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University of Minnesota Hospitals
and
Minnesota Medical Foundation

Isuprel, A New Bronchodilating Agent

Volume XIX | Friday, May 7, 1948 | Number 25

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
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INDEX

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

May 10 - May 15, 1948

No. 202

Monday, May 10

9:00 - 9:50	Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
9:00 - 10:50	Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns' Quarters, U. H.
9:15 -	Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.
10:00 - 12:00	Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.
11:00 - 11:50	Physical Medicine Conference; Nodules in the Subcutaneous Tissues and Muscles; Benjamin Clawson; E-101, U. H.
11:00 - 11:50	Roentgenology-Medicine Conference; Staff; Veterans' Hospital.
11:00 - 12:00	Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.
12:15 - 1:20	Obstetrics and Gynecology Journal Club; M-435, U. H.
12:50 - 1:20	Pathology Seminar; Subject to be announced; H. E. Michelson; 104 I. A.
12:00 - 1:00	Physiology Seminar; Phenolases and Cellular Oxidation; Mark Graubard; 129 M. H.
12:30 - 1:50	Surgery Grand Rounds; A. A. Zierold, Clarence Dennis and Staff; Minneapolis General Hospital.
1:30 - 2:30	Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
2:00 - 3:00	Surgery Problem Case Conference; C. Dennis and Staff; Small Class Room, General Hospital.
4:00 - 5:00	Pediatric Seminar; Kala-azar; HuaK'ang Chow; 6th Floor Seminar Room, U. H.
4:00 - 5:00	School of Public Health Seminar; Subject to be announced; William Roemich; 113 MeS.
5:00 - 6:00	Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

Tuesday, May 11

8:30 - 10:20 Surgery Seminar; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.

9:00 - 9:50 Roentgenology Pediatrics Conference; L. G Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans' Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. B. Visscher; Eustis Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; J. Richards Aurelius and Staff of Ancker Hospital; Powell Hall Amphitheater.

Wednesday, May 12

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M 515, U. H.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Bleeding Duodenal Ulcer; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Infectious Disease Rounds; Todd Amphitheater, General Hospital, Veterans' Hospital.

Thursday, May 13

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-109, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans' Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, General Hospital.

12:00 - 12:50 Physiological Chemistry Seminar; Secretion of HCl by the Stomach; Rex Neihof; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Value and Methods for Calculating Volume of the Gall Bladder; J. S. Summers; Powell Hall Amphitheater, U. H.

Friday, May 14

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Subphrenic Abscess; Arnold J. Kremen and Donald Ferguson; New Powell Hall Amphitheater.

12:00 - 1:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Class Room.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, May 15

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U. H.

8:00 - 9:30 Psychiatry and Neurology Grand Rounds; Staff; Veterans' Hospital.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

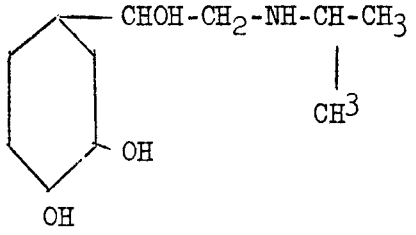
10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 12:20 Anatomy Seminar; Osteoblasts and osteoclasts in bone marrow smears, Dorothy Sundberg; Effects of sex hormones upon the embryonic development of the reproductive organs, Rachel Fralick; 226 I. A.

II. ISUPREL, A NEW BRONCHODILATING AGENT

Ellis N. Cohen
Frederick Van Bergen

The early work of the German experimenters Loewi and Meyer[1], as well as that of the English investigators Dakin[2], and Barger and Dale[3] showed the sympathomimetic action of a series of N alkyl homologues of epinephrine including the compound isopropyl adrenalin.



(Isopropyl Adrenalin - "Isuprel")

This compound had previously been synthesized under the direction of Dr. Scheuing in the chemical laboratories of C. H. Boehringer and Son, Igleheim, Germany[4]. Konzett concluded that the bronchodilator activity of isopropyl adrenalin was ten times that of adrenalin alone.

In 1947 Lands et al[5,6] studied the vasopressor and bronchodilator actions of isopropyl adrenalin and related compounds. In studying the carotid blood pressure in anesthetized dogs, they found that as alkyl substitution took place on the nitrogen atom, there was a reduction in pressor potency, and that with substitution of groups larger than methyl, the compounds gave a depressor effect. In perfused guinea pig lung utilizing a modified technique of Tainter[7] and Sollman, he further studied the bronchodilating action of this compound. He found the flow before histamine to measure 56 cc. per minute and after histamine the flow was 28 cc. per minute. When histamine and isopropyl adrenalin were used together, the flow was 54 cc. per minute.

In 1947 Siegmund[8] et al studied artificial asthma produced in the guinea pig by a fine histamine spray. They found that intraperitoneal injection of isopropyl adrenalin delayed onset or actually prevented symptoms of asthma in the guinea pig.

