

[Asthma]

MEDICAL GRAND ROUNDS

[November 6, 1958?]

CASE 1. [REDACTED] A 48-YEAR-OLD WHITE MALE KNOWN ASTHMATIC SINCE 1943 WHO GAVE A 35-YEAR HISTORY OF NASAL ALLERGY. IN THE 3 YEARS PRECEDING THIS ADMISSION, PROGRESSIVE RESPIRATORY SYMPTOMS MADE IT IMPOSSIBLE FOR HIM TO WORK MOST OF THE TIME. THIRTY-SIX HOURS PRIOR TO ADMISSION HE WAS IN VIRTUAL STATUS ASTHMATICUS. IN SPITE OF INTRAVENOUS AMINOPHYLLINE, NEBULIZED BRONCHODILATOR AND WETTING AGENT DRUGS BY OXYGEN WITH AN OEM MASK, HE BECAME SEMI-COMATOSE, HYPOTENSIVE, AND CYANOTIC. CO<sub>2</sub> COMBINING POWER WAS 36 MEQ, PH 7.20; RESPIRATIONS WERE VERY RAPID, SHALLOW AND LABORED. CONTINUOUS IPPB-O<sub>2</sub> WITH WARM MIST MAINSTREAM NEBULIZATION OF TERGEMIST WAS STARTED; ISUPREL WAS ADMINISTERED Q 2 H. ONE HOUR LATER HE WAS MORE ALERT, RESPIRATIONS WERE MUCH SLOWER; 14 HOURS LATER CO<sub>2</sub> COMBINING POWER WAS DOWN TO 29 MEQ BUT RESPIRATION STILL BECAME DIFFICULT WITHOUT ASSISTANCE WHICH WAS CONTINUED MOST OF THE TIME FOR THE NEXT 3 DAYS. IN THE MEANTIME, STEROID THERAPY WAS INSTITUTED, ACTH IV 20 MGM. BID AND PREDNISONE, 40 MGM. PER DAY. IMPROVEMENT WAS STEADY. TEN DAYS AFTER ADMISSION HE WAS DISCHARGED WITH NORMAL BREATHING BUT IN A MODERATE HYPOMANIC STATE PRESUMABLY DUE TO STEROIDS WHICH, BY THIS TIME, WERE REDUCED TO 5 MGM. OF PREDNISONE T.I.D. CO<sub>2</sub> COMBINING POWER WAS 22 MEQ. DURING THE INTERIM, HUGE AMOUNTS OF MUCOID SPUTUM WITH DENSE PLUGS HAD BEEN EVACUATED. THE FOLLOWING TABLE EXHIBITS A COMPARISON BETWEEN PULMONARY FUNCTION STUDIES DONE 11 DAYS PRIOR TO ADMISSION TO THE HOSPITAL AND THE DAY OF DISCHARGE FROM THE HOSPITAL.

|                | [REDACTED] - 57 |      | [REDACTED] - 57 |      |
|----------------|-----------------|------|-----------------|------|
|                | BBD             | ABD  | BBD             | ABD  |
| 1.0 Sec. EC    | 1100            | 1700 | 3000            | 3200 |
| 0.5 Sec. EC    | 500             | 800  | 2500            | 2700 |
| VITAL CAPACITY | 2800            | 3500 | 4700            | 5200 |

THE IMPORTANT POINTS IN THIS CASE ARE: 1. THAT ASSISTED BREATHING CORRECTED AND LATER PREVENTED CO<sub>2</sub> NARCOSIS WHILE ADEQUATE OXYGENATION WAS MAINTAINED. 2. RESPIRATION WAS MAINTAINED TOLERABLY COMFORTABLE WHEREAS WITHOUT ASSISTANCE THE PATIENT WAS CONTINUOUSLY IN DISTRESS. 3. STEROID THERAPY INDUCED A FAR GREATER REVERSIBILITY THAT WOULD ORDINARILY BE ANTICIPATED IN A PATIENT WITH SUCH A LONG-STANDING HISTORY AND SUCH SEVERE FUNCTIONAL DISABILITY.

CASE 2. [REDACTED], A 62-YEAR-OLD COLORED FEMALE ADMITTED [REDACTED]-56 WITH A 3-WEEK HISTORY OF COUGH AND MALAISE. SHE HAD A FEVER OF 101° AND CLINICAL AND ELECTROCARDIOGRAPHIC EVIDENCE OF ACTIVE PERICARDITIS. SHE HAD A HECTIC FEBRILE COURSE AND THE PRESUMPTIVE CLINICAL DIAGNOSIS WAS TUBERCULOUS PERICARDITIS. ON [REDACTED]-56, SHE WAS STARTED ON ANTI-TUBERCULOSIS THERAPY AND ON [REDACTED] A PERICARDIAL BIOPSY WAS DONE WHICH REVEALED CASEOUS GRANULOMATOUS INFLAMMATORY CHANGE CONSISTENT WITH TUBERCULOSIS IN SPITE OF THE FACT THAT REPEATED SPUTUM AND GASTRIC SMEARS HAD BEEN NEGATIVE AND, SUBSEQUENTLY, CULTURES WERE ALSO NEGATIVE FOR AFB. A BRONCHOSCOPY DONE AT THE SAME

TIME REVEALED NARROWING AND REDDENING OF THE MUCOSA OF THE RIGHT, MIDDLE AND LOWER LOBE BRONCHI. THERE WAS ALSO A MARKED TENDENCY FOR THESE BRONCHI TO COL-LAPSE DURING EXPIRATION. FOLLOWING THIS, THE PATIENT SPIKED FEVER TO 105° AND SUBSEQUENTLY CONTINUED TO SPIKE FEVER INTERMITTENTLY TO 101° WHILE SIGNS OF CONSOLIDATION AND RIGHT PLEURAL EFFUSION DEVELOPED. AFTER REMOVAL OF THE PLEURAL FLUID, WHICH PROVED TO BE AN EXUDATE, EVIDENCE OF RIGHT MIDDLE LOBE ATELECTASIS REMAINED, BOTH CLINICALLY AND BY X-RAY. REPEAT BRONCHOSCOPY WAS URGED BUT COULD NOT BE ACCOMPLISHED UNTIL [REDACTED]-56, AT WHICH TIME 125,000 UNITS OF TRYPTAR WAS INSTILLED INTO THE RIGHT MIDDLE LOBE ORIFICE AFTER IT HAD BEEN DILATED WITH NEOSYNEPHRINE AND EPINEPHRINE. THE PATIENT WAS PLACED PRONE FOR ABOUT AN HOUR AND SUBSEQUENTLY COUGHED UP LARGE AMOUNTS OF MUCOPURULENT PLUGS, WHEREAS PRIOR TO THE PROCEDURE COUGH WAS INFREQUENT AND NON-PRODUCTIVE. VITAL CAPACITY AT THIS TIME WAS 1.6 LITERS, THE 0.5 SECOND EXPIRATORY CAPACITY WAS 1 LITER. SUBSEQUENT X-RAY ON [REDACTED]-56 REVEALED SOME CLEARING. VITAL CAPACITY HAD INCREASED TO 2.0 LITERS AND THE 0.5 SEC. EC TO 1.3 LITERS. THE PATIENT WAS TRANSFERRED TO [REDACTED] AND A FOLLOW-UP FILM 5 MONTHS LATER SHOWED COMPLETE CLEARING.

