By Morris Collen, MD
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Perspective—Kaiser Permanente Medicine 50 Years Ago

This is the second in this series of reprints from a quarterly publication, the* Permanente Foundation Medical Bulletin*, which Dr. Morris Collen edited from 1943 to 1953. This entry (from Vol. 1, No. 1; July, 1943) is one of Dr. Collen's numerous splendid contributions to the Bulletin. The article is accompanied by a perceptive analysis written by Dr. Elizabeth Anderson, an Infectious Disease subspecialist who knows Dr. Collen.

- Arthur Klatsky, MD, Section Editor

The Management of Pneumonia (A Review of 517 Cases)

Morris F. Collen, MD and Gerhardt L. Dybdahl, MD

In the eight month period from September 1942 to May 1943, 517 patients with pneumonia were treated at this hospital. The diagnosis of pneumonia was substantiated in every case by a positive roentgenogram of the chest. No questionable cases of "minimal pneumonia," "pneumonitis," or similar indefinite diagnosis were included in this series. Patients with pneumonia as a contributory diagnosis to another illness were excluded.

Etiological Classification

Table 1 indicates that in the great majority, the pneumonia was due to the pneumococcus. Type VII pneumococcus was the most frequent specific type encountered and was also associated with the highest mortality. The gross mortality for the 338 patients with pneumococcal pneumonia was 11.5 percent. This figure compared favorably with the report by Bortz[1] of 11.7 percent mortality on over 9000 patients with pneumococcal pneumonia. Of the 121 cases of "undetermined" etiology, the majority were probably pneumococcal in origin, but the organisms were not isolated due to unsatisfactory sputum samples.

Table 1. Etiological Classification of 517 cases of Pneumonia

	Cases	Deaths	% Mortality
Pneumococcal	338	39	11.5
Staphylococcal	12	1	8.3
Streptococcal	15	0	0.0
Virus	31	0	0.0
Undetermined	121	2	1.6
Totals	517	42	8.1

Thirty-one patients were classified as having pneumonia of virus etiology, or "atypical" pneumonia, because of the characteristic roentgenogram showing a pneumonic infiltration of the central or lower left lung fields, associated with a low leukocyte count, slow pulse, scanty sputum and failure to respond to sulfadiazine therapy.

Complicating Conditions

Since sulfadiazine has been used in the treatment of pneumonia, the incidence of complicating conditions has markedly decreased. In this series of 517 patients, sterile pleural effusions were the most frequent complication and occurred in eleven patients (2%). All of these effusions

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remained uninfected and cleared under the management as outlined below. Empyema did not occur in a single patient in this series.

Asthmatic bronchitis was a common associated complicating condition, which tended to exhaust the patient, and make the treatment more difficult.

Acute glomerulonephritis, non-purulent arthritis, and erythema nodosum each occurred twice. Septic arthritis, acute bacterial endocarditis, meningitis, pulmonary embolism (on first ambulatory day), pelvic thrombophlebitis, and spontaneous pneumothorax, each occurred once.

Severity of Cases

In this series, 145 patients (28%) had pneumonic involvement of more than one lobe.

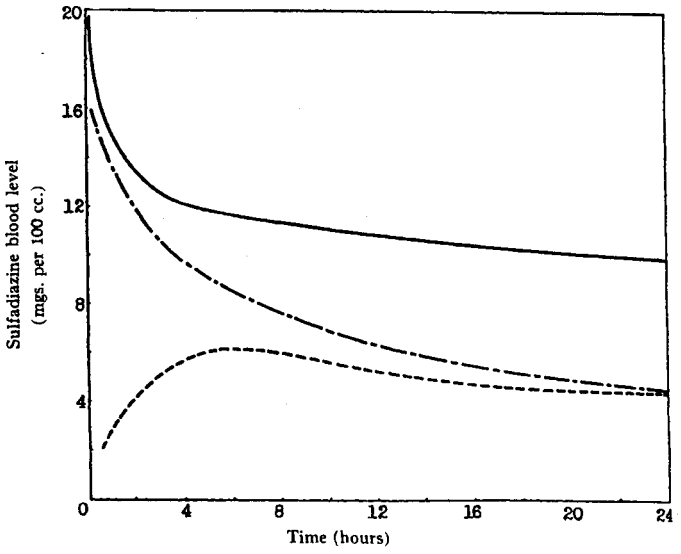
The gross mortality of the entire group of 517 patients with pneumonia was 8.1 percent, which is comparable to that of other large series, however, although gross mortality statistics are interesting, they are not significant, because of the multiplicity of factors which influence the mortality in pneumonia (age, number of lobes involved, complicating conditions, associated disease, etiological organisms, etc).