With the release for clinical investigation of isopropyl adrenalin under the trade name of "Isuprel" by Winthrop Stearns Company, we decided to undertake a clinical and laboratory study of this compound with special emphasis on its bronchodilating action. Most bronchodilating substances have either a strong vasopressor action or other undesirable concomitant side reactions. On the basis of favorable preliminary reports, we thought it worthwhile comparing "Isuprel" with other compounds commonly in use for this purpose. We were most interested in a drug which would produce maximum bronchodilation under general anesthesia and yet have little effect on pulse or blood pressure.

It was necessary to use all drugs by the intravenous route since this is the channel most accessible to the anesthesiologist who needs both an immediate and full response. There were no reports available as to the therapeutic dosage of "Isuprel" given intravenously, but after preliminary investigation we found .001 mg. per kilo given intravenously to the dog to be an adequate amount. Accordingly this dose was utilized in all our animal studies.

Bronchospasm under general anesthesia represents a considerable problem. Known asthmatics must be conceded as a major anesthetic risk. With the overwhelming acceptance of Baird's pentothal-curare mixture at our hospitals, there remained but two contraindications to its use, i.e., asthma and myasthenia gravis[9,10]. If we could find a drug which would control the former hazard, it should prove a definite advance in anesthesia and especially in pentothal-curare anesthesia.

Blood Pressure Studies

The animals, unpremedicated mongrel dogs, were anesthetized with pentothal-curare mixture[10], an endotracheal tube inserted, and a mixture of 500 cc.

oxygen and 500 cc. nitrous oxide with overflow given by inhalation. The plane of anesthesia was maintained at a level where the animal just tolerated the endotracheal tube, since this closely simulated our clinical pentothal-curare, nitrous oxide anesthesia. The carotid artery was then cannulated, and blood pressure studies were carried out with a recording kymograph. Our results are tabulated in the following chart:

Drug	Dose in mg. per kilo	Initial B.P.	Initial Pulse	Maximum B.P.	Maximum Pulse	Minimum B.P.	Minimum Pulse	Minutes to return to normal
Ephed. Sulf.	1	94/84	82	144/108	88	94/80	60	52
Adren. HCl	.01	98/80	88	172/130	112	98/80	88	12
Amino-phylline	7.5	98/78	88	112/90	140	40/32	88	16
Butanefrine	.2	94/84	74	94/84	74	86/76	60	5
Benadryl	.5	110/102	100	124/118	140	110/102	100	12
Isuprel	.001	96/86	96	102/88	100	96/86	96	8

It is thus apparent that both adrenalin and ephedrine evoke marked vasopressor responses, while aminophylline produces both tachycardia and a marked temporary fall in blood pressure. Benadryl causes a slight vasopressor action and Butanefrine some vasodepressor effect. "Isuprel" alone, given in dosage of .001 mg. per kilo, apparently has little effect on the cardiovascular system of the dog.

Bronchodilation Studies

Since our first study showed that "Isuprel" given intravenously has little effect on blood pressure or pulse, it was now necessary to compare its effects on the bronchi with other agents. We wanted a technique which would both utilize the intact animal and give direct measurements of bronchial caliber. It was found that this could best be accomplished as follows.

With the animal anesthetized, the carotid artery was isolated and cannulated. A number 10 bronchoscope was then introduced and a small fiber catheter with attached cuff inserted through the bronchoscope under direct vision into a subdivision of the dog's right or left main stem bronchus. This usually represented a bronchus of small caliber since the dog's long trachea divides into relatively small right and left main stem bronchi and even smaller subdivisions. A larger bore 10 mm. tube with an inflatable cuff was then introduced into the trachea after the bronchoscope was removed. This allowed the endobronchial catheter to lie along side the tracheal catheter in the trachea and to emerge to the outside. The endobronchial catheter composed of a number six ureteral catheter with polythene tubing leading to the inflatable cuff, was left open to the atmosphere in order to maintain equalized pressures in the segment of lung supplied by that subdivision of bronchus. The inflatable cuffs were connected to water manometers and expanded to a positive pressure of six centimeters. With the cuffs slightly inflated on both endobronchial and endotracheal tubes, we produced bronchoconstriction in a series of dogs with mecholyl and then measured the release of spasm with various bronchodilating substances.

