	3 mg.

all as resin complexes, plus guaiacol carbonate 20 mg. combined in a suitable base.

The dosage schedule seen in Table 2 was the protocol observed throughout the study, excepting those notations made in the discussion of side effects.

TABLE 2
Dosage schedule.

Age, Groups	Initial Dosage Schedule
Infants and Children to age 3	20 drops b.i.d.
Children, ages 4 to 9	$\frac{1}{2}$ teaspoon b.i.d.
Children, ages 10 to 14	$\frac{3}{4}$ teaspoon b.i.d.
All patients over age 14	1 teaspoon b.i.d.

SIDE EFFECTS

These consisted of extreme drowsiness in a very small number of the patients. In less than 8 per cent of the study group, dryness of the throat and upper respiratory tract was observed, as well as extreme jittery sensations one to two hours after medication. Whenever excessive coughing or wheezing was more than usual in any respective patient, dosage was doubled and well tolerated with good results. In seven patients, however, extreme nervous irritability followed such increased dosages and the dose had to be reduced. Twenty-five per cent of the patients experienced insomnia. This high percentage was reduced to three per cent when the patients were advised to take the night-time dose not later than two hours before retiring.

TABLE 3

Function	Definition	Predicted
<i>A. Lung volumes (Pulmonet study).</i>		
Inspiratory Capacity IC	The maximal volume of air that can be inspired from end of normal expiration.	2500-3600 cc.
Expiratory Reserve Volume ERV	The maximal volume of air that can be expired at end of normal expiration.	1000-1500 cc.
Inspiratory Reserve Volume IRV	The maximal volume of air that can be inspired at end of normal inspiration.	2000-3000 cc.
Vital Capacity VC	The maximal volume that can be expired after maximal inspiration.	3500-5000 cc.
Residual Volume RV	The volume of gas in the lungs at end of maximal expiration.	1000-1500 cc.
Functional Residual Capacity FRC	The volume of gas in the lungs at end of ordinary expiration.	2000-3000 cc.
Total Lung Capacity TLC	The volume of gas in the lungs at end of maximal inspiration.	4500-6500 cc.
RV/TLC	The residual volume divided by total lung capacity times 100.	20-30 %

B. Ventilation studies (Pulmonet study).

Tidal Volume TV	The volume of one inspiration or expiration during normal breathing, or any level of physical activity.	600-800 cc.
--------------------	---	-------------

TABLE 3 (cont.)

Function	Definition	Predicted
Frequency/minute F	Breathing rate.	11-14 min.
Minute Volume MV	The volume of air moved into the lung in one minute while the patient is at rest.	8-12 L/min.
Ventilation Factor VF	Average of 3 sec. VC, MBC, and RV/TLC, each expressed as % observed over predicted.	100 %
Helium Washout HeW	Time required for He % to equalize between spirometer and patient.	2-4 min.

C. Mechanics of breathing (Pulmometer study).

Maximal Breathing Capacity MBC	Maximal amount of air which can be moved in and out of the lungs per unit of time, 1 minute	90-170 L.
Timed Vital Capacity TVC	Maximal volume that can be expired in 1 second after maximal inspiration.	80-83 % VC/ 1 sec.
Air Velocity Index AVI	% predicted MBC divided by % predicted VC.	100 %

D. Alveolar gases (Campbell and Howell method).

PCO ₂ Concentration	5.3 % or 40 mm. Hg
--------------------------------	-----------------------

Each value corrected for body temperature, pressure, and saturation with water vapor.

RESULTS

In order to determine results, subjective response had to be considered. The double-blind phase of the study proved the efficacy of antitussive medication in the treatment of bronchial asthma and in those patients in whom emphysema was present in addition to or complicating the primary asthmatic state. Objective data included those findings determined by spirometric methods and mechanics of breathing studies. Lung volumes and ventilation changes were observed in 10 of the total patient group. Table 3 is included merely to refresh the reader in the elementary physiology concerned. Table 4 demonstrates the measurements observed before and after treatment with the final antitussive formulation stated above. The changes are self-explanatory. Table 5 presents the results of the entire study group. Table 6 demonstrates the actual tracings obtained before and after therapy.

TABLE 5
Diagnostic classification and therapeutic results.

Group	Diagnosis	No. of Patients	Degree of Relief			
			Excellent	Good	Fair	None
I	Bronchial Asthma (Atopic)	47	30-63.8%	8-17%	3-6.2%	6-12.5%
II	Bronchial Asthma (Non-Atopic)	13	8-61.5%	2-15.3%	1-7.6%	2-15.3%
III	Bronchial Asthma with Emphysema:					
	1. Atopic	18	10-55.5%	4-22.2%	1-5.5%	3-16.6%
	2. Non-Atopic	3	1-33.3%	1-33.3%	1-33.3%	0
IV	Chronic Bronchitis with intermittent episodes of chronic nasal allergy	22	14-63.6%	6-27.2%	1-4.5%	1-4.5%
Totals		103	63-61.1%	21-20.3%	7-6.7%	12-11.6%

TABLE 4
Ventilation and volume findings.