Chemotherapy

Chemotherapy is the most important single agent in the treatment of pneumonia. Before sulfadiazine was administered, specimens were routinely obtained for blood culture, sputum typing, complete blood count, and urinalysis.

Sulfadiazine is becoming universally accepted as the drug of choice for pneumonia, because (1) it is the drug most effective against the pneumococcus, streptococcus, staphylococcus, and the Friedlander's bacillus, (2) it is most effective as evidenced by comparative mortality statistics in large numbers of cases,[1] and (3) it is the least toxic of the sulfonamide group.[3]

Throughout the four month period from September to December, all patients with pneumonia received an average initial dose of five grams of sulfadiazine orally, then one gram orally every four hours thereafter, Graph 1 indicates the average curve (dotted line) obtained by plotting blood sulfadiazine determinations found at one, four, eight, twelve and twenty-four hours after an initial oral dose of five grams of sulfadiazine. The maximum concentration of the drug in the blood was reached between four and eight hours after this dose was given, the average level at this time being six to seven milligrams per one hundred cubic centimeters. Graph 1 emphasizes that (1) sulfadiazine is slowly absorbed from the gastrointestinal tract, forcing a delay of four to eight hours before therapeutic concentrations of the drug are obtained, (2) the initial oral dose which is usually administered, is entirely insufficient to obtain the full therapeutic blood concentrations necessary for optimum curative effect, (3) it is not necessary to administer sulfadiazine orally every four hours, since a proportionately higher dose every six to eight hours is just as effective. A few patients were given five grams each of sodium bicarbonate and sulfadiazine orally, but no changes in blood sulfadiazine concentrations, and no increase in absorption of sulfadiazine was evident.



Graph 1. Relationship between Blood Sulfadiazine Concentration and Method of Administration

Graph 1 also indicates the average curve (dot-dash line) obtained by plotting blood sulfadiazine determinations at one-quarter, one, four, eight, twelve and twenty-four hours after an intravenous dose of five grams of sodium sulfadiazine. Within fifteen minutes after the injection, a concentration of over sixteen milligrams per one hundred cubic centimeters was uniformly obtained. The blood level of sulfadiazine then fell gradually over the next twelve hours, so that between twelve to twenty-four hours the curves with oral and intravenous sulfadiazine were about the same.

By combining various initial oral and intravenous doses of sulfadiazine, it was finally determined that an initial dose on admission of five grams of sodium sulfadiazine intravenously and two grams orally, followed by two grams orally every six hours thereafter was optimal. This dosage produced an immediate rise in the blood sulfadiazine concentration to between sixteen to twenty milligrams per one hundred cubic centimeters (graph 1, solid line), then decreased within four hours to about ten to fifteen milligrams, where it remained fairly constant as long as the drug was continued.

During the four month period from December to May, all patients with pneumonia, received immediately on admission to this hospital, five grams of sodium sulfadiazine intravenously and two grams of sulfadiazine orally, followed by two grams orally every six hours thereafter. Table 2 indicates the mortality statistics of these two groups of patients, both treated identically in all ways by the same staff, except for the difference in dosages and route of sulfadiazine as indicated.

Table 2. Relationship between Sulfadiazine Administration and Mortality

Initial Dose	Cases	Deaths	% Mortality
1. Oral	108	10	9.3
2. Intravenous	409	32	7.7
Total	517	42	8.1

It should also be noted that the second and larger series included the majority of the winter group of patients with pneumonia, which it was felt, were on the whole more virulent in nature than the fall group. The average mortality for the group treated with five grams of sulfadiazine orally and one gram every four hours thereafter was 9.3 percent. The average mortality for the group treated with five grams of sodium sulfadiazine intravenously and two grams of sulfadiazine orally, then two grams orally every six hours thereafter, was 7.7 percent.

No greater incidence in sulfadiazine toxic reactions was noted in the higher dosage group than in the lower dosage group. Dowling[10] has shown that the incidence of relapse, spread of pneumonia to another lobe, and slow resolution was less than half as frequent in a group treated with small doses.