CASE 3. [REDACTED], A 46-YEAR-OLD COLORED MALE ALCOHOLIC WAS ADMITTED WITH LEFT UPPER LOBE PNEUMONIA ON [REDACTED]-57. A CAVITARY LESION WAS FOUND IN THE LUL AND KLEBSIELLA PNEUMONIAE WERE CULTURED FROM THE SPUTUM. ALL SPUTUM EXAMINATIONS FOR TUBERCLE BACILLI WERE NEGATIVE; TUBERCULIN SKIN TEST WAS ONLY 1+. HE WAS TREATED WITH 2.4 MILLION UNITS OF PENICILLIN PER DAY AND 2 GM. OF ACHROMYCIN UNTIL 11-10-57, AT WHICH TIME THESE WERE DISCONTINUED AND CHLORAMPHENICOL, 2 GM. PER DAY, WAS INSTITUTED. IN ADDITION, NEBULIZATION OF BRONCHODILATOR AND WETTING AGENT WAS ADMINISTERED INTERMITTENTLY 3 TO 4 TIMES A DAY. THERE WAS ESSENTIALLY NO FURTHER CLEARING FOR A 2-WEEK PERIOD FROM [REDACTED]-57 UNTIL [REDACTED]-57. AT THIS TIME, ORAL TRYPSIN WAS INSTITUTED IN DOSES OF 40 MGM. EVERY 3 HOURS FOR 3 DAYS AFTER WHICH IT WAS DECREASED TO 40 MGM. EVERY 6 HOURS UNTIL DISCHARGE ON [REDACTED]-57. A FILM TAKEN ON [REDACTED]-57, SEVEN DAYS AFTER THE INSTITUTION OF TREATMENT, HAD SHOWN MARKED CLEARING; A FOLLOW-UP FILM ON [REDACTED] ONLY REVEALED RESIDUAL FIBROTIC PLEURAL AND PARENCHYMAL REACTION. ON ADMISSION, THE VITAL CAPACITY WAS 3 LITERS AND THE 0.5 SECOND EC WAS 1.6 LITERS. PREDICTED VITAL CAPACITY WAS 4.2 LITERS. ON [REDACTED]-57, AT WHICH TIME ORAL TRYPSIN WAS INSTITUTED, THE VC WAS 3.2 LITERS OR 78% OF PREDICTED, AND THE 0.5 SEC. EC WAS 1.9 LITERS. ON [REDACTED]-57, THE VITAL CAPACITY WAS 3.5 LITERS OR 83% OF PREDICTED AND THE 0.5 SEC. EC WAS 2.2 LITERS. ON [REDACTED]-57, AT THE TIME OF DISCHARGE, THE VC WAS 4.1 LITERS OR 98% OF PREDICTED AND THE 0.5 SEC. EC WAS 2.6 LITERS.

CASE 4. [REDACTED], A 65-YEAR-OLD WHITE MALE ADMITTED ON [REDACTED]-56 FOLLOWING AN AUTO-MOBILE ACCIDENT 2 DAYS PREVIOUSLY WHICH HAD RESULTED IN MULTIPLE RIB FRACTURES ON THE LEFT AS WELL AS MULTIPLE MINOR CONTUSIONS AND ABRASIONS. THERE WAS BOTH CLINICAL AND RADIOLOGIC EVIDENCE OF BILATERAL CONGESTION AND CONSOLIDATION SECONDARY TO CONTUSION AND HYPOSTASIS. MULTIPLE INTERCOSTAL NERVE BLOCK WAS UTILIZED TO RELIEVE CHEST PAIN; FOLLOWING EACH BLOCK, TREMENDOUS AMOUNTS OF SPUTUM WERE RAISED AND BREATH SOUNDS ALWAYS IMPROVED THEREAFTER. THE PATIENT CONTINUALLY REFUSED TO COUGH AS SOON AS ANY CHEST PAIN RETURNED. AS A RESULT, THICK

SECRETIONS ACCUMULATED AND ON [REDACTED], NEBULIZATION OF BRONCHODILATOR AND WETTING AGENT BY IPPB WAS FIRST STARTED. ON [REDACTED], BECAUSE OF REPEATED EPISODES OF CYANOSIS AND UNCONSCIOUSNESS, A TRACHEOSTOMY WAS PERFORMED FOLLOWING WHICH COPIOUS AMOUNTS OF MUCOPURULENT SPUTUM WERE OBTAINED. ON [REDACTED] FOLLOWING AN ENEMA, THE PATIENT DEVELOPED SEVERE ABDOMINAL PAIN AND SUBSEQUENTLY EVIDENCE OF PERITONITIS. A PRESUMPTIVE DIAGNOSIS OF DIAPHRAGMATIC HERNIA, INCARCERATED AND POSSIBLY PERFORATED, WAS MADE. A LAPAROTOMY WAS PERFORMED AND THE HERNIA WAS REDUCED AND A SMALL BOWEL PERFORATION CLOSED. SUBSEQUENTLY THE HIATUS HERNIA WAS REPAIRED. POST-OPERATIVELY, HOWEVER, ATELECTASIS OF THE RIGHT LOWER LOBE PERSISTED IN SPITE OF VIGOROUS NEBULIZATION OF BRONCHODILATOR AND WETTING AGENT DRUGS AS WELL AS FREQUENT INSTILLATION AND STIMULATED COUGHING AND SUCTIONING. BECAUSE OF THIS SEVERAL INSTILLATIONS OF 100,000 UNITS OF PANCREATIC DORNASE INTO THE RIGHT MAIN BRONCHUS WERE CARRIED OUT THROUGH THE TRACHEOSTOMY VIA A CATHETER DIRECTED INTO THE RLL. AFTER THE ASPIRATION OF FAIRLY LARGE AMOUNTS OF THICK PURULENT MATERIAL, BREATH SOUNDS RETURNED TO THE RIGHT LOWER LOBE AND SPUTUM PRODUCTION VIRTUALLY CEASED WITHIN 48 HOURS. THE TRACHEOSTOMY WAS REMOVED AND A FOLLOW-UP FILM 3 WEEKS AFTER DISCHARGE SHOWED ESSENTIALLY COMPLETE CLEARING.

CASE 5. [REDACTED] A 48-YEAR-OLD WHITE MALE WAS ADMITTED ON [REDACTED]-56 WITH A 5-DAY HISTORY OF PAIN IN THE RIGHT CHEST AND COUGH WHICH WAS SUPERIMPOSED ON A 3-YEAR HISTORY OF CHRONIC COUGH. WHEN THE PATIENT DEVELOPED FEVER, CHILLS, AND BEGAN TO RAISE FOUL, GREENISH-YELLOW SPUTUM, ACCOMPANIED BY AN INTENSIFICATION OF HIS RIGHT CHEST PAIN, HE CAME TO THE HOSPITAL. HE WAS FOUND TO HAVE EVIDENCE OF A PLEURAL EFFUSION AND CONSOLIDATION ON THE RIGHT INVOLVING THE RIGHT MIDDLE AND LOWER LOBES. A THORACENTESIS IN THE 9TH INTERCOSTAL SPACE Laterally RESULTED IN THE DRAINAGE OF ONLY 200 CC. OF THICK, TURBID FLUID. BECAUSE OF CHEST PAIN AN INTERCOSTAL BLOCK WAS ALSO DONE. AT THIS TIME, A POLYETHYLENE CATHETER WAS INSERTED THROUGH A 13-GAUGE NEEDLE AND FOLLOWING THE ASPIRATION OF 600 CC. OF TURBID GREEN FLUID, WHICH WAS FOUL BUT NOT CHARACTERISTICALLY PUTRID, 100,000 UNITS OF SK AND 25,000 UNITS OF SD (1 VIAL OF VARIDASE) WITH 150 MGM. OF CORTRIL WERE INSTILLED INTO THE PLEURAL SPACE THROUGH THE CATHETER. THE CATHETER WAS FILLED WITH HEPARIN AND LEFT IN PLACE. FOUR HOURS LATER, IT WAS POSSIBLE TO ASPIRATE 1100 CC. OF MUCH THINNER FLUID FROM THE CHEST. FOLLOWING THIS, THE PROCEDURE OF INSTILLATION OF CORTRIL AND VARIDASE WAS REPEATED TWO TIMES DAILY AND 4 TO 6 HOURS LATER THE CHEST WAS ASPIRATED. TWO DAYS LATER, ASPIRATION PRODUCED ONLY THE APPROXIMATE AMOUNT OF FLUID AS WAS INJECTED AND REPEAT X-RAYS SHOWED MARKED CLEARING OF THE RIGHT LUNG. THE INSTILLATIONS WERE CONTINUED ONCE DAILY FOR SEVERAL MORE DAYS AND A FOLLOW-UP FILM ON [REDACTED] SHOWED FURTHER CLEARING. THE PATIENT HAD BEEN VERY FEBRILE AT THE TIME OF ADMISSION BUT FOLLOWING COMPLETE DRAINAGE OF THE PLEURAL FLUID ON THE 2ND HOSPITAL DAY, HE BECAME AFEBRILE AND REMAINED SO. THERE WERE NO FEBRILE REACTIONS OR PAIN ASSOCIATED WITH THE INSTILLATION OF THE ENZYMES. VITAL CAPACITY FOLLOWING THE FIRST COMPLETE DRAINAGE OF THE RIGHT PLEURAL SPACE WAS 1.9 LITERS AND THE 0.5 SEC. EC WAS 1.5 LITERS. ON [REDACTED], THE VC WAS 2.3 L. AND THE 0.5 SEC. EC WAS 2 L. ON [REDACTED]-56 THE VC WAS 2.6 L. AND THE 0.5 SEC. EC 2.3 L. ON [REDACTED]-56, FOLLOWING DISCHARGE, THE VC WAS 3.0 L. AND THE 0.5 SEC. EC WAS 2.6 L. THE PATIENT'S ANTIBIOTIC THERAPY HAD CONSISTED OF ERYTHROMYCIN, 200 MGM Q 4 H. AT THE TIME OF FOLLOW-UP ONE MONTH AFTER DISCHARGE, THE PATIENT WAS ASYMPTOMATIC AND EVIDENCED COMPLETE RESOLUTION. THE PATIENT FAILED TO RETURN FOR SUBSEQUENT FOLLOW-UPS.