Name	Age	Sex	Therapy	TV	FRC	TLC	IC	IRV	ERV	RV	VC	RV/TLC	RF	MV	HeW
				Tidal volume cc.	Functi- onal residual capa- city cc.	Total lung capa- city cc.	Inspira- tory capa- city cc.	Inspira- tory reserve volume cc.	Expira- tory reserve volume cc.	Resi- dual volume cc.	Vital capa- city cc.	Residual volume ratio to total lung capacity	Respi- ratory fre- quency pr. minute	Minute volume l	Helium washout minute
H.R.	75	M	Before Rx Two weeks after Rx	490	4400	5030	1044	554	683	3717	1692	73 %	25	24.5	7
B.D.	55	F	Before Rx Three weeks after Rx	555	4700	5660	1140	585	1300	2400	2440	43 %	20	22.2	5
				916	2745	4510	1765	850	33	2712	1830	59 %	10	18.3	4½
				818	2367	6179	2812	1995	229	2138	3051	35 %	10	16.4	4
D.P.	63	F	Before Rx One week after Rx	294	2311	3063	752	458	65	2246	883	73 %	26	15.3	4
				327	2342	3323	981	654	523	1810	1472	54 %	28	18.3	4
F.D.	58	M	Before Rx Three weeks after Rx	1330	N.A.*	N.A.*	2275	945	553	N.A.*	2860	N.A.*	21	29.2	4
				1302	3500	5782	2282	980	890	2610	2995	44 %	22	57.0	3

M.S.	49	F	Before Rx Four weeks after Rx	916	2335	3741	1406	491	200	2135	2100	57 %	13	23.8	5
				785	2932	4829	1897	1112	N.A.*	N.A.*	1500	N.A.*	17	27.0	4
M.R.	27	F	Before Rx Three weeks after Rx	732	3799	5414	1615	883	556	3243	2191	61 %	16	23.5	4
				981	3284	4984	1700	719	916	2368	2616	47 %	8		7
E.J.	57	M	Before Rx Four weeks after Rx	818	4430	7600	3170	2350	556	3874	3728	51 %	16	26.0	3
				850	2627	5897	3270	2420	360	2267	3630	38 %	16	27.0	3
J.R.	20	M	Before Rx Five weeks after Rx	588	2880	5136	2256	1668	1341	1539	3597	30 %	23	27.0	3
				589	3507	5600	2093	1504	1890	1611	3989	29 %	25	29.4	3 1/2
F.H.	61	F	Before Rx Five weeks after Rx	425	1730	3561	1831	1405	N.A.*	1959	1602	55 %	22	17.0	8
				458	2249	3851	1602	1144	165	2084	2518	53 %	25	23.0	3 1/2
E.E.	45	M	Before Rx One week after Rx	654	2951	4553	1602	948	685	2266	2287	50 %	14	18.3	5
				654	2230	4388	2158	1505	229	2001	2387	45 %	14	18.3	3

* Not Available.

TABLE 6
Representative patient tracings.

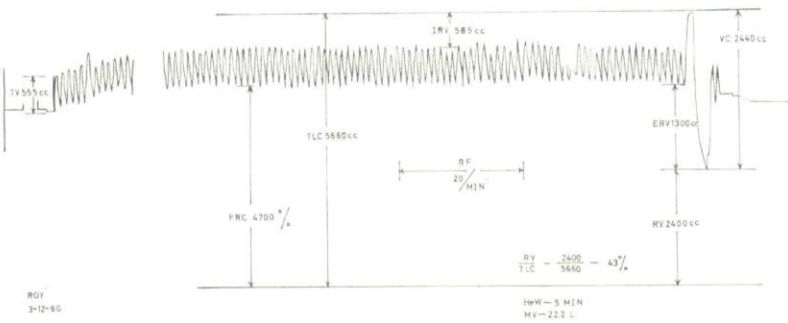
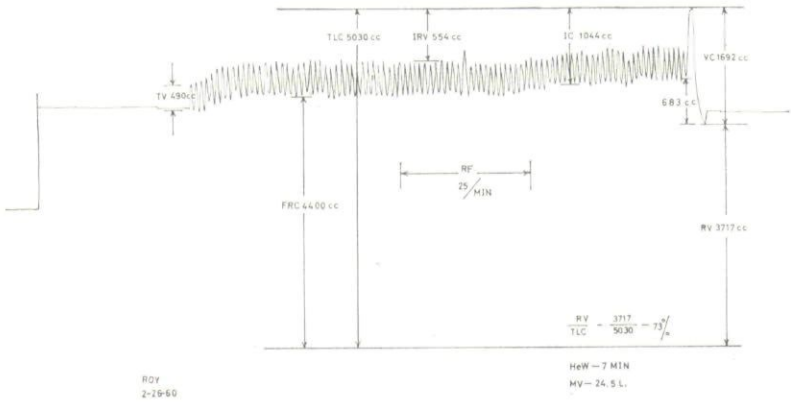