Since the length of time that elapses before treatment is instituted is a very important factor influencing mortality in pneumonia, it is essential that full therapeutic blood concentrations of sulfadiazine be obtained as soon as possible. Treating the patient by an initial oral dose of sulfadiazine implies that the patient lies in the hospital up to one-third of a day before the treatment becomes effective. Certainly where delay in a fraction of a day increases the mortality, it is not desirable to permit a patient with pneumonia to wait four to eight hours in the hospital for the sulfadiazine to be absorbed from the gastrointestinal tract, when within fifteen minutes an effective blood concentration may so easily be obtained by an initial intravenous injection.

All patients having pneumonia are now routinely treated immediately on admission with five grams of sodium sulfadiazine intravenously and two grams of sulfadiazine orally (blood and sputum specimens for the laboratory being obtained first), and then two grams of sulfadiazine orally every six hours thereafter. Patients who cannot take any oral medications are maintained on five grams of sodium sulfadiazine intravenously every twelve hours until oral therapy can be instituted.

Sulfadiazine blood concentrations were routinely determined between twelve to eighteen hours after admission. This was found to be imperative, since even though the majority of patients showed a blood level of ten to fifteen milligrams per hundred centimeters, in the individual case the actual blood concentration was unpredictable due to variations in hydration and renal function. If the blood concentration of sulfadiazine was found to be between seven to ten milligrams per hundred cubic centimeters, 2.5 grams of sodium sulfadiazine were immediately given intravenously, and the blood sulfadiazine level was again determined in twelve hours. If the blood sulfadiazine concentration was found to be less than seven milligrams, the full dose of five grams of sodium sulfadiazine was gain repeated intravenously, and further blood sulfadiazine concentrations were subsequently determined. If the blood level was found to be over twenty milligrams, sulfadiazine was discontinued for the next two doses, and the blood non-protein nitrogen or urea nitrogen was immediately checked. (Impaired renal function was the usual cause for excessively high blood sulfadiazine levels.) Fluids were forced in this latter group, and the blood sulfadiazine level was again determined in twelve hours; further dosage of the drug was governed accordingly. The blood sulfadiazine level was maintained between ten to fifteen milligrams per hundred cubic centimeters as closely as possible.

Sulfadiazine was maintained in full dosage until the temperature was normal for two to three days, then the drug was discontinued. The pulse, respirations, white blood count, and percent neutrophils should all be normal at this time, and the urine should show no albumin or casts (the latter were a valuable index to the toxicity of the pneumonia, since very toxic patients constantly showed marked albuminuria and many granular and hyaline casts.) Tapering of the dosage of the drug before stopping it is unnecessary; Bullowa has shown that this actually may be harmful.[5]

Table 3. Incidence of Sulfadiazine Toxic Reactions

Manifestations	Cases	Percent	(Finland) Percent
Crystalluria	40	7.7	7.4
Hematuria	7	1.4	5.2
Skin eruptions	5	1.0	1.5
Leukipenia	4	0.8	0.7
Psychosis	3	0.6	0.4
Fever	2	0.4	0.2

Sulfadiazine toxicity was encountered in twelve percent of the patients in this series. Table 3 lists the frequency with which each of the various toxic manifestations were encountered. The table also presents the frequency of toxic reactions as reported by Finland[4] in a series of 460 patients treated with sulfadiazine. It is apparent that no remarkable differences in frequency of drug toxicity occurred in the two series. It has been shown[6] that toxic reactions are no more numerous in patients treated with large doses of sulfadiazine than in those treated with small doses.

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Only patients who were reported by the laboratory as showing "many sulfa crystals" or "loaded with sulfa crystals" were included as sulfadiazine toxic reactions. The presence of only a few crystals in the urine was not alarming, and indicated only that the fluid intake of the patient should be increased, and that a daily urinalysis should be performed. The development of sulfadiazine crystalluria with or without hematuria indicated the need to (1) force fluids to 4000 to 5000 cubic centimeters daily, (2) observe output very carefully for oliguria, (3) perform daily urinalyses for pH and crystals, (4) give 500 to 1000 cubic centimeters of one-sixth molar sodium lactate solution intravenously. The pH of the urine is much more important in the solubility of

sulfadiazine crystals than the quantity of urine.[2] The use of sodium lactate solution was found to be very satisfactory; within eight to twelve hours after administering 1000 cubic centimeters of the solution, the pH of the urine rose and the sulfadiazine crystals disappeared in 90 percent of patients. The use of oral sodium bicarbonate is much less reliable and more variable in results. An occasional patient required daily injections of 1000 cubic centimeters of one-sixth molar sodium lactate solution for a few days to maintain relatively alkaline urine.

