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Surgical Sepsis: *
Analysis of Factors Associated with Sepsis Following Appendectomy (1937–1959)

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THIS is the fourth report in a series concerned with the incidence of sepsis and the analysis of associated factors following different standardized operations. Other aspects of the management of appendicitis at this hospital over the past 20 years are presented separately;[5] here we are concerned with the septic complications following appendectomy and appendicitis. Three previous studies considered sepsis following inguinal herniorrhaphies, abdominal hysterectomies, and subtotal gastrectomies.[2-4] These procedures are nominally *clean* operations; a study of an operation directed toward the treatment of a septic process, such as appendicitis, would provide a contrasting experience. The lessons to be learned about the incidence and development of postoperative sepsis vary from one procedure to another. An example of this is the importance of blood transfusions in the prevention of sepsis following subtotal gastrectomies.[4] This relationship was not apparent in the study of lesser procedures where minor blood losses required no replacement. The disease, appendicitis, was chosen to provide a standard septic pathological entity treated by essentially uniform operative technics over the past 20 years.

Since appendicitis follows a uniform pathological pattern in thousands of patients over the years, alterations in the clinical course may be correctly ascribed to treatment and not to alteration in the basic disease process such as we see, for example, in attenuated forms of pelvic in-

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TABLE 1. *Classification of 7,810 Cases in Appendectomy Study, 1937–1959, Massachusetts General Hospital*

Group	Gross Pathology	Deaths, No. Cases, %	Survivors: Drainage of Incision or Secondary Closure, No. Cases	Survivors: Primary Closure, No. Cases	No. Cases
A	Normal appendix	4 0.2	12	1,962	1,978
B	Inflamed appendix, not gangenous	5 0.1	136	3,990	4,131
C	Gangrenous appendix, not perforated	4 0.6	85	555	644
D	Perforated appendix with or without small abscess formation	29 3.6	457	320	806
E	Appendiceal abscess *not* treated initially by appendectomy	33 13.1	142*	76**	251
Totals		75			7,810

* These cases had initial incision and drainage of appendiceal abscess followed, in 82 per cent of the cases, by interval appendectomy.

** These cases had initial period of non-operative management for appendiceal abscess. Subsequently they had interval appendectomy or right colon surgery for treatment of sepsis of appendiceal origin.

flammatory disease now cared for on an ambulatory basis. By restricting our review to appendectomies we have, as with the previous operations studied, a highly uniform surgical experience to analyze. This report considers in sequence: organization, results, and interpretation.

Organization

Record Survey. This study was conducted in a fashion similar to the previous ones on surgical sepsis reported from this hospital. The case records were reviewed by a panel of four nurses who had been carefully coached and drilled in the interpretation of the hospital case records. All records with clear evidence or suggestive evidence of a septic complication were set aside for a subsequent review by a panel of four surgeons. In addition to these records the surgeons reviewed all records of patients who had appendectomy with drainage through the incision. Consistent and accurate classification of such cases in regard to the development of a significant septic complication obviously requires careful surgical judgment. Two categories of sepsis were defined as follows:

Minor Sepsis. Inflammation of the abdominal wall incision of unusual degree requiring local or systemic treatment or associated with febrile response or leukocytosis or prolonged hospitalization. Except for the most trivial of reactions all that were localized around skin sutures or through-and-through sutures were placed in this category. Drainage or positive cultures were not requirements for minor sepsis.

Major Sepsis. Inflammation of the abdominal wall incision or peritoneal cavity, or both, associated with spontaneous or surgically induced purulent drainage greater than a few drops. Intra-abdominal inflammatory masses and abscesses, when diagnosed clinically and even when external drainage was not apparent, were considered major sepsis. Positive cultures were not a requirement for inclusion in this category.

In considering those patients who had appendectomies with drainage the reviewing surgeons decided whether or not the procedure resulted in a satisfactory resolution of the septic process noted at operation or had been followed by a septic complication developing and extending after the operation. Thus, where the septic process despite drainage did not resolve smoothly, was inordinately prolonged, or spread to other anatomical sites removed from the appendix, a septic complication was *ipso facto* present. In short, this distinction allowed the classification of the cases of appendectomy with drainage into two groups: those in which appendectomy and drainage satisfactorily handled the septic condition and those in which the outcome fell short of reasonable surgical expectations for progressive recovery.

Cases with appendiceal abscess formation (Group E), in view of localized or generalized sepsis at the time of initial treatment, were not classified as septic or non-septic. However, 33 deaths in this group were separated into those primarily due to sepsis and those primarily the result of a nonseptic process such as cerebrovascular accident, nonspecific cardiorespiratory failure, pulmonary embolus, and so forth.

