



Kaiser Permanente Medicine 50 Years Ago:

A Study of Acute Appendicitis with Perforation with Special Emphasis on Sulfonamide Therapy —A Preliminary Report

By RB Henley, MD; NL Haugen, MD
Commentary by John T Igo, MD, FACS

There have been 427 appendectomies performed in this hospital since August 1942. Fifty-one perforated appendixes were encountered. There have been no deaths in the combined series. The different pathological forms and other data of acute appendicitis with perforation, which we have encountered, are outlined in the charts below accompanied by a discussion of each type.

In the following charts, statistics have been compiled concerning the length of illness prior to hospital entry, the number of days sulfonamides were given postoperatively, sulfonamide levels maintained postoperatively, the complications and the number of days in the hospital. In addition, indications are made as to whether sulfonamides were placed in the wound and whether the wound was drained. The same routine was carried out in all the patients with regards to sulfonamide therapy except for a few minor variations. Ten grams of sulfathiazole were placed within the abdomen in the form of an emulsion. Five grams of sulfathiazole were placed in the form of an emulsion in the separate layers of the wound. Wangenstein naso-gastric suction was used in most cases postop-

eratively for one to three days and during this time 2 1/2 gr of sulfadiazine were given intravenously three times a day accompanied with 500 cubic centimeters of 1/6 M sodium lactate solution to maintain an alkaline urine. After the removal of the stomach suction, 2 gr of sulfadiazine were given four times each day with liberal amounts of soda. The patients were usually kept on this regime until afebrile. An effort was made to maintain a blood sulfadiazine level between 10 and 15 mg per hundred cubic centimeters in those patients who were quite ill. It is difficult to maintain high levels unless large amounts are given. The weight of the patient, the fluid intake and output and the time of blood collection for sulfonamide level determinations, are all factors to be considered when one is analyzing blood levels. The blood levels indicated in the charts were obtained on different postoperative days. We routinely obtained the first level some time within the first 24 hours after surgery and subsequent levels every three or four days. A small rubber drain was inserted down to the peritoneum in most cases and this was removed in one to three days.

A reprinted article from *The Permanente Foundation Medical Bulletin* with a current commentary

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Commentary

By John T Igo, MD, FACS

In 1944, *The Permanente Foundation Medical Bulletin* published a review by RB Henley, MD, and NL Haugen, MD, about the then-young¹ Oakland and Richmond Permanente Foundation Hospitals' experience with complicated appendicitis. I am delighted to have this opportunity to offer my commentary on the article because Norman Haugen was on the teaching staff of the Kaiser Permanente (KP) Oakland Medical Center when I arrived there as a junior surgical resident in 1960. Dr Haugen remained on the staff until his retirement in the mid-1970s. He was for decades a tireless and generous mentor to young men and women working in the General Surgery Program, and, to this day, he remains my good friend and neighbor. After being influential in KP's early teaching program in surgery, Dr Henley returned to fee-for-service practice in post-WWII Oakland.

Appendicitis: Historical Evolution of its Diagnosis and Treatment

Since the Middle Ages, physicians have recognized a clinical entity associated with severe inflammation of the cecal region. Termed "typhlitis" or "paratyphlitis" (from the Greek *typhlos*, meaning "blind" and referring to the anatomy of the first part of the cecum), the disease was for hundreds of years considered fatal. In 1886, Professor Reginald Fitz at Harvard Medical School gave the first clear, logical description of the clinical and pathologic features of the disease by using the term appendicitis.^{2,919} In 1889, New York surgeon Charles McBurney advocated prompt diagnosis and early appendectomy—recommendations that led the medical profession toward modern treatment of the disease.^{3,1192} Subsequently, surgical results in patients with an acutely inflamed, nonperforated appendix were satisfactory, but rates of postoperative morbidity and mortality were high among patients for whom delayed diagnosis led to a perforated appendix with peritonitis.^{3,1192}

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Several of these patients remained in the hospital for a surprisingly short time. The average number of postoperative days in the hospital was 18.5.

In the majority of patients, peritoneal cultures were obtained and all were positive. In some instances, cultures were not obtained by the operating surgeon or they were not reported from the laboratory.