We found the effects of histamine in producing bronchoconstriction to be irregular, and dosage large enough to cause consistent bronchoconstriction also pro-

duced precipitous falls in blood pressure. For this reason histamine was not used in this study. Mecholyl .01 mg. per kilo was found to be the most effective agent in producing bronchoconstriction in the dog. Difficult breathing usually lasted twelve to fifteen minutes if unchecked. Changes in the lumen of the bronchus or trachea as it dilated or constricted were reflected in terms of rise or fall of the water column in the manometers. The latter responded directly to pressure exerted or released on the cuffs. As the bronchus constricted, the cuff constricted with it. Responses of the animals to mecholyl were slightly variable, however, we attempted to give the release substance at the peak of mecholyl effect. Measurements on the water manometer were recorded as the average reading of that on inspiration and expiration. (See pages 428-429)

At attempt was now made to calibrate the changes in water pressure as recorded on the manometer and to correlate them in terms of actual change in diameter of the bronchus or trachea. In order to do this a cylinder was constructed with screw adjustment which would produce a decreasing or expanding concentric circle. The endobronchial and endotracheal tubes used in our experiments were then inserted into this metal cylinder, and the cuffs slightly inflated. As the diameter of the cylinder decreased, a constriction of the cuff occurred, and we obtained a rise on the manometer scale similar to that in the experiments. A one centimeter rise on the scale measured a 15% decrease in diameter of the cylinder when the endobronchial tube was used. However, a one centimeter rise on the same scale represented only a 4% decrease in the diameter of the tracheal tube cuff. Therefore it follows that most marked proportionate changes in constriction and dilation take place in the smaller bronchi and very little in the trachea itself. It is also apparent that "Isuprel", adrenalin, and aminophilline are the most effective and rapid bronchodilators, even dilating past the resting diameter of the trachea or bronchus.

Toxic Action of "Isuprel"

From the previous experiments it appeared that we had an effective bronchodilating agent and one which produced little effect on the cardiovascular system of the dog. It was then necessary to determine the relative toxicity of this compound.

An animal was anesthetized as previously described, a tracheal tube inserted, and the carotid artery cannulated. An electrocardiograph machine was then connected and we proceeded to give the animal first a therapeutic and then ever increasing doses of intravenous "Isuprel". Our first therapeutic dose (.001 mg. kilo) showed no effect on the E.K.G. This dose was then increased by increments until we had given a total of 61.36 mg. intravenously to a 15 kilo dog in a period of less than fourteen minutes. As will be noted in the subsequent chart, a marked tachycardia of 230 beats per minute developed and blood pressure fell to 62/56. However, even with this large dose, 4086 times our therapeutic intravenous dose, we were unable to drop the blood pressure past that level. Furthermore, even at this extreme heart rate, the electrocardiogram recorded no changes in rhythm of the heart. The only changes in the recording of the electrocardiogram were extreme tachycardia, ST depression, and an inverted or diphasic T wave. The last two changes may be interpreted as coronary insufficiency secondary to the extreme heart rate. Our findings are summarized in the following chart. (p.427)

From this chart it is noted that after one hour the animal's pressure had returned to normal levels even though its heart rate was still rapid at 150 per minute. It had evidently been able to tolerate temporarily over 4,000 times the therapeutic dose. This animal lived for another twelve hours, however never did recover full consciousness. The autopsy revealed no gross organ changes. Microscopic sections of the liver, kidney, adrenal, and heart muscle were all negative. Microscopic sections of the brain, however, showed changes suggestive of cerebral anemia or anoxia. There were small petechiae and areas of vascular congestion, as well as scattered nerve cell changes and hyperchromic distorted cells. These changes are probably entirely secondary to lack of an adequate blood supply to the brain from a heart compro-