## REFERENCES

### ANTIBIOTIC PROPHYLAXIS

1. McVEY, L.V., AND SPRUNT. AMA ARCH. INT. MED. 92:833, 1953. THERE ARE FEW REPORTS ON CONTROLLED STUDIES SUCH AS THIS WHERE 500 MGM. OF CHLORTETRACYCLINE WAS ADMINISTERED DAILY FOR AN AVERAGE OF 11 MONTHS TO 21 PATIENTS. NINE PATIENTS WERE GIVEN PLACEBOS. THE INCIDENCE OF RESPIRATORY INFECTIONS WAS MORE THAN 50% LESS IN THE TREATED GROUP AND ONLY 10% OF THE TREATED GROUP WERE HOSPITALIZED DURING THE PERIOD OF OBSERVATION, WHEREAS 33% OF THE UNTREATED GROUP HAD TO BE HOSPITALIZED. THE TREATED GROUP SHOWED GREATER WEIGHT GAIN AND IMPROVED APPETITE. THERE WAS NO INCIDENCE OF SUPER-INFECTION IN THE TREATED GROUP.

2. MAY, R.J., AND OSWALD, N.C. LANCET 2:814, OCT. 20, 1956. THESE AUTHORS REPORT ON A 6-YEAR STUDY OF 37 PATIENTS WHO RECEIVED 1 TO 3 GM. OF TETRACYCLINE DRUGS DAILY OVER THIS PERIOD OF TIME. IN SPITE OF THE MUCH HIGHER DOSAGE THEIR RESULTS DID NOT APPEAR TO BE MUCH BETTER THAN THOSE OBTAINED ON LOWER DOSAGE. TWENTY-FIVE PER CENT OF THEIR PATIENTS WERE CARRIERS OF RESISTANT COAGULASE-POSITIVE STAPHYLOCOCCI, A FINDING NOT NOTED IN REPORTED SERIES UTILIZING MUCH SMALLER DOSAGES OF DRUG.

IN OUR OWN CLINIC, 250 TO 500 MGM. DAILY OF BROAD-SPECTRUM ANTIBIOTICS HAVE BEEN UTILIZED (IN SOME PATIENTS FOR AS LONG AS 4 YEARS). IN MOST INSTANCES, NORMAL FLORA PERSIST IN THE SPUTUM AND ONLY RARELY ARE GRAM-POSITIVE STAPHYLOCOCCI OR PSEUDAMONAS GROWN FROM THE SPUTUM. WHEN THESE ORGANISMS ARE FOUND, THEY WERE ALMOST INVARIABLY PRESENT PRIOR TO THE INSTITUTION OF ANTIBIOTIC PROPHYLAXIS. THE ANTIBIOTIC PROPHYLAXIS MOST COMMONLY USED IN OUR EXPERIENCE IS BICILLIN, 1.2 MILLION UNITS EVERY 3 OR 4 WEEKS.

### BRONCHODILATOR DRUGS

1. BRESNICK, E., BEAKEY, J.F., LEVINSON, L., AND SEGAL, M.S. J. CLIN. INVEST. 28:1182, 1949. THESE ARE STUDIES OF THE PROTECTIVE CAPACITY AGAINST INDUCED BRONCHOSPASM FROM HISTAMINE OR METHACHOLINE. THE DRUGS STUDIED WERE EPINEPHRINE, NEOSYNEPHRINE, VAPONEFRIN (WHICH IS 2.25% RACEMIC EPINEPHRINE), ISUPREL AND EPHEDRINE. EPINEPHRINE HYDROCHLORIDE, 0.5 ML. OF A 1:1000 SOLUTION SUBCUTANEOUSLY, PROTECTED AS WELL AS OR BETTER THAN ANY OTHER AGENT TESTED AND AFFORDED GREATER DURATION OF SIGNIFICANT PROTECTION. HOWEVER, ITS CARDIOVASCULAR AND CENTRAL NERVOUS SYSTEM STIMULATING REACTIONS PROVED DISAGREEABLE AND UNDESIRABLE. AEROSOL ISUPREL, 1:100, OR VAPONEFRIN, 2.25%, PROVIDED PROTECTION EQUAL TO EPINEPHRINE BUT OF LESSER DURATION AND WITHOUT ANY OF THE UNDESIRABLE SIDE EFFECTS.

2. SEGAL, M.S., LEVINSON, L., BRESNICK, E., AND BEAKEY, J.F. J. CLIN. INVEST. 28:1190, 1949. THIS STUDY IS AN EVALUATION OF AMINOPHYLLINE ADMINISTERED IN VARIOUS FORMS. ALTHOUGH THE BEST IMMEDIATE PROTECTION WAS AFFORDED BY 0.5 GM. OF AMINOPHYLLINE INTRAVENOUSLY, THE DURATION OF EFFECTIVE PROTECTION WAS CONSIDERABLY SHORTER THAN WHEN AMINOPHYLLINE WAS ADMINISTERED IN THE SAME DOSE IN 15 CC. OF WATER PER RECTUM. THE EFFECTIVENESS OF RECTAL INSTILLATION OF AMINOPHYLLINE WAS FIRST REPORTED BY BARACH (J.A.M.A. 128:589, 1945).



3. HERSCHFUS, J.A., RUBITZKY, H.J., BEAKEY, J.F., BRESNICK, E., LEVINSON, L., AND SEGAL, M.S. INTERNAT. ARCH. ALLERGY & APPL. IMMUNOL. 2:97, 1951. THIS IS A REVIEW ARTICLE ON EVALUATION OF THERAPEUTIC SUBSTANCES EMPLOYED FOR THE RELIEF OF BRONCHIAL ASTHMA. BELLAFOLINE (L-HYOSCYAMINE) PROVIDED MAXIMAL PROTECTION AGAINST BOTH MECHOLYL AND HISTAMINE AMONG ANTI-CHOLINERGIC AGENTS TESTED. ATROPINE AFFORDED VERY GOOD PROTECTION AGAINST MECHOLYL BUT LITTLE OR NONE AGAINST HISTAMINE. OF 10 ANTIHISTAMINIC COMPOUNDS TESTED, BENADRYL AND CHLORTRIMETON AFFORDED MAXIMAL PROTECTION AGAINST HISTAMINE, AS DID DRAMAMINE. ONLY DRAMAMINE AND TRIMETON AFFORDED ANY SIGNIFICANT PROTECTION AGAINST MECHOLYL. ANTIHISTAMINE AEROSOLS AFFORDED FAIR PROTECTION FOR SHORT PERIODS OF TIME.

4. KORY, R.C., TRIBEK, R.A., AND STERNLIEB, R.O. AM. REV. TUBERC. 77:729, 1958. THE AUTHORS REPORT A COMPARATIVE PULMONARY FUNCTION EVALUATION OF THE IMMEDIATE INJECTION OF 0.3 MGM. OF EPINEPHRINE SUBCUTANEOUSLY AND 0.5 GM. OF AMINOPHYLLINE INTRAVENOUSLY. EPINEPHRINE WAS FOUND TO BE EQUAL TO AMINOPHYLLINE, BOTH IN EFFECT AND DURATION. SIDE EFFECTS WERE SLIGHTLY MORE FREQUENT WITH INTRAVENOUS AMINOPHYLLINE.