The 14 patients in Table 1 had had symptoms of appendicitis for one to four days prior to hospital entry except in one individual who had been ill for ten days with a very atypical history. In all of these, a generalized peritonitis was found as indicated by large amounts of turbid fluid with a distinct odor and in some instances, fluid which was almost milky in color. The appendiceal perforation was open and no form of real localization had taken place.

Wound infections developed in three of the patients who had sulfathiazole placed in wounds, and these did not require surgical drainage in the operating room except in one instance. One out of the two patients without sulfathiazole in their wounds developed a low-grade wound infection and the other did not. Six out of 13 patients developed various complications but none of these were serious except in patients EA and ET. None of these complications required further surgical draining except ET. Several of these patients remained in the hospital for a surprisingly short time. The average number of postoperative days in the hospital was 18.5.

In those patients outlined in Table 2, a perforated appendix was found which was fairly well walled off by the omentum or adjacent mesentery but with a definite abscess formation of some size and with evidence of a local surrounding peritonitis. Fourteen such cases are tabulated here and in general, these patients were not as ill as in Group 1. Sulfathiazole was placed in the wound of 11 of these patients and a low-grade wound infection developed in one. No wound infections occurred in three patients not receiving sulfathiazole locally. A total of three complications took place and these were minimal. The average number of postoperative hospital days equaled 9.7.

In those fourteen patients outlined in Table 3, perforation of the appendix had taken place only shortly before removal or during removal of a very gangrenous appendix. This type of pathology caused only local soiling around the regions of the cecum, but the total number of complications was greater here than in Groups 1 and 2. In 12 patients, sulfathiazole was applied locally and two developed wound infections. Neither of the other two cases without local sulfathiazole developed wound infections. Complications occurred in 11 patients, but many of these were minimal in character. In two patients, further

Table 1. Acute appendicitis with perforation with generalized peritonitis without abscess formation or any form of localization

Patient	Days ill	Days on Sulfa	Sulfa in wounds	Wound drained	Sulfa blood levels (mgs %)	Complications	Days in hospital
RS	2	8	No	No	18.0-7.0	Spontaneous wound drainage one week	19
JK	2	4	Yes	Yes	8.5-18.7	Pneumonia	13
EA	10	11	Yes	Yes	9.8-9.1	Pelvic and intra-abdominal masses, both subsiding. Hypoproteinemia. Wound drained seven weeks	36
EC	1	12	Yes	Yes	7.9-10.0	Subcutaneous wound abscess drained	20
JD	4	7	Yes	Yes	15.7	None	7
HG	1	12	Yes	No	8.3-10.0	Pelvic mass subsided	23
MM	18 hrs	14	No	Yes	18.7-5.3-9.2	None	22
OR	2	3	Yes	Yes	12.1-19.8-10.4	None	9
TS	3	6	Yes	Yes	5.3-6.3	None	9
JS	2	9	Yes	Yes	10.5	None	16
DS	2	14	Yes	Yes	11.4-9.5-11.9	None	16
GS	2	9	Yes	Yes	17.8	None	9
ET	1	20	Yes	No	8.7-9.9-8.6-10.2-10.3	Deep wound infection. Pelvic abscess. Pneumonia	60
DT		1	No	Yes	No report	None	7

**Table 2. Acute appendicitis with perforation with abscess formation and with local peritonitis only**

Patient	Days ill	Days on Sulfa	Sulfa in wounds	Wound drained	Sulfa blood levels (mgs %)	Complications	Days in hospital
JL	1.5	11	Yes	No	7.2	Ileus	16
FE	3	4	Yes	Yes	Non-reported	None	8
LR	2	None	None	Yes	Non-reported	None	7
GT	3	8	Yes	No	8.7-9.9	Subcutaneous wound drainage	14
CK	3	10	Yes	Yes	3.7	None	7
AH	1	17	Yes	Yes	3.1-3.5	None	19
WH	2	4	No	No	Non-reported	None	6
RK	4	1	Yes	Yes	Non-reported	None	12
OM	2	6	Yes	No	5.4-14.1	None	7
JP	3	6	Yes	No	2.7-14	None	7
UR	1	7	Yes	Yes	12.8	Subcutaneous hematoma	7
KS	3	5	Yes	Yes	3.5	None	10
RW	4	9	No	Yes	9.2	None	7
WR	2	10	Yes	Yes	7.1	None	10