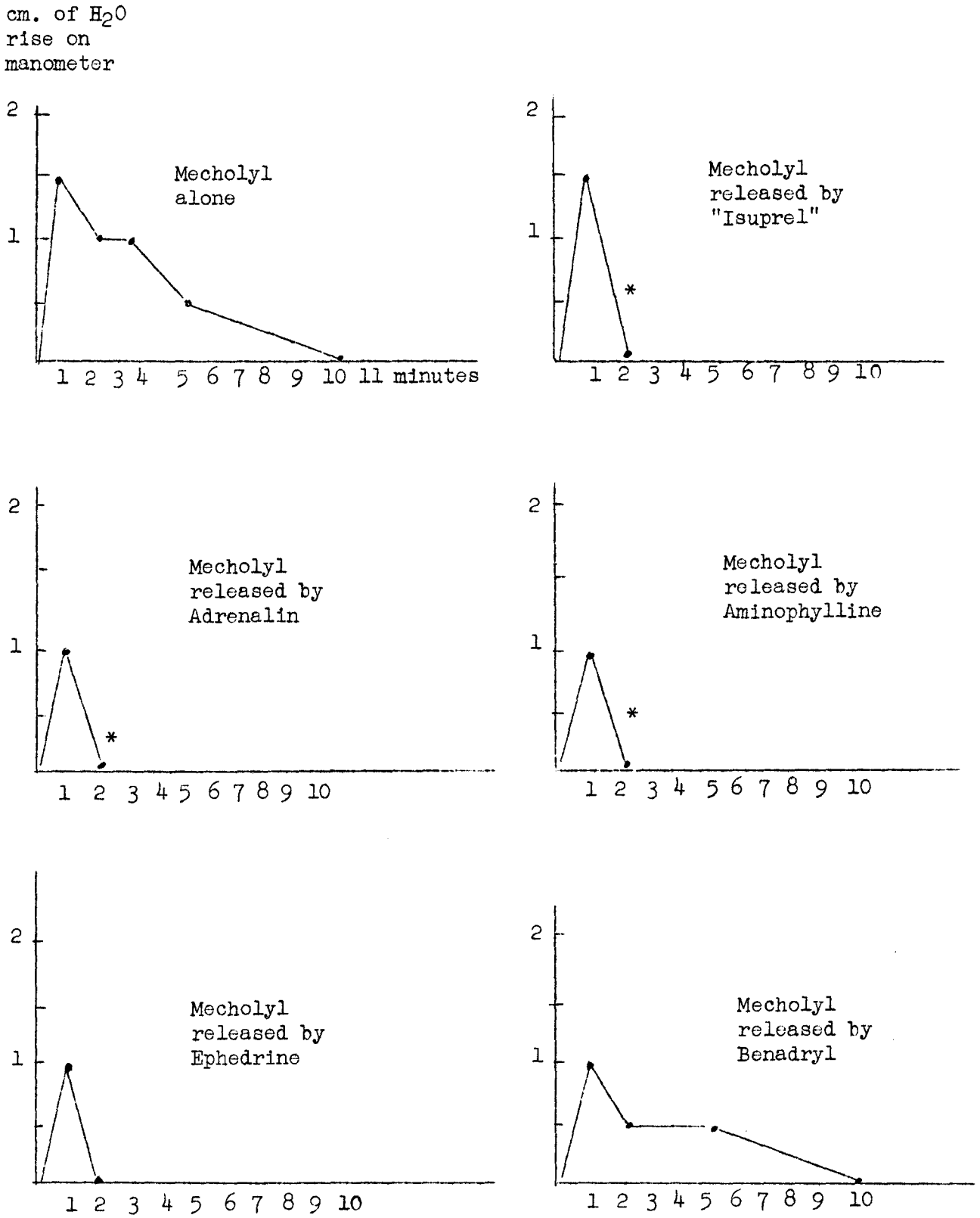
Time	Indiv. Dose of Isuprel	Total Dose of Isuprel	Heart Rate	Resp. Rate	Blood Pressure	E.K.G.
0"	.02 mg.	.02 mg.	100	20	88/82	Normal
40"	.04 mg.	.06 mg.	120	25	88/82	Normal
2'25"	.10 mg.	.16 mg.	200	35	64/56	ST depressed T diphasic
3'45"	.20 mg.	.35 mg.	210	34	66/60	"
5'10"	1.00 mg.	1.36 mg.	220	34	64/58	"
6'35"	5.00 mg.	6.36 mg.	220	34	64/58	"
7'55"	10.00 mg.	16.36 mg.	225	34	62/56	"
10'45"	20.00 mg.	36.36 mg.	230	27	64/58	"
13'35"	25.00 mg.	61.36 mg.	230	26	62/56	"
16'25"	-	-	225	26	64/58	"
30'10"	-	-	200	22	66/56	ST rising T upright
34'10"	-	-	175	24	74/66	tachycardia
50'20"	-	-	170	24	80/68	Tachycardia
60'	-	-	150	24	80/68	Normal

mised by extreme acceleration over a period of 30 to 45 minutes.

Further experiments were then carried out in order to determine as accurately as possible the actual toxic dose for animals under anesthesia. It was found that all animals were able to tolerate at least 1 mg. of "Isuprel" per kilo given intravenously; two animals were able to survive 1.5 mg. per kilo intravenously. Animals that recovered, regained consciousness ten to fifteen minutes after the anesthetic was discontinued. The latter was stopped as soon as the dose of "Isuprel" had been given. In these animals the pulse remained at elevated levels, at about 15 to 20% above normal, for 1½ to 2 hours. Blood pressure falls were to within 40% of normal and returned to normal levels in 45 minutes to an hour. It thus appears that "Isuprel" can be safely used by the intravenous route since over 1,000 times the therapeutic dose can be tolerated by dogs under anesthesia. In our clinical studies we found that the therapeutic dose could be still further reduced proportionately in man. Thus the toxic dose in dogs converted to the amount used clinically would be 2,500 times the therapeutic one.