5. BICKERMAN, H.A. CHAPTER ON PHARMACOLOGICAL THERAPY IN PULMONARY EMPHYSEMA BY BARACH & BICKERMAN, WILLIAMS AND WILKINS CO., BALTIMORE, 1956. THE VALUE OF MIXTURES OF EPHEDRINE AND AMINOPHYLLINE ORALLY IS MENTIONED. DAINITE (DAY) TABLETS AND HYADRINE ARE PROBABLY THE MOST USEFUL PREPARATIONS. HE EMPHASIZES THAT SELF-MEDICATION BY HYPODERMIC INJECTION OF EPINEPHRINE IS FREQUENTLY A TROUBLESOME AND POTENTIALLY DANGEROUS PROCEDURE AND SHOULD NOT BE RECOMMENDED. HE FURTHER INDICATES THE EFFECTIVE OF TWO COMPOUNDED AEROSOLS: DYLEPHRIN, WHICH IS A MIXTURE OF 2.5% RACEMIC EPINEPHRINE AND 0.5% ATROPINE SULFATE IN PROPYLENE GLYCOL; AND AEROLONE COMPOUND, CONTAINING ALUDRINE, 0.25%, AND CYCLOPENTAMINE HYDROCHLORIDE, 0.5%, IN A PROPYLENE GLYCOL VEHICLE. THREE NEW ANTI-CHOLINERGIC DRUGS HAVE BEEN FOUND USEFUL IN SELECTED CASES, EITHER IN THE FORM OF AEROSOL OR BY PARENTERAL INJECTION. 1. PAMINE (EPOXYPROPINEPROPATEMETHYLBROMIDE); 2. ANTRENYL (DIETHYLMETHYL AMMONIUM BROMIDE); 3. PRANTAL (DIPHENMETHANYL). THE ANTI-CHOLINERGIC DRUGS HAVE FOUND THEIR GREATEST USEFULNESS IN THE CHOLINERGIC TYPE HYPERREACTORS WHO EXHIBIT MARKED HYPER-SECRETORY ACTIVITY IN ADDITION TO BRONCHOSPASM.

#### OTHER DRUGS USED IN ASTHMA

1. HERSCHFUS, J.A., SOLOMON, A., AND SEGAL, M.S. ANN. INT. MED. 40:506, 1954. THIS IS A REPORT ON THE OBJECTIVE AND SUBJECTIVE VALUE OF DEMEROL. GREAT CAUTION SHOULD BE EXERCISED IN THE SELECTION OF PATIENTS FOR THIS DRUG, BOTH BECAUSE OF ITS DEPRESSANT EFFECTS AND THE TENDENCY TO INDUCE HABITUATION.

2. GESCHICKTER, C.S. SO. M.J. 48:497, 1955. THE PAPER REPORTS THE CLINICAL TRIAL OF A NEW DRUG, PHTHALAMAQUIN, WHICH IS A DERIVATIVE OF 6-METHOXY-4-AMINOQUINOLIN, A SUBSTITUTED FORM OF NATURAL QUININE. THE COMPOUND IS SAID TO HAVE BOTH BRONCHODILATOR ANTIHISTAMINIC PROPERTIES, AS WELL AS AN UNUSUAL ADVANTAGE OF LOCALIZING IN RESPIRATORY TISSUES. IT IS ADMINISTERED EITHER ORALLY

OR INTRAMUSCULARLY IN 50 MGM. DOSES IN THE FORM OF AN ORGANIC SALT, OR INTRAVENOUSLY IN THE FORM OF AN ASCORBIC SALT IN DOSES OF 200 TO 500 MGM. THE RECOMMENDED DOSE FOR PROLONGED THERAPY IS 3 MGM. PER KILO PER DAY. THE TOXICITY OF THIS DRUG IS REPORTED TO BE NEGLIGIBLE WHEN USED IN PROPER DOSES. OVERDOSAGE LEADS TO LOSS OF APPETITE, NAUSEA AND VOMITING WHICH OCCURRED IN 3% OF THE PATIENTS AFTER PROLONGED THERAPY. REDUCTION OF THE DOSAGE ELIMINATED THESE EFFECTS. UNFORTUNATELY, THESE OBSERVATIONS HAVE NEVER BEEN CONFIRMED. PHTHALAMAQUIN IS PRESUMABLY NOT KNOWN TO BE AN APPROVED DRUG.

3. HANSEN-PRUSS, O.C. So. M.J. 48:270, 1955. HE DISCUSSES THE USE OF ARSENIC IN THE TREATMENT OF ASTHMA. THIS VERY VINDICTIVE PAPER IS FOLLOWED BY AN EQUALLY VINDICTIVE DISCUSSION WHICH SERVES LARGELY TO CONDEMN THIS AGENT, CHIEFLY BECAUSE OF THE DUBIOUS RESULTS ACHIEVED IN THE FACE OF ACTUAL, AND EVEN MORE SERIOUS POTENTIAL, TOXIC REACTIONS. CERTAIN PHYSICIANS IN GULFPORT AND BILOXI, MISSISSIPPI, PRESUMABLY USING SMALLER DOSES OF ARSENIC, ALLEGE ASTONISHINGLY SUCCESSFUL RESULTS WITH THIS AGENT. NO KNOWN RATIONAL BASIS FOR THE USE OF THIS AGENT IN THE TREATMENT OF BRONCHIAL ASTHMA IS AVAILABLE AND IT SHOULD PROBABLY BE SUBJECTED TO FURTHER EVALUATION BEFORE IT CAN SAFELY BE RECOMMENDED FOR TREATMENT.

4. HURST, A., LEVINE, M.H., AND RICH, D.R. ANN. ALLERGY 13:393, 1955. ON THE ASSUMPTION THAT SOME DEGREE OF COR PULMONALE IS PRESENT IN ALL CASES OF SEVERE PULMONARY EMPHYSEMA, THE AUTHORS REASONED, ON THE BASIS OF THE RATIONALE PROPOSED BY BLUMGART, THAT BY LOWERING BASAL METABOLIC OXYGEN NEEDS, MORE OXYGEN WOULD BE MADE AVAILABLE TO THE TISSUES FOR UTILIZATION FOR PURPOSES OTHER THAN THE BASAL STATE. THE REPORT COVERS THE RESULTS OF 28 CASES TREATED BETWEEN 1953 AND 1955. THE FOLLOWING REGIMEN WAS ULTIMATELY FOUND SATISFACTORY: AN INITIAL DOSAGE OF 20 MILLICURIES OF RADIOACTIVE IODINE FOLLOWED IN 2 MONTHS BY AN UPTAKE AND AN ADDITIONAL 20 MILLICURIES WITH 200 MGM. OF PROPLTHIOURACIL BEING GIVEN DAILY FOR ONE WEEK PRIOR TO THE SECOND DOSE OF IODINE. ADDITIONAL RADIATION WAS USED IN THOSE CASES WHERE IT WAS NECESSARY TO ACHIEVE EFFECTIVE ABLATION OF THYROID FUNCTION. THE RESULTS WERE EVALUATED PURELY ON A SUBJECTIVE BASIS. OF THE 24 CASES TREATED, 2 WERE SAID TO HAVE HAD EXCELLENT RESULTS, 8 GOOD RESULTS, 9 FAIR RESULTS, 5 DIED SOON AFTER THE INSTITUTION OF TREATMENT, AND THE REMAINDER WERE LOST TO FOLLOW-UP.