TABLE 6
Representative patient tracings.

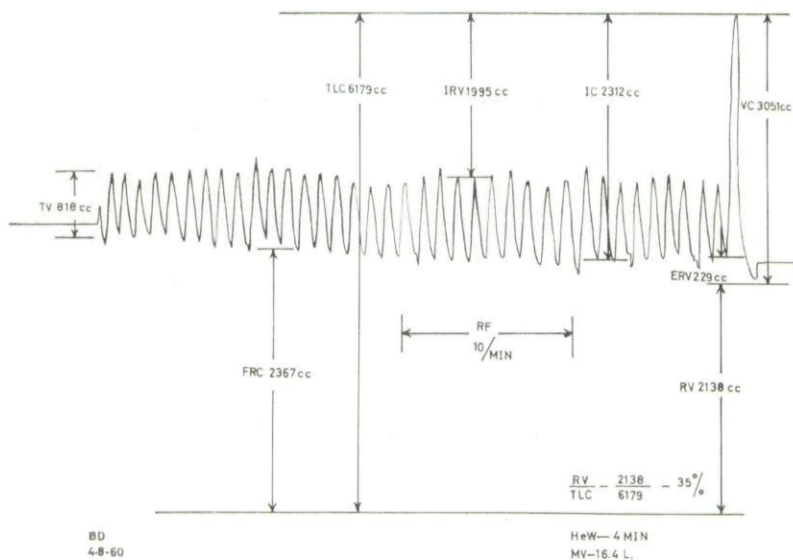
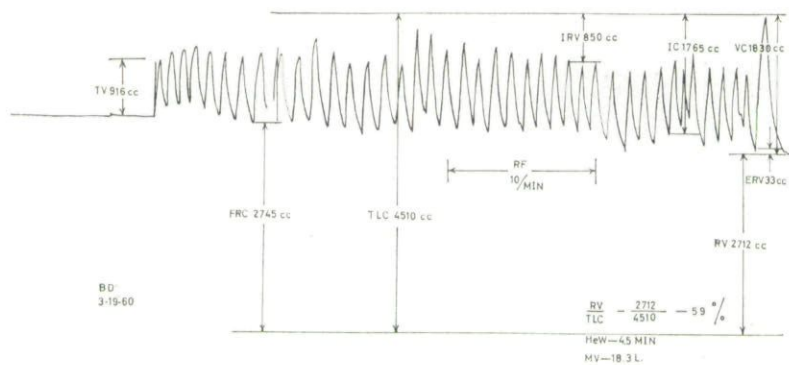


TABLE 6
Representative patient tracings.