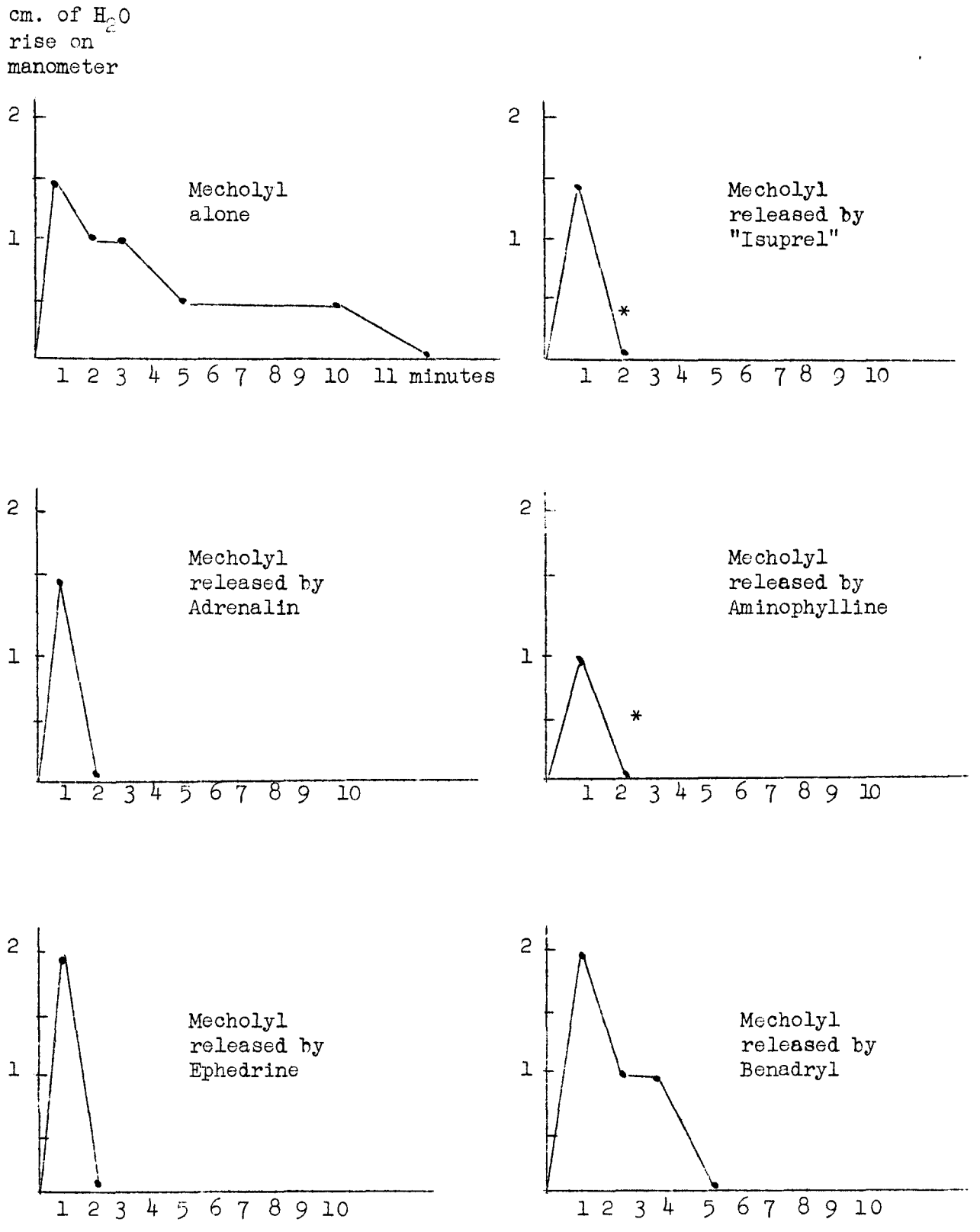
The only toxic effects of "Isuprel" seemed to involve an acceleration of the heart manifested by coronary insufficiency as shown in the electrocardiogram. For this reason we thought it worthwhile to observe by direct vision any change in lumen of the coronaries when "Isuprel" was given. An animal was anesthetized in the manner previously described. The pericardium was incised, and the heart and exposed coronary vessels held under direct observation. A 1% solution of

CHANGES IN ENDOBRONCHIAL PRESSURES (Measured in cm. of H_2O)



*Carried on to negative values, i.e., the bronchus dilated past its resting diameter.

CHANGES IN ENDOTRACHEAL CUFF PRESSURE (Measured in cm. of H_2O)



*Carried on to negative values, i.e., the trachea dilated past its resting diameter.

novocaine was sprayed into the surrounding areas to prevent cardiac irregularities. When a therapeutic dose of "Isuprel" was given to the animal, no gross change was apparent in the lumen of the coronary arteries. When large doses of "Isuprel" were given (.75 mg. per kilo), the heart was observed to increase rapidly in rate and in forceful beat; the coronary vessels appeared to dilate about 50% and at the same time the veins became fuller and congested. As a comparative study we gave the animal aminophylline (7.5 mg. per kilo) and obtained marked dilatation. When given pitressin (1 unit per kilo) the coronaries constricted markedly.