Table 3. Acute appendicitis with perforation which occurred during or shortly before removal

Patient	Days ill	Days on Sulfa	Sulfa in wounds	Wound drained	Sulfa blood levels (mgs %)	Complications	Days in hospital
NJ	1	1	Yes	Yes	8.3	Pelvic cellulitis	14
IR	1.5	16	No	No	24.9-6.5-5.0-14.0	Pelvic abscess with post-colpotomy	46
CD	3	4	Yes	No	2.2-4.5	Peritonitis. Bowel obstruction	8
LF	3	8	Yes	Yes	11.8	None	8
DH	1	4	Yes	No	9.5-3.0	Subcutaneous wound infection	20
VJ	1	None	Yes	Yes	4.2	None	6
WK	1	9	Yes	Yes	8.7-9.0	Wound induration	11
EL	1	10	Yes	Yes	13.4	Pelvic abscess which drained spontaneously	13
EM	1	10	Yes	No	3.8-6.6-8.0-7.9	Deep retro cecal abscess which required drainage	21
OM	1	None	Yes	No	No report	Subcutaneous hematoma	8
LN	2	10	Yes	No	6.8	Subcutaneous wound infection	12
MG	2	5	None	Yes	8.2	Subcutaneous hematoma	11
WM	1	None	Yes	No	No report	None	5
MC	1	11	Yes	Yes	6.1	Wound induration	9

Table 4. Acute appendicitis with perforation with abscess formation and with generalized peritonitis

Patient	Days ill	Days on Sulfa	Sulfa in wounds	Wound drained	Sulfa blood levels (mgs %)	Complications	Days in hospital
EC	11	23	Yes	No	7.4-10.3-14.2	Subcutaneous wound infection	28
EB	2	6	Yes	No	10.7-7.3	Wound induration. Pelvic cellulitis subsided	21
RG	2	16	Yes	Yes	4.7-9.8	Pelvic cellulitis subsided	32

The incidence of wound infections is greater in wounds that are not drained as compared to those that are.

Statistics vary but most reports in the literature quote mortality percentages ranging from 10 to 14 ...

surgery was required. In one with a perforated pelvic appendix, a posterior colpotomy was necessary after the development of a pelvic abscess. In the other with a retro-cecal perforated appendix, drainage of a large retro-cecal abscess, was carried out nine days later. The average number of postoperative days in this group was 13.2.

In those three patients outlined in Table 4, a perforated appendix with a localized abscess had occurred, but in addition, there were signs of generalized peritonitis. Sulfathiazole was placed in all three wounds. A subcutaneous wound infection occurred in one. Another wound became indurated. The third wound healed without difficulty. Complications occurred in all three cases but none of these required surgical intervention. The average number of postoperative hospital days was 27.

The four patients outlined in Table 5 had palpable masses in the right lower quadrant without generalized findings. They were treated conservatively. Two of the patients developed a pelvic cellulitis which subsided spontaneously. All but one returned a short time later for interval appendectomies.

There was only one patient in our series with a history of several days of illness and he entered with findings of a generalized peritonitis without any form of localization. This data is outlined in Table 6. He was quite toxic and was treated conservatively. A pelvic cellulitis was the only complication and this subsided. He was discharged 37 days after entry. An interval appendectomy was performed four months later.

The patient in Table 7 was the only one in the series operated on immediately but did not have an appendectomy. He entered the operating room after a three-day history of abdominal complaints. A well-localized mass was found in the right lower quadrant with evidence of recent perforation. This was not disturbed and the appendix was not removed.

He developed a pelvic abscess which drained spontaneously through the rectum and later a subphrenic exploration was carried out for a cellulitis but no abscess collection was found. This patient remained in the hospital for 60 days and returned two months later for interval appendectomy.

The charts labeled 8 and 9 contain the types and numbers of complications and the incidence of wound infections with and without local sulfonamides and with and without drainage. These statistics indicate that the incidence of wound infections is greater in wounds that are not drained as compared to those that are. Wound infections were more frequent in those cases with local sulfathiazole implantation as compared with those without although the latter group of cases is very small. The incidence of wound infections was considerably greater when local sulfathiazole was used without wound drainage as compared to local sulfathiazole implantation with wound drainage.