Hematuria without crystalluria was observed in four patients. No other explanation for the hematuria was apparent, and upon discontinuing the sulfadiazine and administering sodium lactate solution intravenously, the hematuria promptly cleared.

Skin eruptions were manifested in two patients as a morbilliform rash, and in three patients as a scarlatiniform rash. Sulfadiazine was discontinued whenever a toxic rash appeared, since maculopapular eruptions have been observed to progress into bullous and exfoliative dermatoses upon failure to discontinue the drug promptly.

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Leukopenia with a white blood count below 5000 cells per cubic millimeter, was observed in only four patients. The lowest count observed was 3200 white cells per cubic millimeter. The white count promptly rose in each case after the drug was discontinued and ten cubic centimeters of pentnucleotide was given intramuscularly three to four times daily.

Psychosis, manifesting itself primarily as a toxic delirium, developed in three patients on the fourth to sixth day of chemotherapy. Symptoms cleared within forty-eight hours after discontinuing the drug and forcing fluids. It has not been definitely shown that this psychosis is directly due to the sulfadiazine; giving full doses of the drug within a week after the psychosis cleared did not produce a return of the delirium.

Fever as a toxic manifestation of sulfadiazine was extremely rare. When a previously normal temperature became elevated it was found much safer to assume that there had developed an effusion, a spread of pneumonia, or some other complication, rather than to discontinue the drug on the basis of possible drug fever.

Serum Therapy

About one-fourth of the patients required adjuvant therapy, either in the form of specific serum, oxygen, or treatment for various complicating or associated diseases.

Forty-six, or nine percent, of this series of patients received type specific rabbit serum in addition to sulfadiazine. Six patients received 50,000 units each, twenty-one patients received 100,000 units each, five received 150,000 units each, twelve received 200,000 units each, and two patients received 250,000 units of serum each. A total of 6,050,000 units of serum was administered to this series of patients. Reactions to the rabbit serum occurred in only two cases, both of which had mild serum sickness. Indications for serum therapy which were encountered in this series were:

(1) patients with pneumococcal pneumonia who were sulfadiazine "sensitive" or sulfadiazine "fast," or for other reasons did not satisfactorily respond to chemotherapy, were given serum therapy;

(2) patients with pneumococcal pneumonia, who had not shown marked improvement by the time a positive blood culture was reported, received 50,000 units of serum intravenously every four hours until a definite fall in pulse and temperature occurred;

(3) patients with pneumococcal pneumonia with negative blood cultures, who showed no improvement in twelve to eighteen hours, received 50,000 units of type specific rabbit serum intravenously (after proper testing for sensitivity). Every four hours 50,000 units were injected until a definite fall in pulse and temperature occurred. Pneumococcal type VII pneumonia proved especially virulent this winter, and required serum more frequently than any other type;

(4) all patients with typed pneumococcal pneumonia who were over fifty years of age, or had multiple lobe involvement, acute or chronic alcoholism, (patients admitted with pneumonia and delirium tremens had an especially high mortality), severe liver or kidney damage, heart disease, diabetes, or pregnancy were carefully observed as possible candidates for serum therapy.

Indications varied, of course, with the toxicity of the individual case and with all the other factors which influence the mortality of pneumonia.

In severely ill patients with staphylococcic pneumonia, staphylococcus antitoxin was used as an adjunct. In two patients 40,000 units of antitoxin were administered intramuscularly twice daily up to a total of 240,000 units, with apparent benefit in one case.

Patients with virus or "atypical" pneumonia were treated by general supportive and symptomatic therapy. Sulfadiazine was usually discontinued when the diagnosis became certain and a coccal pneumonia was ruled out. No therapy which definitely hastened recovery was found.