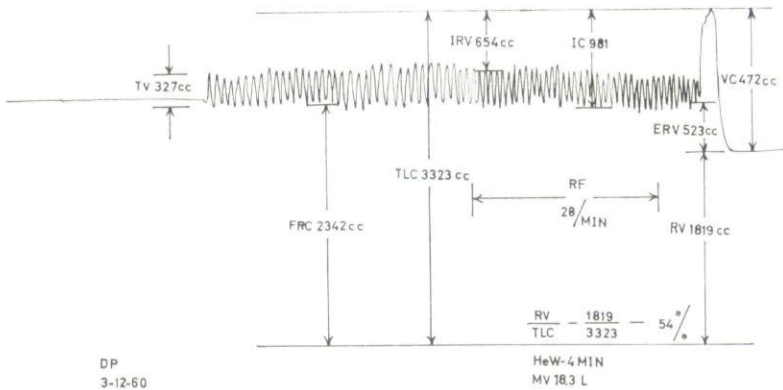
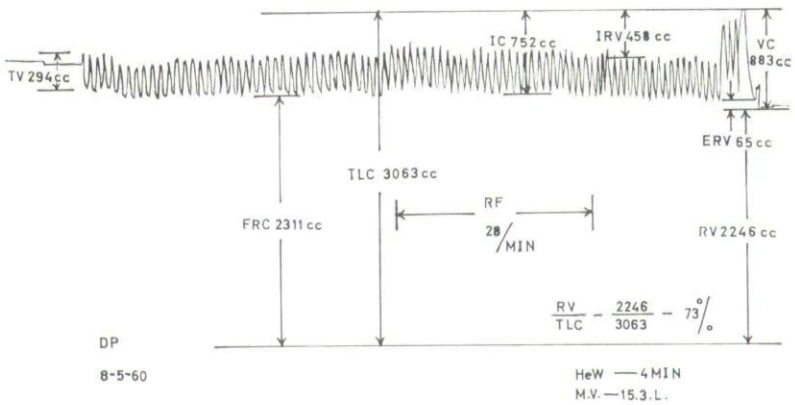
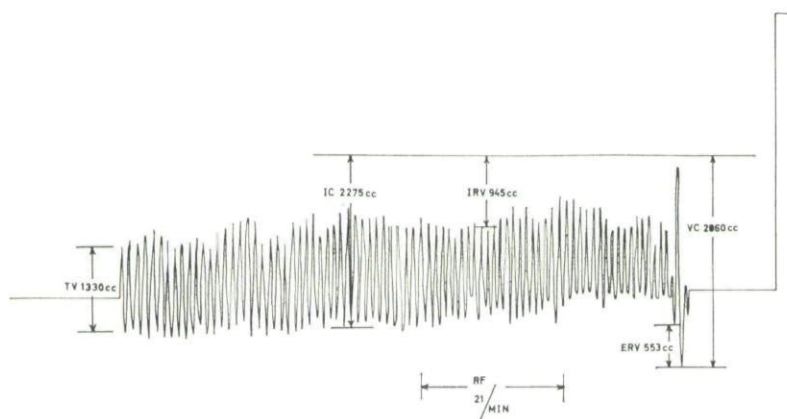
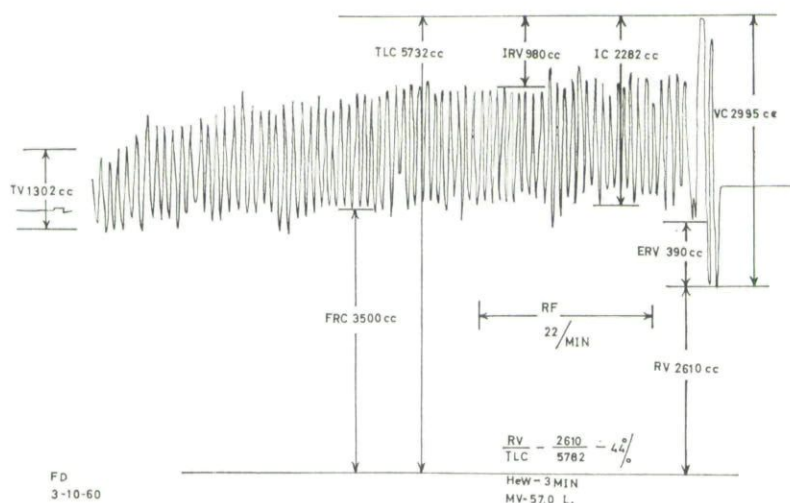


TABLE 6
Representative patient tracings.



FD
2-19-60

He W—4 MIN
MV—29.2 L.



FD
3-10-60

$\frac{RV}{TLC} = \frac{2610}{5782} = 45\%$
He W—3 MIN
MV—57.0 L.

TABLE 6
Representative patient tracings.

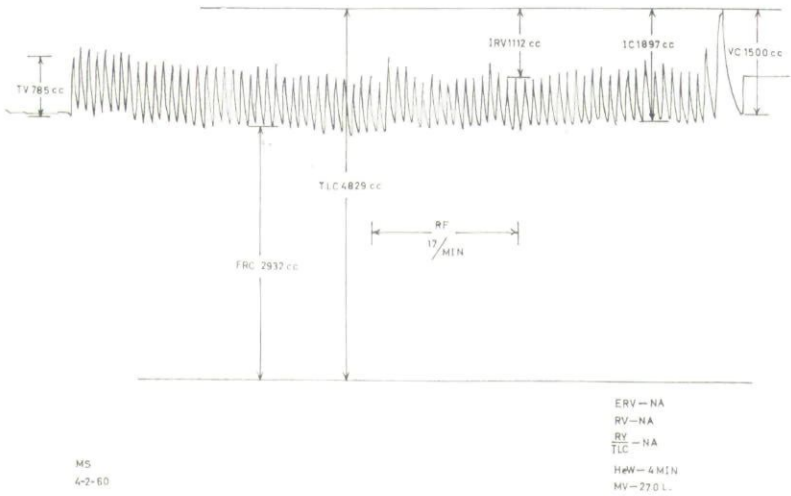
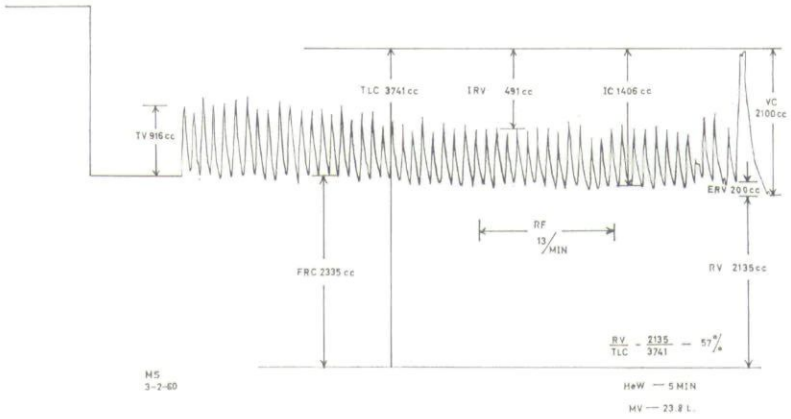