The majority of complications outlined in Table 9 were minimal. Two wound infections and a pelvic abscess were drained in surgery. Subphrenic exploration was carried out in one patient. There were 22 patients in the series who recovered without any complications.

Discussion

The mortality in the surgical treatment of perforated appendicitis has been lowered in the past few years by the judicious use of the Ochsner regime. Statistics vary but most reports in the literature quote mortality percentages ranging from 10 to 14 with this regime. These figures are a great improvement over former mortality rates found prior to the use of the Ochsner treatment. Guerry,² in his discussion of a paper by Collier and Potter,¹ quotes two deaths occurring in a group of 135 cases of gangrenous, ruptured appendixes with diffuse peritonitis or a mor-

Table 5. Acute appendicitis with perforation with a localized mass; non-operated

Patient	Days ill	Days on Sulfa	Sulfa blood levels (mgs %)	Days in hospital	Complications	Follow-up
WE	7	4	10.4	9	None	Returned eight weeks later for interval appendectomy
PG	3	5	7.1-6.9	12	Pelvic cellulitis	Returned two months later for removal of acute appendix
CS	14	5	No report	8	None	Returned six weeks later for removal of retro cecal appendix with small abscess
WW	4	2	14.0	6 signed release	Pelvic cellulitis	Returned to work in four weeks. Hasn't returned for appendectomy.

**Table 6. Acute appendicitis with perforation with a generalized peritonitis without a local mass; non-operated**

Patient	Days ill	Days on Sulfa	Sulfa blood levels (mgs %)	Days in hospital	Complications	Follow-up
CF	6	22	8.2-35.5 16.0-14.3	37	Pelvic cellulitis	Interval appendectomy four months later

Table 7. Acute appendicitis with perforation with exploration and non-removal of the appendix

Patient	Days ill	Days on Sulfa	Sulfa blood levels (mgs %)	Days in hospital	Complications	Follow-up
EO	3	30	9.3-14.7-4.3	60	Pelvic abscess drained spontaneously Right subphrenic exploration	Returned two months later for interval appendectomy

Table 8. Relationship between incidence of wound infections and management of operative wound

	Number of cases	Incidence of wound infections number (%)
Sulfathiazole implantation with wound drainage	22	3 (13.6)
Sulfathiazole implantation without drainage	15	7 (46.6)
Wound drainage without sulfathiazole implantations	5	0
Wound closed without sulfathiazole implantation	3	1
Cases with local sulfathiazole implantation	37	9 (24.3)
Cases without local sulfathiazole implantation	8	1 (12.5)
Cases with wound drainage	27	3 (24.3)
Cases without wound drainage	18	7 (39.8)

tality of 1.4%. This is the smallest mortality rate for ruptured appendicitis found in the literature. Most authors quote percentages between five and ten with the use of the Ochsner regime.

The sulfonamides are a valuable adjunct to be utilized in the surgical management of perforated appendicitis. No deaths have occurred to date in any of our cases with a ruptured appendix. In those patients who have been ill for several days and have a localized mass in the right lower quadrant without generalized findings, it is probably better to wait and see if the mass will become smaller and resolve. If this occurs, interval appendectomy can be carried out later. If the mass increases in size, drainage will have to be instituted. These patients are given large doses of parenteral or oral sulfonamides.

In individuals with generalized abdominal findings, no local palpable masses, with relative short histories of illness such as one to four days and who are not moribund, immediate appendectomy should be

carried out, accompanied by the liberal use of intraperitoneal sulfathiazole followed by parenteral and oral sulfadiazine.

Sulfathiazole will remain within the peritoneal cavity several days since its absorption is quite slow. Large doses of sulfadiazine can be given orally or parenterally and the incidence of untoward effects is very low. There were no complications in our series and only occasionally did red blood cells appear in the urine. The precipitation of crystals was prevented by adequate alkalization and increased fluid intake.

There is considerable variation in the blood sulfadiazine concentration levels even when patients are receiving the same amounts of the drug and these are probably largely due to the weight of the patient, the fluid intake and output and the time at which the technician obtains the blood sample. The amounts of the drug given by us, however, usually maintained a level of 6 to 10 mg per hundred cubic centimeters.