"Isuprel" with Cyclopropane Anesthesia

Since "Isuprel" is a homologue of epinephrine, and it has been shown that the latter compound influences the conductive mechanism of the heart under Cyclopropane anesthesia, it was decided to study the action of "Isuprel" on the dog's heart under Cyclopropane. We anesthetized a dog with Cyclopropane, intubated the animal, and connected it to the electrocardiograph machine. The animal was then given succeedingly larger doses of "Isuprel" until twenty times the therapeutic dose had been given. There was no perceptible change in the rhythm of its heart. On the other hand equivalent amounts of epinephrine given intravenously produced distinct abnormalities of rhythm continuing on to gross irregularity and ventricular fibrillation.

Clinical Investigations

Bronchospasm presents a definite problem in anesthesia, and asthmatics in particular frequently take a difficult anesthetic. Many patients who have no past history of allergy first develop evidence of asthma under anesthesia. The converse of this is of course also true. A safe drug that would relieve bronchospasm and still not produce side cardiovascular effects would remove an important hazard. To date we have had the opportunity to use "Isuprel" in seven patients under general anesthesia, and a short case history of each follows.

Case No. 1 -

This 65 year old white male was brought to surgery for rectosigmoid resection. His preoperative diagnosis was carcinoma of the colon. The patient's record yielded a long history of allergy with allergic rhinitis, hay fever, and hives. No previous story of asthma was elicited. This patient had previously taken histamine desensitization treatment with fair results. Admission examination showed evidence of allergic rhinitis, and occasional wheezes were heard in his chest. Premedication consisted of morphine sulfate grains 1/6 and hyoscine grains 1/150. Induction was carried out with 17 cc. of pentothal-curare mixture. As the last few cc. were injected and the laryngoscope introduced, the patient developed laryngospasm which rapidly became more violent and bronchospasm ensued, expiration becoming difficult and noisy, and wheezing was present. The endotracheal tube was inserted with difficulty, but the patient's respirations continued to be labored and noisy. Five minutes later, "Isuprel" .016 mg. was given intravenously, and within two minutes respirations became free, and symptoms of asthma and bronchospasm were entirely gone. Immediately after injection of "Isuprel" the patient's pressure rose from 104/84 to 120/80 while his pulse remained at 120 beats per minute. At the end of 15 minutes the patient's pressure was 104/78 and his pulse 88 at which level he continued throughout four and one half hours of surgery. The patient had no further episodes and was delivered from the operating room in very satisfactory condition.

Case No. 2 -

The patient was a 58 year old white male with a preoperative diagnosis of right indirect inguinal hernia. His premedication consisted of morphine sulfate grains 1/6 and scopolomine grains 1/150. Past history gave evidence of a chronic cough, exertional dyspnea, but no history of frank allergy. Preoperatively moist rales were heard at both bases. Pontocaine spinal 1-1-1

technique was selected for the anesthesia. Anesthesia progressed satisfactorily, but after an hour and 45 minutes the patient began to complain of slight pain in the operative site. He was given pentothal-curare mixture slowly. After ten cc. were injected, the patient appeared to go into a frank asthmatic attack, and musical rales could be heard throughout the chest. An endotracheal tube was inserted, but respirations continued to be labored. Patient was then given "Isuprel" .016 mg. intravenously with immediate relief of wheezing and difficulty in breathing. His blood pressure rose from 140/80 to 148/84 and his pulse from 98 to 108. At the end of ten minutes his pressure was 144/82 and his pulse again 98 per minute. Patient remained symptom free until the termination of surgery 50 minutes later and was returned to the ward in excellent condition.

Case No. 3 - ____

This patient was a 65 year old white male with a preoperative diagnosis of carcinoma of the colon. His past history for allergy was negative. Patient was induced with pentothal-curare mixture and ten minutes later showed a beginning and progressive bronchospasm. The Nitrous Oxide inhalation was changed to Helium and Oxygen with no improvement. The patient was then given "Isuprel" .016 mg. intravenously and in five minutes bronchospasm was entirely gone. His blood pressure rose from 140/80 to 148/82 and his pulse remained constant at 84 beats per minute. Twenty minutes later his pressure was again 140/80, and his pulse had dropped to 74. Some two hours later the patient began to show a very slight return of his wheezing, and "Isuprel" .016 mg. was repeated intravenously. His asthma disappeared, but his pressure rose to 170/90, and his pulse from 84 to 104. Within ten minutes, however, his pulse had again returned to 84 and his pressure back to 140/80. Patient was returned to his room in good condition, with no signs of asthma present.