TABLE 6
Representative patient tracings.

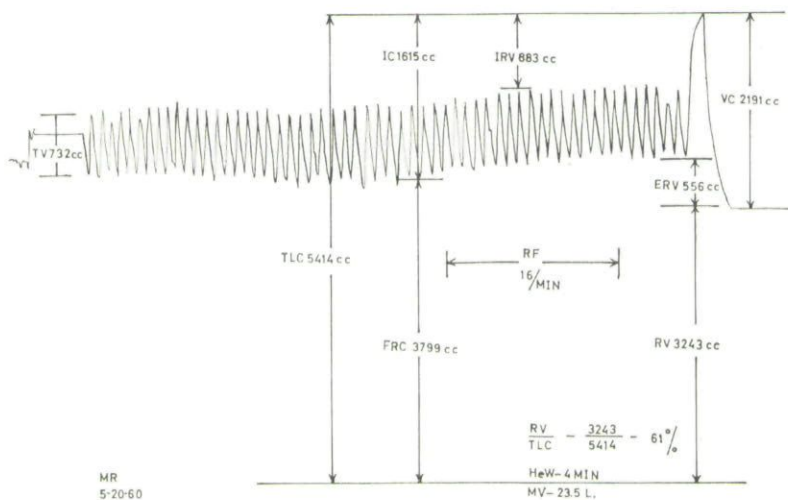
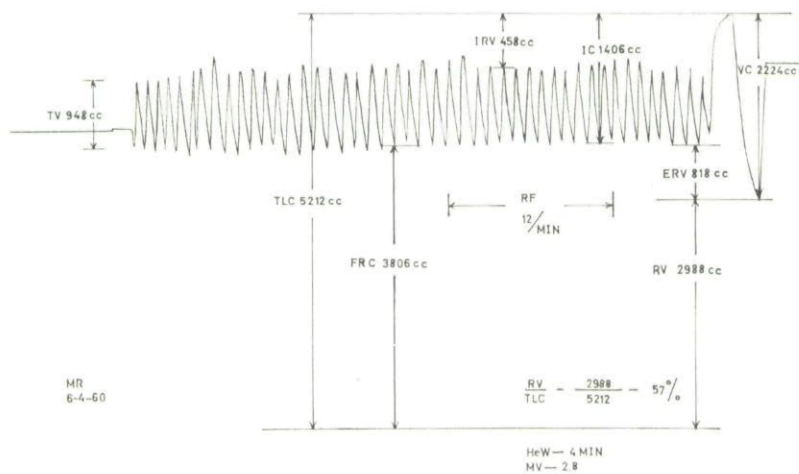


TABLE 6
Representative patient tracings.