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Table 9. Types of complications

Complications	Number of cases
Wound infections	10
Pelvic cellulitis	4
Pelvic abscess	3
Pneumonia	2
Intra-abdominal abscess	1
Ileus (paralytic)	1
Subcutaneous hematoma	3
Partial bowel obstruction	1
Wound induration	3
Subphrenic inflammation	1

The liberal use of sulfonamides has enabled us to operate early on several cases who might otherwise have been treated conservatively for the time being, with the Ochsner regime. Sulfonamides will probably increase the early operability of perforated appendixes.

A McBurney incision was used routinely and patients were allowed to become ambulatory as soon as they became afebrile. Cotton was used routinely as the suture material and only one persistent sinus was found in the series. Many retro-cecal and pelvic appendixes are mechanically difficult to remove. In these, we divided the base first, inverting the stump after phenolization and then pushed the cecum back within the peritoneal cavity. Small tapes were then placed to give a good view of the appendix, the cut end of the appendix being held like a handle with two previously placed Kelly hemostats. The appendix was then removed in a retrograde manner.

Four additional cases can be added to our series at this date of publication. This makes a total of 55 perforated appendixes. One of these four patients was a

three-year-old girl and she made an uneventful recovery except for a low-grade wound infection. No complications occurred in the other three cases. The amount of sulfonamides were increased in these three cases in an effort to maintain a blood level of 15 to 20 mg. Fifteen grams of sulfathiazole were placed intraperitoneally and 5 gr in the wound; 2 1/2 gr of sulfadiazine were given three to four times daily intravenously after surgery and when the Wangenstein suction was removed 3 gr were given four times daily instead of twice. We believe that higher blood level concentrations will decrease the incidence of complications which we have found.

Conclusion

1. No deaths occurred in 55 cases of perforated appendicitis.
2. Immediate operation with removal of the appendix was carried out in all but five cases. Interval appendectomy was carried out later in these.
3. Intraperitoneal sulfathiazole, parenteral and oral sulfadiazine are valuable adjuncts used in the surgical treatment of perforated appendicitis.
4. Sulfonamide therapy used intensively will probably increase the early operability of late perforated appendicitis.
5. An operative mechanical maneuver is described which facilitates the removal of difficult appendixes situated in a retro-cecal or pelvic position. ♦

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Commentary

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Ochsner⁴ and others concluded that for patients initially seen late in the course of the disease, conservative treatment was sometimes safer. "Conservative treatment" in this context meant bedrest, fluids administered parenterally, and nothing given orally—along with close observation of patients with prolonged symptoms, a mass in the right lower quadrant, and not more than minimal peritonitis.⁴ For these patients, surgery might impair the barriers built by the body to contain and neutralize infection and might introduce risk of serious wound infection.⁴ If clinical improvement was seen, the patient was sent home after the mass became smaller and inflammatory signs diminished.⁴ Recurrence was frequent, and interval appendectomy at about six weeks after discharge was therefore advised.⁴

Two types of cases remained unsolved: 1) patients with a mass and spreading peritonitis and 2) patients who have obvious perforation and generalized peritonitis and for whom surgery (with its attendant risk of

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Commentary

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morbidity) is the only treatment option. Endless debate raged about types of drainage, best choice of irrigation fluids, the question of whether irrigation of the peritoneal cavity dilutes or spreads infection, and safe ways to clean the contaminated abdominal wound. Development of antibiotic agents offered a way to treat complicated appendicitis and promised to make these questions unnecessary and to reduce morbidity and mortality from complicated appendicitis to a rate closer to that of nonperforated appendicitis. The article by Drs Henley and Haugen was an early attempt to understand the benefits of the new drugs.

Five of the 51 patients described in the article were treated by the conservative Ochsner method with addition of sulfa drugs. Results were good: No mortality occurred, and mean length of hospitalization was 14 days (one patient remained hospitalized for 37 days, but this data point was the sole outlier). Four patients returned for interval appendectomy before recurrence, and one patient was unavailable for follow-up.