Adjuvant Therapy

Fluids were forced to 4000 to 5000 cubic centimeters daily, preferably by mouth. Water, sweetened fruit juices, and the more nutrient fortified milk and egg drinks were encouraged. Frequently, certain fruit juices and milk distressed a toxic patient by aggravating tympanites; these were then withheld for a few days. When necessary, parenteral fluids were given by venoclysis, or hypodermoclysis in elderly and cardiac patients. During the initial period of marked toxicity, more than 1000 cubic centimeters of saline parenterally was advised against, since patients in impending shock may be thrown into pulmonary edema by excess salt. All patients' fluid intake and output was carefully measured and recorded. Oliguria was regarded as a grave sign, and was usually associated with a state of shock superimposed upon the "febrile nephritis" which is present in all patients with severe pneumonia.

Expectorants of the saline group were freely used to attempt to decrease the tenacious consistency of the muco-purulent sputum and permit free expectoration. Ammonium chloride

and potassium iodide were used in small doses three to four times daily. Patients occasionally became nauseated on treatment, and these drugs were discontinued first, as they were usually the cause; sulfadiazine was found to be extremely rare in producing nausea.

Oxygen was a very important agent in the treatment of these patients with pneumonia. The majority of the patients tolerated the soft rubber Barach-Eckmann injector mask[7] very well, and 95 percent oxygen was administered if the patient manifested high fever, rapid pulse or respirations, cyanosis, marked toxicity, or any evidence of impending shock. When the condition improved, 50 percent oxygen was continued as long as necessary. Due to the frequent momentary lifting of the mask to give fluids to the patient, excessive drying of the pharynx was rarely observed even when using 95 percent oxygen. An occasional patient in toxic delirium was unable to tolerate the mask, and then an oxygen tent was used for the first twenty-four to forty-eight hours.

Treatment of Complicating Conditions

Asthmatic bronchitis was a frequent complication in pneumonia and added to the dyspnea and anoxia of the patient. The bronchiolar obstruction being on an inflammatory basis, the usual measures which are successful in combatting allergic bronchial asthma were not as effective in asthmatic bronchitis. Epinephrine was usually tried first, using small doses so as not to increase an already excessive heart rate; minims five given hypodermically every fifteen minutes for three to four doses was much more effective than a larger dose given in one injection. If relief was observed, then one cubic centimeter of epinephrine in oil was given intramuscularly every eight hours until the asthmatic symptoms subsided. If epinephrine was not effective, aminophylline (theophylline with ethylenediamine) was used in doses of one-fourth to one-half gram intravenously; if relief was obtained, then one-half gram of aminophylline intramuscularly was given every eight hours until the symptoms of asthma subsided. Potassium iodide and ammonium chloride were helpful adjuvants in decreasing the tenacity of the mucoid sputum, permitting free expectoration.

Tympanites was infrequently seen, but it occasionally became a serious problem in very toxic patients. The individual or combined use of continuous 100 percent oxygen, pitressin or prostigmine in doses of one cubic centimeter hypodermically, an indwelling rectal tube, and/or enemas usually produced rapid decompression. All cathartics were routinely prohibited in patients with pneumonia; low tap water enemas every second or third day were effective in combating constipation and produced less abdominal distention.

Pleuritic pain was often a most distressing and disabling symptom. Intradermal injection of one percent procaine in a linear series of confluent wheals, perpendicularly to the course of the intercostal nerves, across the area of maximum pain, relieved about 60 percent of these patients. As indicated by the work of Lewis[8] the mechanism of relief is similar to that of referred pain. A tight scultetus binder across the chest was usually also very helpful. Immobilizing the chest with adhesive tape strapping has been strongly advised against, since complete fixation of the chest is undesirable, and severe blistering of the skin frequently results. Occasionally these measures do not furnish sufficient relief and the use of codeine is necessary.

Patients who coughed considerably frequently complained of upper abdominal and lower chest pain. This was apparently due to straining the abdominal musculature by paroxysms of coughing, and was usually completely relieved by a tight scultetus binder applied over the lower chest and upper abdomen.