Case No. 4 - ____

This patient was a 54 year old white male with a preoperative diagnosis of fractured hip. His past history was that of severe asthma since 1918. He had been hospitalized for this condition on several occasions and his asthma was so severe that he kept an oxygen tank constantly at home for emergency use. Patient was obtaining some relief from a 1:100 adrenalin nebulizer. Preoperative medication consisted of morphine sulfate grains 1/4 and atropine grains 1/150. At that time musical rales could be heard throughout his chest. The patient was induced with Nitrous Oxide and Cyclopropane to which a small amount of Ether was added. Patient developed an intense bronchospasm and moderate cyanosis. A tracheal tube was inserted and the patient given .012 mg. of "Isuprel" cautiously with some relief of symptoms. Fifteen minutes later "Isuprel" .008 was given producing increased relief of symptoms. This lasted for 45 minutes to an hour, and then asthma began to recur. Patient was then given "Isuprel" .016 mg. intravenously with complete relief of asthma and bronchospasm. His blood pressure remained at 150/100 and his pulse rose from 120 to 130 per minute. Relief lasted for one hour and again asthma began to recur. "Isuprel" was repeated .016 mg., and again there was complete relief of symptoms with no change in blood pressure and a slight rise in pulse rate. One hour and 30 minutes later, just prior to extubation, the patient was given again "Isuprel" .016 mg. intravenously. He was hyperventilated with Oxygen and Helium and returned to the ward in good condition. When seen four hours post-surgery the patient was awake, lucid, and remakred that for the first time in years he was breathing freely. In summary this man was given a total dosage of "Isuprel" .068 mg. intravenously over an anesthetic period of six hours.

Case No. 5 - ____

This patient was a 76 year old white male who was brought to surgery for a gastric resection. His past history was that of chronic peptic ulcer, but no history of allergy was noted. Premedication consisted of morphine grains 1/6 and scopolamine grains 1/150. The patient was induced with pentothal-curare mixture, and endotracheal tube inserted,

and maintained with a flow of 500 cc. Nitrous Oxide and 500 cc. Oxygen per minute. The first hour of anesthesia was uneventful, but during the second hour the patient first began to show signs of difficulty in breathing. This progressed rapidly until full symptoms of an asthmatic attack were present. Wheezing and musical rales could be heard throughout the chest. An attempt to improve respiration by suctioning through the endotracheal tube and by controlling respirations through manual pressure on the breathing bag was unsuccessful. The patient was then given .02 mg. "Isuprel" intravenously, and immediately breathing returned to normal. His color improved, and all signs of asthma disappeared. The patient's pressure before giving the intravenous "Isuprel" was 150/78 and his pulse 72. Immediately after injection of the "Isuprel", the pressure rose to 160/80 and his pulse to 92. Within ten minutes, however, his pulse had returned tc 76 per minute. The Patient continued throughout four additional hours of uneventful anesthesia and was returned to the ward in excellent condition.

Case No. 6 - ___

This patient was thirteen year old white male with a preoperative diagnosis of supra-sellar cyst. He was brought into the operating room for craniotomy. Premedication consisted of codeine grains 1 and hyoscine grains 1/150. Past history for allergy was negative. Patient was induced with pentothal-curare mixture, intubated and the Nitrous Oxide, Oxygen flow set at 500 cc. of each per minutes. Within a few moments the patient began to have inspiratory wheezes and ronchi could be heard through the breathing tubes. The patient was suctioned through the endotracheal tube, but no secretion was obtained. During the next twenty minutes breathing continued to be slightly labored, and inspiratory wheezing became more marked. Patient was given "Isuprel" .01 mg. intravenously and immediately breathing cleared and wheezing disappeared. His blood pressure which had risen to 140/90 fell again to its initial level of 130/80. Patient's pulse dropped from 110 to 100 beats per minute at which level it remained for the duration of surgery. Patient was returned to the ward in very satisfactory condition.

Case No. 7 - ___

This 47 year old white female was brought to surgery for an exploratory laparotomy. Her premedication consisted of Demerol 75 mg. and scopolamine grains 1/200. No history of allergy was elicited. Patient was induced with pentothal-curare, intubated and Nitrous Oxide given by inhalation. She tolerated the first hour of surgery well except for a slight episode of difficult breathing which was controlled by deepening the anesthesia. Thirty minutes later the patient suddenly began to have further difficulty exchanging. A check showed the endotracheal tube to be patent and in place and some exchange could be forced by pressure with the breathing bag, but by this time bronchospasm was intense and generalized. "Isuprel" .02 mg. was then given intravenously with complete relief of spasm. Patient's blood pressure rose from 110/80 to 114/80 and her pulse rose from 88 to 94. These returned to normal in ten minutes. The remainder of anesthesia was uneventful and the patient was brought to her room in good condition.