5. GALLAHER, S.B., HAMILTON, W.F., JR., LAMOTT, I.F., ELLISON, R.G., ELLISON, L., AND HAMILTON, W.F., SR. J. MED. ASSN. GEORGIA, NOV. 1955. A CLINICAL EVALUATION OF 16 CASES, PART OF A LONG-TERM STUDY, WHICH IS SAID TO INCLUDE PHYSIOLOGICAL FINDINGS TO BE REPORTED ELSEWHERE. THOSE PATIENTS IN WHOM NO CHANGE IN BLOOD CHOLESTEROL, PROTEIN-BOUND IODINE, OXYGEN CONSUMPTION, OR BLOOD GAS TENSIONS COULD BE INDUCED WERE CONSIDERED TO BE "IODINE SATURATED," AND WERE USED AS CONTROLS. NO CHANGE IN THEIR CLINICAL COURSE WAS APPRECIATED. THE GROUP EVALUATED ARE SAID TO SHOW AN INCREASE IN SERUM CHOLESTEROL, A DECREASE IN OXYGEN CONSUMPTION, A DECREASE IN PROTEIN-BOUND IODINE, AND AN INCREASE IN ARTERIAL  $PO_2$  AND A DECREASE IN ARTERIAL  $PCO_2$ . THE PHYSIOLOGICAL CHANGES WERE IN PROPORTION TO THE CLINICAL IMPROVEMENT. AS MIGHT BE LOGICALLY EXPECTED, NO CHANGE IN VENTILATORY FUNCTION WAS NOTED. SEVENTY-FIVE PER CENT OF THE SERIES WAS SAID TO HAVE ACHIEVED EITHER AN EXCELLENT, GOOD OR FAIR RESULT. THE VERY NATURE OF THIS TREATMENT WILL LEAVE IT AS A LAST-RESORT FORM OF THERAPY.

6. SEVERAL STUDIES HAVE BEEN MADE ATTEMPTING TO EVALUATE THE EFFECTS OF TRANQUILIZERS IN THE TREATMENT OF THE DISTRESS OF CHRONIC BRONCHOPULMONARY DISORDERS. THESE AGENTS HAVE CERTAIN NON-SPECIFIC PHARMACOLOGIC ACTIONS THAT CAN, PROBABLY, BE ATTRIBUTED TO A PHYSIOLOGICAL ALTERATION IN THESE PATIENTS. BENEFIT HAS BEEN ATTRIBUTED TO THE NON-SPECIFIC SEDATIVE EFFECT IN MODIFYING PSYCHOMOTOR TONE AND THUS AWARENESS OF SYMPTOMS, AS WELL AS MODIFYING SOMATIC REACTIONS TO PSYCHIC STIMULI. IN PATIENTS WITH CHRONIC OBSTRUCTIVE DISEASE, PSYCHIC MODIFICATION BECOMES AN IMPORTANT FORM OF THERAPY SINCE IT TENDS TO DIMINISH THE PATIENTS' HABIT OF FORCED BREATHING OFTEN ARISING OUT OF EMOTIONAL STIMULI. CERTAIN OF THE PROMAZINE COMPOUNDS ARE SERATONIN ANTAGONISTS SO THAT IN THOSE INSTANCES IN WHICH SERATONIN MAY BE PLAYING A ROLE IN THE SYMPTOM COMPLEX, THE USE OF THESE AGENTS MIGHT HAVE CONSIDERABLE VALUE.

7. GRAVENSTEIN, J.S., DEVLOO, R.A., AND BEECHER, H.K. J. APPL. PHYSIOL. 7: 119, 1954. THIS IS A CRITICAL EVALUATION OF A NUMBER OF ANTITUSSIVE AGENTS. THE STUDY WAS DESIGNED TO DETERMINE WHETHER TREATMENT OF CLINICAL COUGH IS EFFECTIVE PRIMARILY IN REDUCING THE NUMBER OF COUGHS FOR A GIVEN PERIOD OR WHETHER THE EFFECTIVENESS COMES THROUGH ALTERATION OF SUBJECTIVE RESPONSE TO THE COUGH, THAT IS, BY PRODUCING A STATE OF MIND (PSYCHIC MODIFICATION) WHICH RENDERS THE COUGH LESS IMPRESSIVE, PERHAPS LESS DISTRESSING, THUS GIVING A FEELING OF IMPROVEMENT. IN NORMAL SUBJECTS, ANTITUSSIVE AGENTS DO NOT CONSISTENTLY REDUCE THE FREQUENCY OF COUGH EXPERIMENTALLY INDUCED BY THE INHALATION OF AMMONIA GAS OR CITRIC ACID MIST OR INTRAVENOUS INJECTION OF PARALDEHYDE. THESE AGENTS DO TEND TO REDUCE THE NUMBER OF COUGHS ARISING IN DISEASE BUT THIS REDUCTION IS NOT STATISTICALLY SIGNIFICANT. CODEINE WAS THE MOST EFFECTIVE AGENT; HOWEVER, ITS ESSENTIAL ACTION APPEARS NOT TO BE SPECIFICALLY TO REDUCE THE FREQUENCY OF COUGH BUT PROBABLY BY ALTERATION OF THE SUBJECTIVE STATE THROUGH A EUPHOROGENIC OR HYPNOTIC ACTION.

8. SHANE, S.J., KRZYSKI, T.K., AND KOPF, S.E. CANADIAN MED. ASSN. J. 77: 600, 1957. THESE AUTHORS REPORT ON A SUBSTANCE KNOWN AS TESSALON, WHICH IS ALLEGED TO BE 2 1/2 TIMES AS EFFECTIVE AS CODEINE AND CONTROLS THE FREQUENCY OF COUGH WITHOUT DECREASING THE PRODUCTIVITY OF THE SPUTUM. TESSALON HAS A PERIPHERAL ACTION OF REPRESSING STRETCH RECEPTORS IN THE LUNGS, BRONCHI, AND PLEURA BY ACTING ON BOTH AFFERENT AND EFFERENT BRANCHES OF THE REFLEX ARC. A CENTRAL ACTION SUPPRESSES CENTRAL REFLEX TRANSMISSION IN VAGAL NUCLEI OF THE MEDULLA. TESSALON IS NON-HABITUATING AND NON-ADDICTING.

9. TINNEY, S.M., MITHOEFER, J.C., AND HUTCHINS, S.L. NEW ENG. J. MED. 249: 886, 1953. THIS IS A REPORT ON THE RESPIRATORY DEPRESSANT ACTION OF N-ALYL-NORMORPHINE, KNOWN AS NALINE, BOTH IN NORMAL SUBJECTS AND IN PATIENTS WITH RESPIRATORY ACIDOSIS SECONDARY TO PULMONARY EMPHYSEMA. THE SIGNIFICANCE OF THIS REPORT IS THAT IT EMPHASIZES THE FACT THAT NALINE IS A POTENT RESPIRATORY DEPRESSANT AND DOES NOT LEND ITSELF AS A RESPIRATORY STIMULANT IN RESPIRATORY DEPRESSION EXCEPT THAT WHICH IS SECONDARY TO MORPHINE INTOXICATION. IT SHOULD THUS NOT BE USED INDISCRIMINATELY IN THE TREATMENT OF RESPIRATORY DEPRESSION.



10. PEACOCK, L.B., AND DAVISSON, H.M. ANN. ALLERGY 15:150, 1957. THESE AUTHORS REVIEW THE QUESTION OF THE USE OF IODIDES IN THE TREATMENT OF BRONCHIAL ASTHMA WITH PARTICULAR INTEREST IN THE UNTOWARD REACTIONS TO IODIDE. SUCH REACTIONS ARE USUALLY ONE OF TWO TYPES, EITHER THOSE DUE TO OVERDOSAGE OR THOSE DUE TO TRUE HYPERSENSITIVITY. IT IS GENERALLY FOUND THAT 15 TO 20% OF PATIENTS RECEIVING IODIDE WILL HAVE SOME REACTION. ORGANIC IODIDES SUCH AS LIPOIODINE ARE LESS TOXIC. THE VALUE OF ORGANIC IODIDE IN 29 PATIENTS KNOWN TO HAVE HAD REACTIONS TO INORGANIC IODIDE IS DESCRIBED. LIPOIODINE IS AVAILABLE IN  $4\frac{1}{2}$  GRAIN TABLETS CONTAINING 41% IODINE. ONE TABLET IS EQUIVALENT TO  $\frac{1}{4}$  TO  $\frac{1}{6}$  THE USUAL DOSE OF SSKI; SINCE EACH TABLET IS APPROXIMATELY 8¢, THIS IS A VERY EXPENSIVE FORM OF THERAPY.

STEROIDS HAVE BEEN FOUND USEFUL IN CONJUNCTION WITH IODIDE IN PATIENTS WHO HAVE A TENDENCY TO REACTIONS.