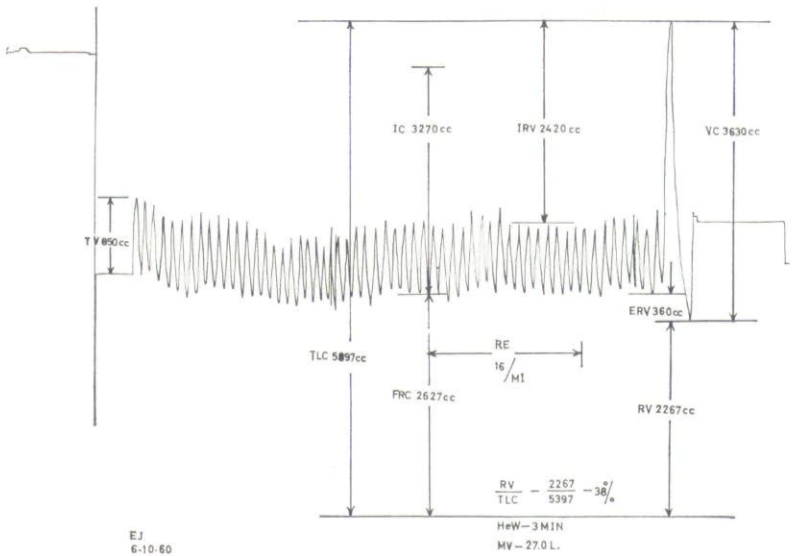
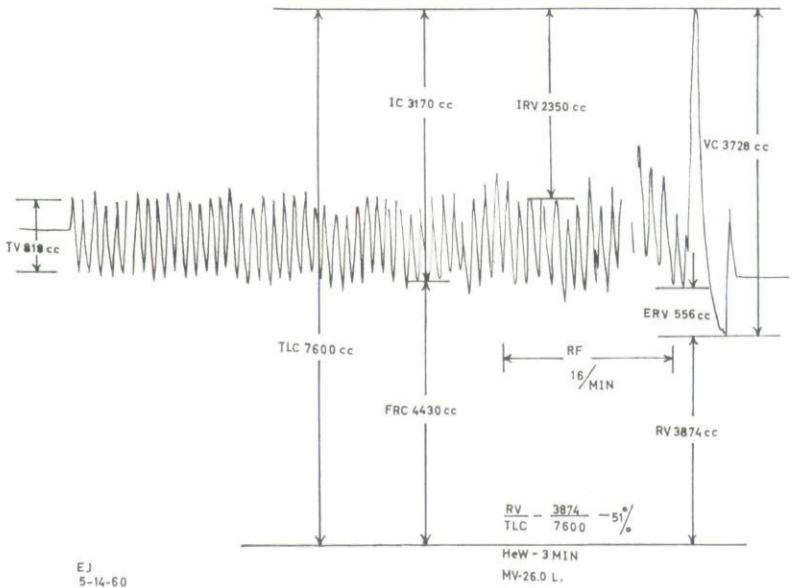


TABLE 6
Representative patient tracings.

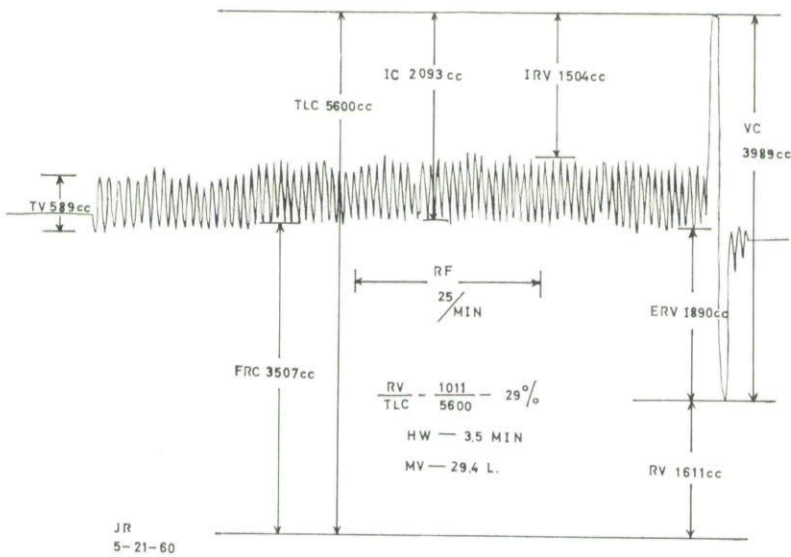
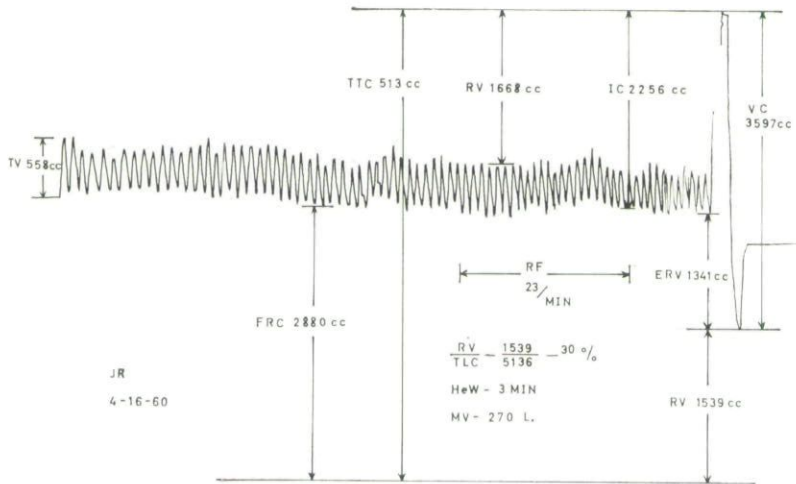


TABLE 6
Representative patient tracings.