Selection of Cases. Over the 23-year period covered by this study all cases of appendicitis were collected from the diagnostic and operative files of the hospital record room. Appendectomies carried out in the absence of any recognizable appendiceal disease are also included when not combined with major abdominal procedures such as cholecystectomy, hysterectomy or gastro-intestinal resection. Thus appendices removed in conjunction with such diagnoses as mesenteric lymphadenitis or ruptured ovarian cyst or with such simple procedures as oophorectomy, presacral neurectomy, diagnostic explorations of the abdominal cavity, or biopsy procedures were included to provide statistics on postoperative sepsis when the appendix was not inflamed.

An accurate and consistent method of classification was available through the description of gross pathologic changes recorded in most cases by the surgeon, the assistant at operation, and the pathologist. In general the surgeon's detailed operative note was given the greatest weight in determining the classification. Cases were divided into five groups representing successive stages of the disease and designated by letter. In Table 1 are listed these groups with their definitions, total number of cases in each group, mortality of each group, and number of survivors in each group divided into those with primary closure and those with drainage of the incision or secondary closure.

The pathological process of acute appendicitis spans all stages of inflammation from the minimally inflamed appendix to abscess formation. The consequences of treatment of a mildly inflamed appendix have little in common with those of an appendiceal abscess. Hence, the data are presented in terms of one of the five individual groups. The necessity of such interpretation is obvious, and many reports on appendicitis have adopted a similar approach.[6-8, 11-13] An over-all mortality figure is not given in Table 1 since it would merely be a reflection of the relative size of the different groups rather than anything more significant.

The relative proportion of the different groups did not alter in the 23-year period of this study. Table 2 provides evidence

TABLE 2. *Distribution of Groups in Three Periods*

Group	1937–40 %	1941–45 %	1946–59 %	1937–59 %
A	27	26	24	26
B	55	53	52	53
C	7	8	9	8
D	8	10	12	10
E	3	3	3	3
	100	100	100	100
No. Cases	2,387	2,016	3,407	7,810

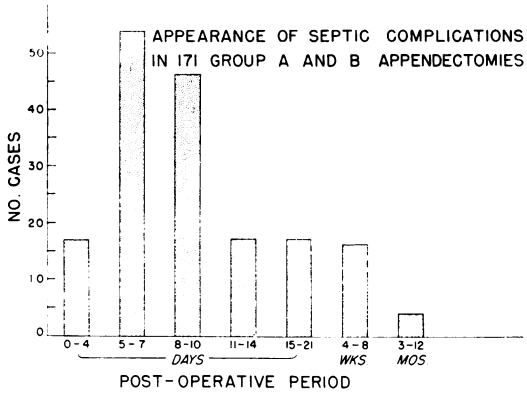

FIGURE 1.

of the constant distribution of the various groups. Apparently for more than 20 years the surgeon has been confronted with 18 per cent

$$\left(\frac{D+E}{B+C+D+E}\right)$$

of cases of acute appendicitis in an advanced unfavorable stage of the disease. There is no suggestion that patients are referred to this institution earlier now for operation than 20 years ago. The three periods selected in Table 2 coincide with the pre-blood bank and pre-antibiotic era (1937–1940), the post-blood bank and pre-antibiotic era (1941–1945), and the post-blood bank and post-antibiotic era (1946–1959). In subsequent discussion, data are analyzed in these three periods in view of the potential effects of liberal use of whole blood and plasma and massive use of antibiotics on the treatment of appendicitis.

Follow up Study. Follow up study was not continued beyond one year. If a complication developed, however, the record was reviewed until the patient recovered. In cases cared for on the general service of the hospital and subsequently followed in the outpatient department 20 per cent of all the septic complications were noted on follow up visits to the clinic, and these were mostly minor ones as defined above. On the private service it was not practical to obtain similar information after discharge from the hospital. Therefore, the total figures on incidence of sepsis may be 5.0 to 10 per cent less than the absolute value, but for comparative purposes extending over the years we have no reason to believe that this difference in the follow up should alter our interpretations because the relative proportion of general service cases and private service cases has remained the same. Figure 1 indicates the approximate times when septic complications were identified in general service cases in Groups A and B.