MISCONCEPTIONS CONCERNING THE ACTION OF IODIDES HAVE BEEN COMMON FOR MANY YEARS. IT SEEMS QUITE CLEAR THAT THE ONLY KNOWN ACTION OF IODIDES IS THAT THEY ARE EXCRETED INTO THE BRONCHIAL TREE RESULTING IN THE ELABORATION OF AN INCREASED AMOUNT OF THIN MUCOUS, THUS PROVIDING A VEHICLE FOR MUCOUS AND MUCO-PURULENT PLUGS TO BE EVACUATED, WITHOUT ANY EFFECT OF EXISTING MUCO-PURULENT SECRETIONS. WHETHER IODIDES HAVE ANY OTHER EFFECT IN RESPIRATORY ALLERGY HAS NEVER BEEN ELUCIDATED ON ANY PHYSIOLOGICAL BASIS. THE APPARENT CLINICAL EFFECTIVENESS IN SOME CASES IS DIFFICULT TO EXPLAIN ON THE BASIS OF THE EFFECT OF IODIDES ON MUCOUS GLANDS ALONE.

11. BANYAI AND CADDEN, AM. J. MED. SCI. 203:479, 1942. THIS IS A CLEAR-CUT DEMONSTRATION OF THE VALUE OF CO<sub>2</sub> AS AN EXPECTORANT. CO<sub>2</sub> HAS BEEN SO FREQUENTLY MISUSED THAT IT HAS, FOR THE MOST PART, FALLEN INTO DISREPUTE IN INHALATION THERAPY.

12. BOSH, AND HALLINGER, AM. J. DIS. CHILD. 62:981, 1941. THESE EARLIER STUDIES METICULOUSLY EVALUATED EXPECTORANTS OF VARIOUS KINDS AND PROVIDE ADDITIONAL SUPPORT FOR THE JUDICIOUS USE OF CO<sub>2</sub> INHALATION IN CONCENTRATIONS OF 5% OR LESS AS AN EXPECTORANT. HERE AGAIN, THE ACTION IS OBSCURE BUT MAY BE SIMILAR TO THAT OBSERVED WITH IODIDES.

AEROSOL WETTING AGENTS - OVER THE PAST 8 YEARS A GREAT DEAL OF CONTROVERSY HAS ARISEN CONCERNING THE USE OF SURFACE ACTIVE AGENTS SUCH AS ALEVAIRE AND, MORE RECENTLY, TERGEMIST. THERE IS LITTLE DOUBT, WHEN THESE AGENTS ARE USED IN SUFFICIENT QUANTITY, THAT THEY SUCCESSFULLY AID IN THE CLEARING OF OBSTRUCTING SECRETIONS IN THE TRACHEOBRONCHIAL TREE. THERE ARE THOSE WHO OBJECT TO THE VERY ALKALINE PH OF THESE AGENTS AND INSIST, ON THIS BASIS, THAT THEY ARE IRRITATING TO THE RESPIRATORY TRACT. SUCH REACTIONS HAVE BEEN OBSERVED IN OUR EXPERIENCE ALTHOUGH THEY ARE RARE. THESE AGENTS CAN BE BUFFERED WITH ACETIC ACID SOLUTION IN THE FORM OF WHITE VINEGAR IF NECESSARY (1 PART IN 4). THE COMMONEST ERROR IN THE USE OF THESE AGENTS IS THAT ENTIRELY TOO MUCH IS EXPECTED OF ALMOST INFINITESIMAL QUANTITIES. THESE AGENTS MUST BE USED IN

ABUNDANCE. MORE RECENTLY, IT HAS BEEN SHOWN THAT MORE EFFECTIVE WETTING OF THE TRACHEO-BRONCHIAL TREE AND ELIMINATION OF SECRETIONS CAN BE ACCOMPLISHED BY THE USE OF VARIED DILUTIONS OF WETTING AGENTS WHICH HAVE BEEN HEATED PRIOR TO NEBULIZATION (CUSHING, ET AL, DIS. OF CHEST 34:388, 1958.) THE GENERAL USEFULNESS OF FOGS AND MISTS AS THERAPEUTIC AGENTS, WITH OR WITHOUT WETTING AGENTS, HAS NOW BECOME ACCEPTED AS A GENERAL USEFUL PROCEDURE THROUGHOUT THE WORLD.

### STEROID THERAPY

1. BURRAGE, W.S., AND ERWIN, J.W., NEW ENG. J. MED. 248:679, 1953. THIS REPORT EMPHASIZES THE IMPORTANCE OF A GOOD-SIZED INITIAL DOSE NECESSARY FOR COMPLETE CLEARING OF SYMPTOMS. IF PATIENTS ARE NOT RENDERED COMPLETELY SYMPTOM-FREE AT THE OUTSET, SUBSEQUENT MAINTENANCE THERAPY IS NOT USUALLY AS SATISFACTORY.
2. SPAIN, D.M. DIS. OF CHEST 23:270, 1953. BIOLOGICAL EFFECTS OF STEROIDS AS RELATED TO PULMONARY DISEASE ARE REVIEWED EMPHASIZING THE BASIC PROPERTY OF SUPPRESSION OF ACUTE INFLAMMATION AND INHIBITION OF GRANULATION TISSUE FORMATION. HE EMPHASIZES THAT ONCE GRANULATION TISSUE IS PRESENT, STEROIDS TEND TO INHIBIT FURTHER GRANULATION BUT HAVE NO LYTIC EFFECT ON PRE-EXISTING GRANULATION OR FIBROUS TISSUE AND, IN FACT, IN MANY INSTANCES APPARENTLY ENHANCE THE RATE OF DEVELOPMENT OF FIBROSIS.
3. BORDLEY, J.E. BULL. JOHNS HOP. HOSP. 87:42, 1950. OBSERVATIONS ON CHANGES TAKING PLACE IN THE UPPER RESPIRATORY TRACT OF PATIENTS UNDER ACTH AND CORTISONE THERAPY.
4. LUCAS, D.S. AM. REV. TUBERC. 64:279, 1951. SOME EFFECTS OF ADRENOCORTICOTROPHIC HORMONE AND CORTISONE ON PULMONARY FUNCTION OF PATIENTS WITH OBSTRUCTIVE EMPHYSEMA.
5. HERKSIMER, H. BR. M. J. 1:184, JAN. 23, 1954. THE AUTHOR EMPHASIZES THAT THE MECHANISM OF DEVELOPMENT OF HYPOSENSITIVITY AND HYPERSENSITIVITY TO ANTIGEN INJECTIONS OR INHALATION IS FAR FROM BEING UNDERSTOOD. IN THIS STUDY IT IS DEMONSTRATED THAT THE SIMULTANEOUS ADMINISTRATION OF STEROIDS DOES NOT INTERFERE WITH THE PROCESS OF HYPOSENSITIZATION AND, IN FACT, SINCE DOUBLING AND TREBLING THE AMOUNT OF ALLERGEN THAT CAN BE ADMINISTERED IS POSSIBLE UNDER STEROID THERAPY, THE RATE OF HYPOSENSITIZATION CAN BE ENHANCED. MOREOVER, THE PHENOMENON OF HYPERSENSITIVITY WHICH ORDINARILY OCCURS UNDER CIRCUMSTANCES OF RAPID ADMINISTRATION OF ANTIGEN CAN BE AVOIDED.
6. SAVAGE, R.S., AND BROCKBANK, W. LANCET, OCT. 30, 1954, PP. 893. THE AUTHORS, IN PRESENTING SEVERAL CASES OF DEATH DURING CORTISONE THERAPY, EMPHASIZE THAT STEROID DOSAGE SHOULD BE GREATLY INCREASED WHEN AN EXACERBATION OF SYMPTOMS APPEARS OR A PULMONARY INFECTION BECOMES APPARENT.