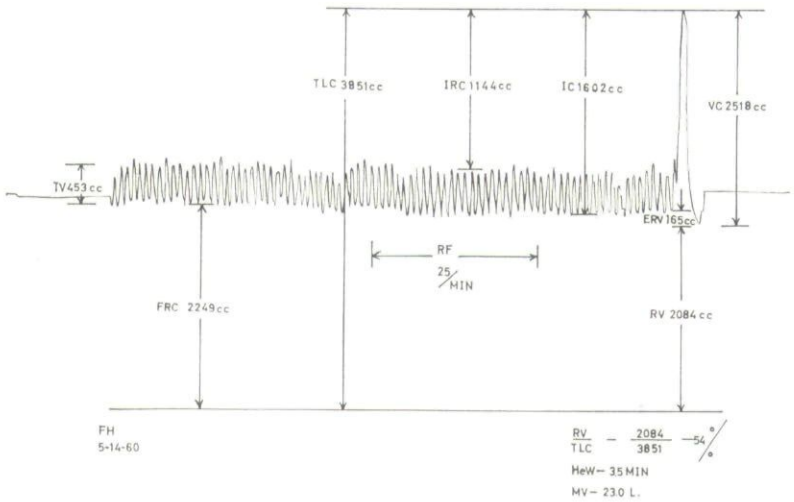
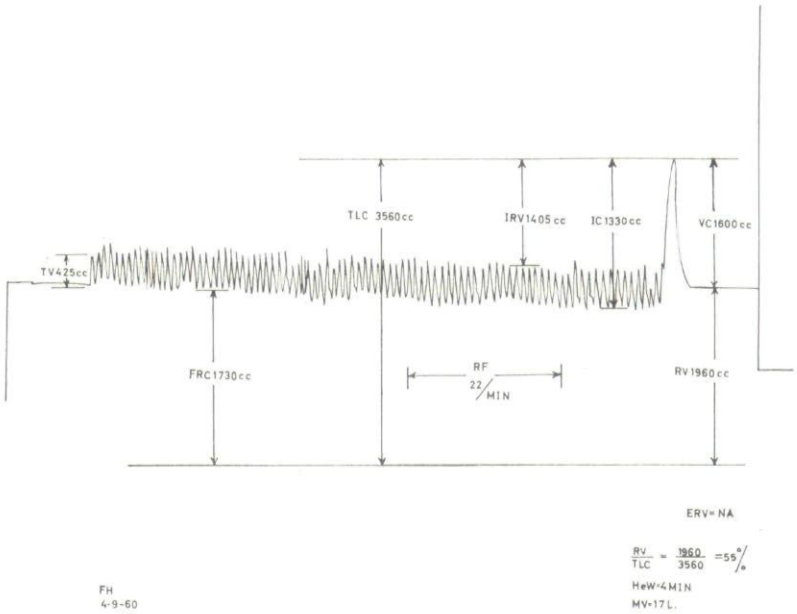
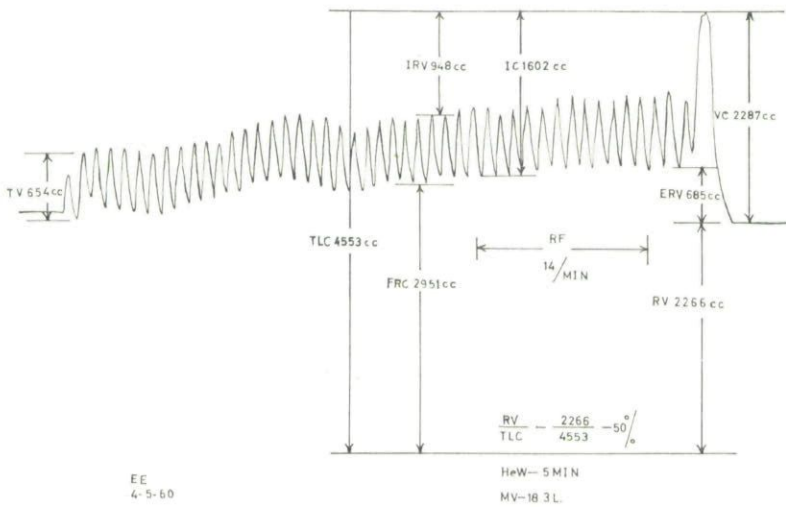
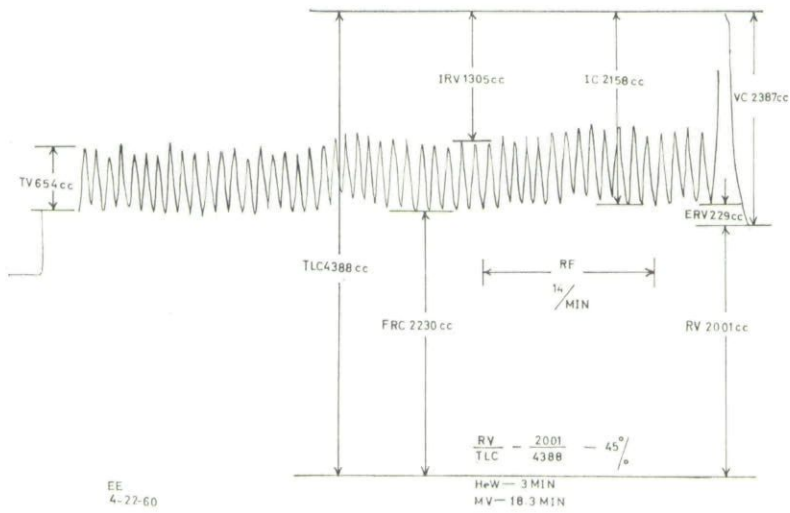