TABLE 3. *Incidence in 1,927 Group A Appendectomies of Septic Complications* *

Year	No. Cases	Minor Sepsis %	Major Sepsis %	Total Sepsis %
1937	202	0.50	2.47	2.97
1938	188	1.06	1.60	2.66
1939	110	0	.91	.91
1940	138	.72	1.45	2.17
1941	116	1.72	0	1.72
1942	96	1.04	0	1.04
1943	94	0	2.13	2.13
1944	112	0	.89	.89
1945	94	0	4.26	4.26
1946	80	0	0	0
1947	62	0	0	0
1948	58	0	0	0
1949	59	0	0	0
1950	62	1.61	0	1.61
1951	53	0	1.89	1.89
1952	56	0	0	0
1953	49	0	4.08	4.08
1954	46	2.17	0	2.17
1955	48	0	0	0
1956	71	0	1.41	1.41
1957	45	2.22	2.22	4.44
1958	22	0	0	0
1959	67	0	0	0
Total	1,927			
All cases		0.52	1.19	1.71

* Chi-square values for total sepsis of individual years, when compared to 1.71 per cent, range from <0.001 in 1941 to 3.6 in 1945. For entire 23-year period sum of chi-squares is 20 with $0.5 < P < 0.8$. Therefore, extreme values in 1941 and 1945 may reasonably be explained on the basis of random sampling of an essentially uniform risk of sepsis. There is no evidence for questioning the homogeneity of surgical material as far as the risk of sepsis is concerned.

Evaluation of Antibiotics. Use of antibiotics led to the division of the Group A patients into three categories. Patients who received no antibiotics at any time or only after a septic complication developed were placed in one category as a control. Those patients who received antibiotics immediately preoperatively or in the immediate postoperative period for at least four successive days were placed in a second category as representative of the prophylactic use of these drugs. A third class of patients included those who had inadequate or irregular doses of antibiotics or had the drugs started later than the immediate postoperative period. These patients were set aside as they would include many who received antibiotics for a specific reason and would include many with a definitely increased risk of sepsis. Antibiotics employed included penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracycline, chloramphenicol and erythromycin. These were prescribed in the generally accepted dose ranges of one-half million units of penicillin or more per day or 1.0 Gm. or more per day of the other antibiotics. Children received doses proportionate to their weight.

Evaluation of the use of antibiotics in Groups C, D, and E could not be achieved by a comparison of the results in two groups of contemporaneous surgery since the group treated with antibiotics would obviously contain the more hazardous cases. The effect of antibiotics and the use of whole blood and plasma in each group was reviewed by a comparison of the results in all cases between the periods defined in Table 2.

Results

Results of this investigation are set forth in Tables 3 through 9 and in Figures 2 and 3.

Incidence of Sepsis. The incidence of sepsis in Groups A and B is shown in Tables 3 and 4 and in Figures 2 and 3. In these numerically larger groups it is possi-

TABLE 4. *Incidence in 3,988 Group B Appendectomies of Septic Complications* *

Year	No. Cases	Minor Sepsis %	Major Sepsis %	Total Sepsis %
1937	394	1.02	1.52	2.54
1938	318	.94	3.46	4.40
1939	289	2.08	3.11	5.19
1940	298	1.01	.67	1.68
1941	295	0	2.71	2.71
1942	233	2.14	1.29	3.43
1943	165	2.42	2.42	4.84
1944	147	0	.68	.68
1945	142	1.42	1.42	2.84
1946	138	0	2.90	2.90
1947	143	0	3.50	3.50
1948	155	0	.65	.65
1949	157	1.27	2.55	3.82
1950	163	.61	3.68	4.29
1951	118	.85	1.69	2.54
1952	95	0	5.26	5.26
1953	115	0	2.61	2.61
1954	108	1.85	2.78	4.63
1955	98	2.04	5.10	7.14
1956	97	0	3.13	3.13
1957	118	.85	3.39	4.24
1958	75	0	1.33	1.33
1959	127	.79	7.09	7.87
Total	3,988			
All cases		.93	2.53	3.46

* Chi-square values for total sepsis of individual years, when compared to 3.46 per cent, range from <0.001 in 1942 to 7.4 in 1959. For entire 23 year period sum of chi-square is 31, with $0.1 < P < 0.2$. Therefore, extreme values in 1942 and 1959 may reasonably be explained on the basis of random sampling of an essentially uniform risk of sepsis. There is no evidence for questioning the homogeneity of surgical material as far as the risk of sepsis is concerned.

TABLE 5. *Influence of Antibiotics on the Healing of 1,811 Group A Appendectomies* *

Healing of Incision	Prophylactic Antibiotics	No Antibiotics	Totals
Nonseptic	118	1,664	1,782
Septic	1	28	29
Totals	119	1,692	1,811
% Sepsis	.84	1.65	

* Test of independence of healing of incisions and of employment of prophylactic antibiotics by chi square (with Yates' adjustment) gives a value of 0.09 with $P > 0.7$. Therefore, there is no evidence that prophylactic use of antibiotics has any influence on incidence of sepsis in the healing.