7. IN REVIEWING THE FATAL CASES OF ASTHMA, SEVERAL POINTS SEEM APPARENT: A) IN MOST INSTANCES INADEQUATE THERAPY DIRECTED AT BRONCHIAL TOILET WAS BEING UTILIZED AND IN MOST INSTANCES EXTENSIVE BRONCHIAL PLUGGING BY INSPISSATED MUCOUS WAS PRESENT. THE EFFECTIVE USE OF EXPECTORANTS AND NEBULIZATION COULD HAVE HELPED PREVENT THESE CHANGES. B) FREQUENTLY THE DEATHS OCCURRED AFTER ABRUPT LOWERING OF THE STEROID DOSAGE OR WITHDRAWAL OF THE DRUG AND FAILURE TO REINSTITUTE STEROIDS IN LARGE DOSAGES WAS A COMMON OCCURRENCE. C) OVERDOSAGE WITH ADRENALIN WAS ALSO COMMON IN THESE CASES. D) SUPERIMPOSED INFECTIONS WERE NOT RECOGNIZED EARLY ENOUGH OR TREATED EFFECTIVELY WITH LARGE DOSES OF ANTI-BIOTICS AND INCREASED LEVELS OF STEROIDS WHEN THESE WERE BEING USED.

8. SEGAL, M.S., AND DUVENCI, J., BULL. TUFTS-NEW ENG. MED. CENTER 4:71, 1958. THE RELATIVE EFFECTIVENESS OF THE VARIOUS STEROIDS HAS BEEN A SOMEWHAT CONTROVERSIAL POINT. THE AUTHORS DESCRIBE A NEW FORM OF STEROID THERAPY ACHIEVED BY 16-ALPHA-HYDROXYLATION OF 9-ALPHA-FLUOROCORTICOID RESULTING IN A NEW SYNTHETIC COMPOUND, TRIAMCINOLONE DIACETATE (ARISTOCORT). THIS AGENT HAS GREATLY ACCENTUATED ANTI-INFLAMMATORY EFFECTS THAT ARE SAID TO BE 10 TIMES THAT OF HYDROCORTISONE. THE AUTHORS FURTHER REPORT GREATLY ENHANCED THERAPEUTIC EFFECTIVENESS IN THE MANAGEMENT OF PATIENTS WITH CHRONIC BRONCHIAL DISEASES. NINETY-TWO PER CENT OF 36 PATIENTS SHOWED EXCELLENT OR GOOD RESULTS. THE IMPORTANCE OF UTILIZING ANTIBIOTICS WITH STEROIDS, PARTICULARLY IN THOSE INSTANCES WHERE INFECTION IS PRESENT OR POTENTIAL, HAS BEEN REPEATEDLY EMPHASIZED.

9. HOYLE, C., DAWSON, J., AND MATHER, G. LANCET 1:638, MARCH 26, 1955. THE AUTHORS OFFER A PROPOSED PLAN FOR THE APPROACH TO STEROID THERAPY IN SARCOIDOSIS AND SUGGEST THAT PATIENTS WITH RECENT SARCOIDOSIS AND MINIMAL SYMPTOMS BE OBSERVED FOR 1 YEAR WITHOUT TREATMENT IN ORDER TO EXCLUDE SPONTANEOUS REMISSION. IF NO IMPROVEMENT OCCURS AFTER THAT TIME, COMBINED STEROID AND ANTITUBERCULOUS THERAPY IS RECOMMENDED. IF SARCOIDOSIS IS SEVERE, STEROID THERAPY MAY BE STARTED EARLIER BUT IF SEVERE DISEASE IS PROTRACTED, THERAPY IS NOT LIKELY TO BE SUCCESSFUL.

OUR OWN EXPERIENCE WOULD SUGGEST THAT PULMONARY FUNCTION STUDIES ARE A VERY USEFUL BASIS FOR GUIDANCE IN PATIENTS WITH PULMONARY SARCOIDOSIS. REPEATED OBSERVATIONS OF RELAPSE OF PULMONARY FUNCTION, ANTEDATING OTHER EVIDENCE OF CLINICAL RELAPSE, IS NOT AN UNCOMMON OBSERVATION.

#### COR PULMONALE AND RESPIRATORY ACIDOSIS

1. HEISKELL, C.L., JR., BELSKI, J.B., AND CLAUMAN, B.F. J.A.M.A. 156:1059, 1954.

2. LYONS, H.A., AND HITT, D.M. AM. J. MED. SCI. 229:193, 1955.

3. BELL, L.A.L., JR., CRAIG, N., AND ANDREAE, E. AM. J. MED. 18:536, 1955.



DESPITE FAVORABLE EFFECTS AND APPARENT LOW TOXICITY REPORTED BY SOME, THE PLACE OF DIAMOX AS A USEFUL DRUG FOR LONG-TERM ADMINISTRATION IN EMPHYSEMA IS NOT ESTABLISHED. HEISKELL ET AL DEMONSTRATED CONSISTENT LOWERING OF THE  $\text{CO}_2$  COMBINING POWER TO WHICH THEY ATTRIBUTED SYMPTOMATIC BENEFIT. LYONS AND CO-WORKERS, HOWEVER, EMPHASIZED THAT THE REDUCTION IN  $\text{CO}_2$  CONTENT WAS NOT ALWAYS ACCOMPANIED BY A REDUCTION OF  $\text{PCO}_2$  AND, IN SOME INSTANCES, IT IS ACTUALLY INCREASED. SYMPTOMATIC BENEFIT APPEARED TO BE RELATED TO LOWERING OF THE  $\text{PCO}_2$ . THEY NOTED NO RELATIONSHIP BETWEEN  $\text{PCO}_2$  AND  $\text{PO}_2$  SINCE THERE WAS NO EFFECT ON VENTILATION DEMONSTRABLE. BELL AND ASSOCIATES, ON THE OTHER HAND, FOUND BOTH A DECREASED  $\text{PCO}_2$  AND AN INCREASED  $\text{PO}_2$  WHENEVER PLASMA BICARBONATE AND PH WERE DECREASED. THIS WAS ALSO ACCOMPANIED BY IMPROVED ALVEOLAR VENTILATION.

THE VALUE OF DIAMOX AS A DIURETIC AID IN COR PULMONALE WAS PREVIOUSLY DESCRIBED BY SCHWARTZ, W.B., ET AL, ANN. INT. MED. 42, 1955. THERE ARE MANY VARIABLES INVOLVED IN DIAMOX STUDIES SUCH AS THESE SO THAT DIFFERENCES OF OPINION ARE NOT SURPRISING. THOSE TIME FACTORS AND EXTREME VARIABILITY IN SEVERITY OF DISEASE UNDER CONSIDERATION LEAD TO A GREAT DEAL OF VARIABILITY IN THE RESULTS.

GALDSTON, M. AM. J. MED. 19:516, 1955. AGAIN, VARIABLE RESULTS WERE OBSERVED. THE SIGNIFICANT DECREASE IN ARTERIAL  $\text{PCO}_2$  WHEN IT WAS OBSERVED WAS RELATED TO INCREASED VENTILATION IN THE FORM OF A SLOWED RESPIRATORY RATE AND INCREASED TIDAL VOLUME. IN CONCLUSION, THE EFFECTS OF DIAMOX IN RESPIRATION ACID BASE BALANCE ARE OBVIOUSLY COMPLEX AND NOT ALWAYS BENEFICIAL IN CASES OF RESPIRATORY ACIDOSIS.

#### ENZYME THERAPY

1. YATES, J.L., AND GOODRICH, B.E. DIS. OF CHEST 24:320, 1953. THE AUTHORS STUDIED 17 PATIENTS WITH DYSPNEA AND VISCID MUCOUS SPUTUM WHO WERE TREATED WITH 50,000 UNITS OF TRYPTAR AEROSOL 3 TO 6 TIMES DAILY. THESE TREATMENTS USUALLY WERE STARTED 3-7 DAYS AFTER FAILURE OF OTHER TREATMENTS. IMMEDIATELY AFTER INSTITUTION OF THE ENZYME, SPUTUM BEGAN TO LIQUIFY AND A 6-10-FOLD DECREASE IN VISCOSITY OF SPUTUM WAS APPARENT. USUALLY AN INCREASE IN SPUTUM VOLUME OCCURRED AT FIRST AND THEN GRADUALLY DECREASED AS THE RESIDUAL MATERIAL IS CLEARED. MILD TRANSIENT LOCAL IRRITATION WAS THE ONLY SIDE EFFECT NOTED. ONLY 2 OF 17 FAILED TO EXHIBIT A GOOD RESPONSE, BOTH BY DECREASE OF THE VISCOSITY OF SPUTUM AND CLINICAL IMPROVEMENT.