TABLE 6
Representative patient tracings.



SUMMARY AND CONCLUSIONS

A fifteen-month study of an antitussive medication, consisting of codeine, phenyltoloxamine, chlorpheniramine and ephedrine as resin complexes, plus guaicol carbonate, demonstrates both objective and subjective clinical effectiveness. The medication afforded relief from annoying coughs and wheezing in cases of chronic bronchitis, allergic bronchitis, bronchial asthma, and emphysema in patients of all ages. Patient acceptance of the drug was impressive.

ACKNOWLEDGMENT

The author wishes to express his appreciation to Mr. Tauno Tamminen, B.S.E., Ed. M., for his assistance in the Lung Volumes, Mechanics of Breathing and Ventilation Studies and to Mr. Bernard A. Becker of the R. J. Strassenburgh Company for their generous cooperation in supplying all of the various formulations used in this study.

Author's address:

214 Ocean Street, Lynn, Mass. U.S.A.

REFERENCES

1. *Sensenbach, W. E. & Hays, E. E.*: "Ion Exchange Resins in the Formulation of Sustained Release Medication", submitted to The American Journal of the Medical Sciences.
2. *Becker, B. A. & Swift, J. G.*: "Effective Reduction of the Acute Toxicity of Certain Pharmacologic Agents by Use of Synthetic Ion Exchange Resins", *Toxicology and Applied Pharmacology*. 1, 42-54, 1959.
3. *Deeb, G. & Becker, B. A.*: "Absorption of Sustained-Release Oral Amphetamine Preparations in the Rat", *Toxicology and Applied Pharmacology*. 2, 410-417, 1960.
4. *Chan, Y. T. & Hays, E. E.*: "A Resin Complex for Prolonged Antitussive Effects", *The American Journal of the Medical Sciences*. 234, 207-212, 1957.
5. *Townsend, E. H.*: "Prolonged Cough Suppression", *New England Journal of Medicine*. 258, 63-67, 1958.
6. *Cass, L. J. & Frederik, W. S.*: "The Clinical Evaluation of Sustained Release Antitussives", *Annals of Internal Medicine*. 49, 151-160, 1958.

7. *R. J. Strassenburgh Company*, Personal Communication.
8. *Silbert, N. E.*: "Evaluation of Chlor-Trimeton Maleate in Hay Fever and a Variety of Allergic Diseases, *New England Journal of Medicine*. 242, 931, 1950.
9. *Silbert, N. E.*: "An Introduction to the Subject of Bronchial Asthma", *The Journal of the American Geriatrics Society*. 6, 27-32, 1958.
10. *Chen, K. H. & Schmidt, K. F.*: "Chinese Materia Medica: Ma Huang", *China Medical Journal*. 39, 982-989, 1925.
11. *Friedlaender, S., Friedlaender, A. S. & Hays, E. E.*: "Prolonging the Effect of Ephedrine and Other Anti-Allergic Drugs by Beans of Ion-Exchange Resin Complexes", presented at the Sixteenth Annual Meeting, American Academy of Allergy, Hollywood Beach Hotel, Hollywood, Florida, January 1960.
12. *Richter, D.*: "Elimination of Amines in Man", *Biochemistry Journal*. 32, 1763-1769, 1938.
13. *Axelrod, J.*: "Metabolism of Ephedrine and other Sympathomimetic Amines, *Physiology Review*. 39, 751-776, 1959.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.