TABLE 6. *Incidence of Septic Complications in 1,417 Surviving Group C and D Cases* *

Postoperative Course	C Cases			D Cases			Totals
	1937–40	1941–45	1946–59	1937–40	1941–45	1946–59	
Nonseptic	149	140	258	139	146	310	1,142
Septic	21	29	43	28	56	98	275
Totals	170	169	301	167	202	408	1,417
% Sepsis	12.4	17.2	14.3	16.8	27.7	24.0	

* There is no significant change in the incidence of septic complications in the C cases. In the D cases testing independence of the incidence of septic complications and the periods before and after January 1, 1941 by chi square gives a value of 4.8 ($0.02 < P < 0.05$). Therefore, there is evidence that the incidence of septic complications has increased since the earliest period in D cases. Testing independence of the C and D cases after January 1, 1941 similarly gives a chi square value of 15.3 ($P < 0.001$). Therefore, there is evidence that the two groups of cases have different rates of septic complications in the last two periods.

ble to present comparative statistics on a yearly basis. The discrepancy between the totals of Tables 3 and 4 with Table 1 is occasioned by the removal of 194 cases from Groups A and B because of an associated septic process such as generalized pelvic inflammatory disease, localized pyosalpingitis, or perforated diverticulitis which alters their likelihood of developing postoperative sepsis. Such selection is essential for standardization.

The hazard of sepsis appears to be half as great in Group A as in Group B with no trend evident over the years. One in 100 develops a major complication of wound healing manifest by purulent drainage when a normal appendix is removed. In Figure 3 the years before and after the initiation of the blood bank and introduction of antibiotics are seen to have equal rates of sepsis in Group B.

In Table 5 are the data from Group A indicating that antibiotics have no significant influence on the healing of the appendectomy incision. The total number of patients selected for this comparison is smaller than the number of Group A cases in Table 1 for the reasons set forth under the discussion concerning the evaluation of antibiotics.

In considering the incidence of sepsis in the less numerous Groups C and D the patients are accumulated in three periods based on the intervals related to the functioning of the hospital blood bank in 1941 and the institution of antibiotic therapy in

TABLE 7. *Incidence of Deaths due to Septic Complications in 1,058 Group D and E Cases* *

Postoperative Course	D Cases			E Cases			Totals
	1937–40	1941–45	1946–59	1937–40	1941–45	1946–59	
Deaths due to septic complications	11	1	2	11	9	6	40
All other cases	171	206	415	66	59	101	1,018
Totals	182	207	417	77	68	107	1,058
% Mortality	6.1	0.48	0.48	14	13	5.6	

* The mortality rate in the first period in the D cases compared with the last two periods and the mortality rate in the first two periods in the E cases compared with the last period tested by chi square give values greater than 22 with $P < 0.001$. These trends in mortality rates are highly significant.

TABLE 8. *Average Number of Days Temperature Elevated to 38.3° C. or Higher in Group C and D Cases with a Septic Complication*

	C Cases			D Cases		
	1937–40	1941–45	1946–59	1937–40	1941–45	1946–59
Average no. days	5.9	5.4	4.7	7.5	4.9	4.7
% with no temperature elevation	25	25	36	15	11	24

1946. Table 6 presents data on the *survivors* in Groups C and D. In the three periods there is no alteration in the incidence of septic complications in Group C of about 14 per cent. However, in the Group D there is a rise in the incidence of septic complications from 17 to 28 per cent in the years following the liberal use of whole blood and plasma. In both groups there is no significant alteration of the incidence of septic complications following the introduction of antibiotics in 1946. However, in Group D a definite trend was apparent in the last period for the septic complications to localize in the region of the right lower quadrant rather than in other parts of the peritoneal cavity.

Another view of the problem of sepsis is had by tabulating *deaths* due to septic complications. Deaths caused by septic complications occurred in sufficient numbers in Groups D and E for analysis (Table 7). The relationship of the patients of Group D in this table to those of Group D listed in the previous table requires comment. The total of Group D in Table 6 is 777, 29 less than the number in Table 7. The explanation consists in the incidence of septic deaths in Table 7 being based on *all* patients, whereas in Table 6 only survivors are considered. Also it should be noted that in Table 7 the number of deaths unrelated to septic complications, such as those occasioned by nonspecific cardiovascular or respiratory failure, by pulmonary embolus or by myocardial infarction, are enumerated with the survivors. Thus in Table 7 we note Group D had only 14 deaths due to septic complications. Apparently in Group D there was a decline in the incidence of deaths due to septic complications after institution of the hospital blood bank, and in Group E a decline in deaths due to septic complications occurred following the introduction of antibiotics.