Pleural effusions were subjected to a diagnostic thoracentesis as soon as the presence of fluid was established. From one hundred to two hundred cubic centimeters of fluid were removed, and fifty to one hundred cubic centimeters of air were usually injected, but the advantages of the latter procedure were questionable. If the effusion was sterile, sulfadiazine blood concentrations were maintained between ten and fifteen milligrams per one hundred cubic centimeters until the temperature was normal for at least ten days and the fluid was absorbed. Repeated determinations of concentrations of sulfadiazine in pleural effusions have shown, without exception, that the concentration of sulfadiazine was always higher in the pleural fluid than in the blood. There was no need for direct injection of sulfadiazine into the pleural cavity. Roentgenogram examinations of the chest for progress were repeated every five to seven days. Thoracentesis was performed again only for the relief of dyspnea, or if evidence of increasing fever and toxicity developed.

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Shock and pulmonary edema were usually associated as the most common immediate cause of death in uncomplicated pneumonia. Shock in pneumonia must be treated as vigorously as shock in any other condition. One must recognize, however, the increased tendency for patients with pneumonia to develop pulmonary edema. The recognition of developing shock indicated immediate treatment; 250 or 500 cubic centimeters of plasma were given intravenously and repeated as necessary. Patients with anemia were given whole blood transfusions. Ninety-five percent oxygen was administered by mask continuously. Parenteral crystalloid fluids were used restrictedly since they often precipitate pulmonary edema in a patient in a state of shock. If pulmonary edema was already apparent, one-half gram of aminophylline (20 cc.), fifty cubic centimeters of fifty percent sucrose, and 250 to 500 cubic centimeters of plasma intravenously were found to be most effective. Each of these having a definite purpose and value, the three agents were usually used together for full effect, and often dramatic clearing of the lungs resulted in an apparently terminal case. Patients were digitalized only if there was definite evidence of congestive heart failure or if auricular fibrillation developed. In these patients, eight cubic centimeters of cedilanid (lanatoside C) were administered intravenously.

Summary and Conclusions

1. In the last eight months, 517 patients with pneumonia were treated in this hospital with a gross mortality of 8.1 percent.

2. Sulfadiazine was advocated in the treatment of pneumonia in the following dosages: five grams of sodium sulfadiazine intravenously and two grams of sulfadiazine orally immediately on admission, then two grams of sulfadiazine orally every six hours thereafter. The advantages of this regime were: (a) the initial intravenous dose of sulfadiazine produced optimum therapeutic blood sulfadiazine concentrations within fifteen minutes; (b) there was a resulting lower gross mortality, lower incidence of relapse and complications, and better maintenance of optimum therapeutic blood sulfadiazine concentrations as compared to those of patients treated by lower doses.

3. No greater incidence of sulfadiazine toxicity occurred in this series as compared to others. Sulfadiazine crystalluria occurred in 7.7 percent of patients. Intravenous one-sixth molar sodium lactate solution was the most effective therapeutic agent in combating crystalluria.

4. Sterile pleural effusions developed in two percent of the patients. Empyema did not occur in a single patient.

5. Specific serum therapy, in addition to chemotherapy, was used in nine percent of the patients.

6. Other adjuvant therapeutic measures for associated or complicating conditions were used as outlined. ❖

Bibliography

1. Bortz, E. L.: Therapeutics of Pneumonia on a Statewide Basis. J.A.M.A. 121:107 January 9, 1943.

2. Jensen, O. L., and Fox, C. L.: Hyrdrogen Ion Concentration and the Solubility of Sulfonamides in Urine. J. Urol. '49:334, February 1943.

3. Dowling, H.F., and Lepper, M.H.: Toxic Reactions Following Therapy with Sulfapyradine, Sulfathiazole, and Sulfadiazine. J.A.M.A. 121:1190, April 10, 1943.

4. Finland, M., Peterson, O.L., Goodman, R.H.: Sulfadiazine; Further Clinical Studies of its Efficacy and Toxic Effects. Ann. Int. Med. 17:920, December 1942.

5. Bullowa, J.G.M., Schackman, N.H., Stals, D.: Chemotherapy of Pneumonias and Immunity Reactions. Ann. Int. Med. 16:57, Jan. 1942.

6. Dowling, H.F., Hartman, C.R., Feldman, H.A., and Jenkins, F.A.: Comparative Value of High and Low Doses of Sulfadiazine in the Treatment of Pneumococcic Pneumonia. Am. J. Med. Sc. 205:197, February 1943.