The other patients described by Drs Henley and Haugen were treated with surgery when the diagnosis was made. The infection was treated by a sulfathiazole emulsion placed both in the abdominal cavity and in the layers of the wound. Sulfadiazine was given postoperatively, first intravenously and then by mouth. One patient received no sulfonamide, and three patients received sulfonamide only locally to the wound. The 46 patients in the series had 21 septic complications (at a total septic complications rate of about 50%) and a mean postoperative hospital stay of 15 days. This finding should be compared with those that were usual in the preantibiotic era: a 75% rate of wound infection in addition to intra-abdominal and chest infections when peritonitis or a gangrenous appendix was found at operation.^{3,1220} To the surgeons' and to sulfonamide's credit, no mortality occurred in the patients in the series. Sulfonamide administered at this dosage would thus seem helpful—but not a complete success—in eliminating morbidity from sepsis. Recognizing this likelihood, the authors reported that subsequent cases were being treated to raise levels of the drug in the blood. The technique used by the authors for retrograde removal of the retrocecal appendix is described near the end of the article and is still being used regularly to good effect at the KP Oakland Medical Center.

Modern Developments

Many antibiotic schedules have been explored in the 57 years that have ensued since publication of the article by Drs Henley and Haugen, and clinicians have had considerable success in reducing sepsis in patients with complicated appendicitis. Current practice usually includes a regimen of multiple antibiotics begun preoperatively and directed at aerobic and anaerobic bacteria. Use of the drugs is discontinued after several doses if the disease is found to be uncomplicated; if the peritoneum is soiled, the drug regimen is continued as long as clinically appropriate. Adequate preoperative levels of antibiotic agents in the blood help protect against wound infection and development of peritonitis. Secondary closure of the wound on the second or third postoperative day may prevent infection.

With use of modern antibiotic agents, sepsis nonetheless develops in 5% to 20% of patients with complicated appendicitis.^{2,925} Modern antibiotic regimens have thus reduced—but have not eliminated—the high cost of treating mixed bacterial infections in the abdominal cavity and surgical wound. In England and Wales during the preantibiotic era, 3000 deaths from appendicitis were reported each year; by 1985, the mortality rate was reduced to 147 deaths per year^{3,1221} and is now less than 1%.^{2,919}

Modern abdominal imaging and nuclear medicine have led to immeasurably improved treatment of complications of appendicitis, but diagnosis of early appendicitis has not been improved since 1944 despite advances in abdominal imaging and laboratory techniques.⁵ Diagnosis still depends on a carefully assembled medical history, skilled physical examination, and routine laboratory testing. Even when a highly capable physician has made the diagnosis, a normal appendix is found in about 15% of operations.⁵ Laparoscopic surgery is well accepted as the primary operation and is especially beneficial when a normal appendix is found and the rest of the abdomen must be searched to establish the postoperative diagnosis.

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Most series report a 15% to 20% rate of gangrene or perforation, and my own clinical experience has shown that about a third of patients we treat for complicated appendicitis endure appendicitis, not seeking help until perforation occurs.

Commentary

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Future Management of Appendicitis

What might be the next step to improve the treatment of appendicitis? Early diagnosis and prompt surgery as taught by McBurney still seems the answer, because removal of the inflamed appendix before it evolves to gangrene or rupture yields both a permanent cure and a low complication rate. Most series report a 15% to 20% rate of gangrene or perforation, and my own clinical experience has shown that about a third of patients we treat for complicated appendicitis endure appendicitis, not seeking help until perforation occurs. They seem not to believe that they are truly ill until rupture convinces them. Another third have perforation that seems to occur simultaneously with onset of illness; for these patients, the earliest possible operation is already late. (The remaining patients are examined early in the course of the illness but do not receive the diagnosis at that time.)

We can hope that breakthroughs in laboratory or imaging techniques will simplify diagnosis of appendicitis. Patient and physician education as to the early signs and symptoms of the disease will certainly allow earlier diagnosis. Progress may well be made in treatment of appendicitis-related infection, but the grim complications of the disease will always be with us. ❖

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After completing his training at the Oakland Kaiser Permanente Medical Center, **John T Igo, MD, FACS**, joined its surgical staff. He moved to the new Martinez Medical Center as its first Chief of Surgery, remaining to become Physician-in-Chief. He is now enjoying retirement. E-mail: johnigo@earthlink.net.