Summary and Conclusions

1. A study of the bronchodilator and cardiovascular actions of adrenalin, Butanefrine, Benadryl, ephedrine, aminophylline, and "Isuprel" was carried out in the laboratory. Of all compounds tested "Isuprel" alone appeared to be both an effective bronchodilator and yet to have little effect on the cardiovascular system.

2. The toxic dose of "Isuprel" is 1,000 times the therapeutic dose in dogs, and calculated to human scale is 2,500 times the therapeutic dose.

3. "Isuprel" in large amounts intravenously had no effect on the rhythm of the anesthetized dog's heart. Cardioacceleration does occur.

4. "Isuprel" given in therapeutic dosage had no effect on the conductive mechanism of the dog's heart under Cyclopropane anesthesia.

5. Seven clinical cases of bronchospasm are reported in which "Isuprel" was used. In all cases complete relief was obtained throughout the surgical and immediate postoperative periods. Rises in pulse rate and blood pressure were minimal in all patients. The largest total dosage of "Isuprel" used was .068 mg.

6. It is suggested that "Isuprel" be used for the treatment of bronchoconstriction and for the control of asthma under general anesthesia. It is recommended that a dosage of $\frac{1}{2}$ to 1 cc. of a 1:50,000 solution be employed and repeated as symptoms recur.

Bibliography

1. Loewi and Meyer
Archiv. fur Exper, Path und Pharm. 53:213, '05.

2. H. D. Dakin
Proc. Royal Soc. of London, 76B, 498, '10.

3. Barger and Dale
Journal of Physiology 41:19, '10.

4. H. Konzett
Archiv.fur exper.Path.und Pharm., 197:27 and 41, '40.

5. A. M. Lands
Journal Pharm. and Exper. Therapeutics, 89:297, '47.

6. A. M. Lands
Journal Pharm. and Exper. Therapeutics, 90:110,'47.

7. Tainter et al
Journal Pharm. and Exper. Therapeutics, 51:371, '34.

8. Siegmund et al
Journal Pharm. and Exper. Therapeutics, 90:254, '47.

9. Baird
Anesthesiology, 8:75, '47.

10. Baird, Johnson, Van Bergen
Anesthesiology, 9:141, '48.

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III. MEDICAL SCHOOL NEWS

Revision of Medical School Curriculum Proposed

For almost two years the Curriculum Revision Committee of the Medical School faculty has been giving consideration to the problem of the curriculum for undergraduate premedical and medical education. Chairman of the committee was Dr. Myron Weaver, Assistant Dean of the Medical School. Sixteen other members of the medical school faculty worked with him and devoted much time and study to this complex and important problem. The committee's report was submitted to the Executive Faculty of the Medical School at its meeting on April 26. The action of the Executive Faculty in acting upon the recommendations of the committee will bring about certain significant changes in the premedical and medical school curriculum.

The study of a foreign language during premedical years will be elective rather than required. Although it was felt that the study of a foreign language had great value both in enhancing the student's facility with English and broadening his cultural perspective, these advantages did not appear to justify it as a requirement for every medical student. Students who plan a career in medical research are, however, urged to study a foreign language during their premedical years.

The committee's report stressed the obligation of the Medical School to develop general practitioners to care for the families of our state. Training medical students to study and to reason critically rather than to profit temporarily from feats of memorization was set down as a prime objective. The number of formally assigned class hours was reduced in order to give the student more time for electives or library work or the advancement of his education in other ways. Under the new curriculum both Physiological Chemistry and Physiology will be taught during the freshman year in Medical School. Pharmacology will be presented during the sophomore year instead of both the sophomore and junior years. There will be an increased emphasis on physical diagnosis during the sophomore year. The junior and senior years which are devoted largely to clinical clerkships will be changed very little. There will be some decrease in the number of didactic lectures and Tuesday and Thursday afternoons will be entirely free for electives.

A new feature of the senior year will be the Applied Medical Science clinics in which members of the departments of Anatomy, Bacteriology, Physiological Chemistry, Physiology, Pharmacology, and Pathology will discuss problems presented by members of the various clinical departments. These clinics will be held three times a week throughout the senior year and will serve to re-emphasize to the student approaching graduation the importance and practical application of the fundamental sciences in his medical practice.

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American Bacteriologists Meet

The Society of American Bacteriologists will meet in Minneapolis May 11 to 14. Headquarters will be at the Nicollet Hotel. Dr. H. O. Halvorson, Acting Head of the Department of Bacteriology of the Medical School, is Chairman of the local committee on arrangements. Members of the University faculty who will present papers are A. H. Brown, Cyrus P. Barnum, Jr., David Glick, J. J. Jezeski, H. O. Halvorson, H. Macy, Richard M. Marwin, George A. Young, Jr., Norman R. Underdahl.

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