7. Cecil, R.L., et al.: Standards of Effective Administration of Inhalational Therapy. J.A.M.A. 121:755, March 6, 1943.

8. Lewis, Sir Thomas: *Pain*. Macmillan Co., New York, 1942.

Commentary by Elizabeth Anderson, MD, Infectious Disease Subspecialist at Oakland

I was fascinated and challenged upon reviewing this article by Dr. Collen and Dr. Dybdahl in the 1943 *Permanente Foundation Medical Bulletin***.** Caring for 517 pneumonia patients in an eight-month period was a major accomplishment. The article demonstrates that our founding physicians had the energy and intellectual curiosity not only to care for a large number of patients, but also: (1) to confirm a specific bacterial diagnosis in 70% by identifying and typing the bacteria, (2) to administer a new antibiotic, sulfadiazine, (3) to perform pharmacokinetic studies of sulfadiazine to determine optimal doses, (4) to record clinical complications of both the disease and the medication in a systematic fashion, and, finally, (5) to describe their findings in writing clearly and concisely.

An analogous study in our time with a similar volume of data might well have resulted in four publications: one on the epidemiology of pneumonia in a specific population—young men, mostly 4F draft rejects, building ships in Richmond in World War II; a second on the pharmacokinetics of a new antibiotic; a third on the efficacy of oral vs. intravenous sulfadiazine; and a fourth on management of a common disease and its complications, comparing outcomes with other reported series of cases. The writing is a fluid narrative with interspersed tables, instead of the formalized structure of today—abstract, introduction, materials and methods, results, discussion, and conclusions. Statistical analysis was not usual in the 1940s; for example, the comparison of mortality with oral therapy (10/108 = 9.3%) compared with intravenous therapy (32/409 = 7.7%) were reported with no p value. To the author's credit, no claim of importance of this mortality difference was made; in fact, one of his major concerns was that toxicity was not greater with intravenous therapy.

In evaluating a patient with pneumonia, clinicians today must to struggle more to identify a pathogen. Published series from academic centers indicate a specific diagnosis in only ~ 50% of cases, despite far more sophisticated diagnostic tools. The Gram stain remains, although bacterial typing by the Quellung reaction is long gone. Just to name a few current techniques suggests the magnitude of the advances: direct fluorescent antibody stains, polymerase chain reaction amplification, viral culture techniques. Almost surely, a substantial proportion of more straightforward cases are not hospitalized and have or need little diagnostic testing. Failure to identify a specific diagnosis is probably related in many to partial treatment before hospitalization, selection of fragile hosts (poor cough or inability to mount a purulent response to infection), and higher prevalence of fastidious organisms (anaerobes, mycoplasma, chlamydia, pneumocystis carinii, legionella, etc).

We are now rich in choices of specific treatment, with hundreds of antibacterial, antifungal, and antiviral agents. Serum

therapy is relegated to a few specific, uncommon situations (eg, gamma globulin for congenital or acquired agammaglobulinemia, or IVIG for immunomodulatory therapy with acyclovir for cytomegaloviral pneumonia in bone marrow transplant recipients). Treatment of pneumonia complications (such as bronchospasm or heart failure) has improved. Nonetheless, the nonspecific treatments are the same: hydration, pain relief, oxygen.

Pneumonia remains a tremendous burden for Kaiser Permanente. Today, pneumonia is less often a devastating interruption in the life of working individuals and more often an end-of-life event for the aged, or for persons with multiple organ failure, or an immunocompromised condition. The clinical challenge is the same as that faced by our colleagues in the 1940s. One should attempt to make a specific diagnosis, administer the proper antimicrobial drug, and always support the patient's comfort needs and recovery. Perhaps we do not often enough meet the intellectual challenge of our profession to systematically examine and record the details of experience, so that we may improve the care we give.

I remember a conversation with Dr. Collen shortly after I arrived at Oakland. I complained that it often seemed hard to provide much help to patients, and that doctors often couldn't really do much to heal the sick. He gently chided me, reminding me of the great advances in medical treatment since the Richmond shipyard days. He painted a vivid picture of country boys from the South and Midwest, many rejected from the military because of illnesses like asthma or rheumatic heart disease. They came to California to build ships; many stepped off the train already exhausted and ill. When they were hospitalized with pneumonia, often to die, "all we had was oxygen, fluids by clysis, and sulfadiazine." He added, "be thankful you are practicing today." ❖

Interdependency

"Interdependency ought to be as sought after as self-sufficiency."
Mohandas Gandhi