2. INNERFIELD, I. ANN. N.Y. ACAD. SCI. 68:167, 1957. THE AUTHORS DESCRIBED THE FOLLOWING CHARACTERISTICS AND CONSISTENT RESPONSES TO PARENTERAL PROTEASE THERAPY. 1. REDUCTION OF INFLAMMATORY EDEMA; 2. REDUCTION OF VISCOSITY AND FIBRIN CONTENT OF EXUDATE; 3. INCREASE IN TISSUE PERMEABILITY. IN THE FINAL ANALYSIS, IT IS RESTORATION OF LOCAL BLOOD FLOW IN SMALL CALIBER VESSELS THAT CONSTITUTES THE SINE QUA NON FOR REVERSING INFLAMMATION OR PRESERVING TISSUE VIABILITY, DESPITE AN INFLAMMATORY REACTION THAT MIGHT OTHERWISE RESULT IN SUPPURATION OR NECROSIS. "IN A MANNER YET TO BE ELUCIDATED, PROTEASES SEEM TO AUGMENT DEPOLYMERASE ACTIVITY IN INFLAMED TISSUE. THE DEFINITIVE EXPERIMENT DEMONSTRATING THIS PHENOMENON NOT ONLY REMAINS TO BE DESIGNED BUT CONSTITUTES ONE OF THE MOST CHALLENGING PROBLEMS IN THE FIELD OF MOLECULAR BIOLOGY."

IN THE EVALUATION OF ENZYME EFFECTS, IT IS IMPORTANT TO REMEMBER THAT NO EFFECT CAN BE EXPECTED ON FORMED IRREVERSIBLE FIBRIN THROMBI. THE EFFECT IS GREATEST IN THOSE AREAS JUST UNDERGOING INFLAMMATORY CHANGE PRIOR TO THE EXTENSIVE DEPOSITION OF FIBRIN AND THE SUPERIMPOSITION OF TOTAL ISCHEMIA. THIS MEANS, OF COURSE, THAT PROTEASE THERAPY SHOULD BE INSTITUTED EARLY. UNFORTUNATELY, THE USE OF THESE AGENTS IN CLINICAL PROBLEMS MUST BE ACCEPTED LARGELY ON AN EMPIRICAL BASIS AND EVALUATION BECOMES DIFFICULT OWING TO THE UNPREDICTABLE STATE OF MANY INFLAMMATORY LESIONS.

3. AYVAZIAN, J.H., JOHNSON, A.J., AND TILLET, W.S. AM. REV. TUBERC. 76:1957.  
THE RATIONALE FOR THE USE OF PANCREATIC DORNASE IS BASED ON THE FACT THAT DESOXYRIBONUCLEIC ACID CONSTITUTES A SIGNIFICANT PROPORTION OF THE PURULENT EXUDATE FOUND IN THE INTERSTITIUM OF INFLAMMATORY TISSUES. THE DEPOLYMERIZING EFFECT OF THIS ENZYME WAS DEMONSTRATED TO ALTER THE QUALITATIVE AND QUANTITATIVE CHARACTERISTICS OF DESOXYRIBONUCLEIC ACID IN SPUTUM AND WAS ASSOCIATED WITH IMPROVEMENT IN THE PATIENT'S CLINICAL COURSE. THIS CLINICAL STUDY FOLLOWED AS A SEQUEL TO AN EARLIER STUDY BY THE SAME AUTHORS REPORTED IN J.C.I. 33:1670, 1954.

4. ELMES, P.C., AND WHITE, J.C. THORAX 8:259, 1953. 'THE AUTHORS DESCRIBE A SPECIAL TECHNIC FOR ESTIMATING THE VISCOSITY OF MIXED SPUTUM. THE STUDY CONCERNS ITSELF WITH THE USE OF DESOXYRIBONUCLEASE BY INHALATION IN THE TREATMENT OF PURULENT BRONCHITIS. ALTHOUGH THE STUDIES INDICATED EVIDENCE OF LIQUIFACTION OF PURULENT SPUTUM, AN EFFECT WHICH LASTS LESS THAN 12 HOURS, THERE WERE NO DEMONSTRABLE DIFFERENCES BETWEEN THE TREATED AND THE CONTROL GROUP. ONLY ONE TREATMENT DAILY WAS GIVEN AND THE CONCLUSION OF THE AUTHORS WAS THAT THE TREATMENT WAS INADEQUATE FOR THIS GROUP OF CASES. THE PRINCIPAL VALUE OF THIS REPORT IS THE DESCRIPTION OF THE METHODS USED FOR STUDYING THE PATIENTS. THESE AUTHORS FURTHER EMPHASIZE A PROBLEM FREQUENTLY DEMONSTRABLE IN ENZYMATIC TREATMENT OF SUCH PATIENTS: THAT IS, THE DETRIMENTAL EFFECTS OF THE FAILURE TO EVACUATE THE INCREASED VOLUME OF SPUTUM THAT FREQUENTLY ACCOMPANIES THE USE OF ENZYMES. IF A PATIENT'S VENTILATORY FUNCTION IS SO IMPAIRED THAT EFFECTIVE EVACUATION CANNOT BE ACHIEVED FOLLOWING LIQUIFACTION OF SECRETIONS, THE PATIENT'S CONDITION IN FACT MIGHT BE WORSENERD.

5. FARBER, S.M., WILSON, R.H.L., AND GRIMES, O.F. AM. J. MED. 22:930, 1957.  
THIS IS A PESSIMISTIC REVIEW ARTICLE CONCERNING THE USEFULNESS OF ENZYME THERAPY IN DISEASES OF THE CHEST. THE AUTHORS EMPHASIZE THE UNPREDICTABILITY OF RESULTS AND THE UNTOWARD REACTIONS. CERTAINLY A JUDICIOUS APPROACH TO THE USE OF EITHER INHALED OR PARENTERAL ENZYMES IS JUSTIFIABLE.

6. INNERFIELD, I., SHUBB, H., AND BOYD, L.J. NEW ENGL. J. MED. 258:1069, 1958.  
THIS STUDY IS CONCERNED WITH BUCCALLY ADMINISTERED VARIDASE. BUCCAL TABLETS CONTAINING 20,000 UNITS OF STREPTOKINASE ACTIVITY WERE ADMINISTERED EVERY 4 HOURS FOR PERIODS FROM 4 DAYS TO 14 WEEKS. IN THIS STUDY, 30 SUBJECTS WERE USED TO ASCERTAIN EVIDENCE OF BUCCAL PENETRATION OF STREPTOKINASE AND EVIDENCE OF PHYSIOLOGICAL ACTIVITY INDUCED BY STREPTOKINASE. ONE OF THE DISTURBING FACTS OF THIS REPORT IS THAT ONLY 70% OF THE PATIENTS EXHIBITED EVIDENCE OF BUCCAL PENETRATION

AND ONLY 50% EXHIBITED EVIDENCE OF PHYSIOLOGIC ACTIVITY AS EVIDENCED BY SERUM ANTITHROMBIN ACTIVITY. YET, IN A SEPARATE CLINICAL STUDY OF 74 PATIENTS WITH VARIOUS INFLAMMATORY REACTIONS, 94% OF THE PATIENTS EXHIBITED GOOD OR EXCELLENT CLINICAL RESULTS WITH BUCCAL VARIDASE THERAPY. THE PATIENTS WERE SAID TO HAVE SERVED AS THEIR OWN CONTROLS SINCE THEY WERE CLASSED AS INTRACTABLE UNDER OTHER FORMS OF THERAPY.

TWO OTHER PHASES OF ENZYME THERAPY UNDER CLINICAL OBSERVATION IN OUR CLINIC ARE THE USE OF ORAL ENTERIC-COATED TRYPSIN AND THE COMBINED USE OF STEROIDS AND ENZYME INSTILLATION DESCRIBED IN ONE OF THE CASE REPORTS. IN GENERAL, TRYPSIN HAS BEEN FOUND MOST USEFUL IN CHILDREN WITH CYSTIC FIBROSIS AND IN ASTHMATIC INDIVIDUALS WHO ARE UNABLE TO GET INTENSIVE NEBULIZATION THERAPY.