The evidence in this study for any favorable influence of antibiotics is confined to the decrease in incidence of deaths due to septic complications in Group E after 1945 and to localization of septic complications to the right lower quadrant in Group D. This reduction is consistent with an effect of antibiotics in preventing fatal spread of a septic process in the peritoneal cavity or elsewhere.

In view of lack of evidence that antibiotics altered the incidence of septic complications in Groups A, B, C, and D, other measures were sought to reveal the putative effectiveness of antibiotics. It is conceivable that although the incidence of septic complications was not altered, the

TABLE 9. *Age-specific Rates of Septic Complications in 445 Survivors* *

Age Group	% Total Sepsis			
	Group A	Group B	Group C	Group D
0–19	1.7	3.3	15	22
20–39	1.2	2.5	9	25
40–59	2.0	6.4	18	24
60–89	6.5	11.3	22	25
No. septic Cases	32	138	93	182

* Test of independence of adjoining age groups and of incidence of sepsis by chi square (with Yates' adjustment) gives only borderline statistical probabilities to suggest that the above age groups have a different incidence of septic complications increasing with age.

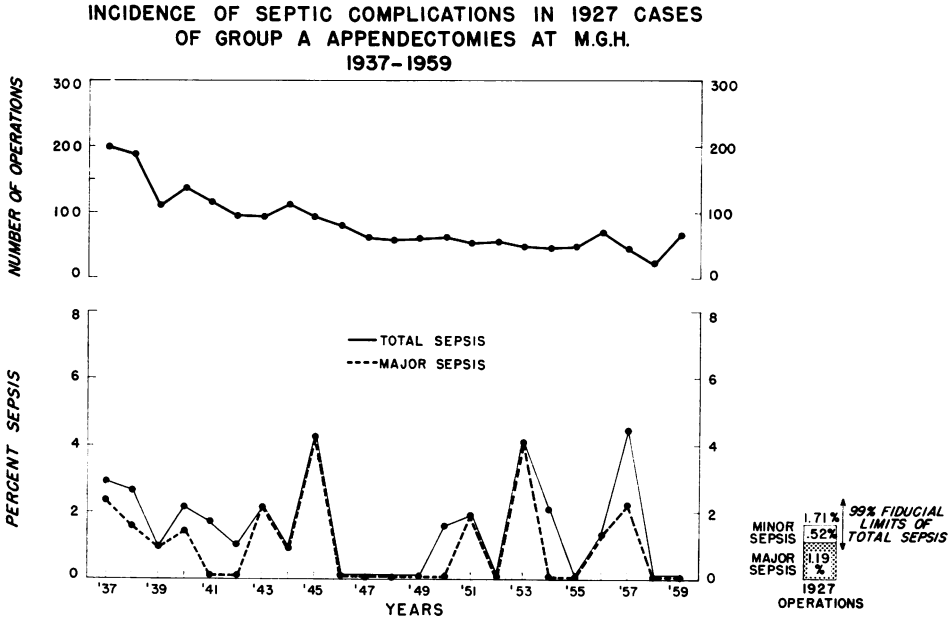

FIGURE 2.

intensity or duration of a septic complication might have been changed. These features of clinical sepsis are notoriously awkward to quantitate, and persistent efforts were made in this direction because there seemed little else to measure that might contribute to our understanding of the role, if any, of antibiotics.

In Table 8 is presented the average number of days that the patient's oral temperature was elevated at any determination to 38.3° C. or higher (38.8° C., rectally) in those cases of Groups C and D with a septic complication. These days were not necessarily consecutive, and this simple evaluation does not consider the height of the fever above 38.3° C. nor its duration on any particular day. The tabulated changes are of no practical significance in regard to any change in the intensity of the septic process.

In summary, in the more rigorous statistics of incidence of sepsis and of incidence of deaths due to a septic complication and in the more qualitative data on duration of temperature elevations there is little evidence that antibiotics have an appreciable effect on the course of appendicitis. The most significant exception to this is the incidence of deaths due to a septic complication in Group E where such deaths have been reduced from over 13 to 5.6 per cent since the introduction of antibiotic therapy.

Age-Specific Rates of Sepsis. In Table 9 are presented the age-specific rates of septic complications in the Groups A through D. There is only a slight increase in the incidence of sepsis as the age of the patient increases. The statistical significance of this trend is not impressive in view of the small size of the older age groups.

Interpretation

These data indicate that at this hospital the incidence of septic complications following appendectomy or treatment of an appendiceal abscess has remained essentially constant over a 23-year period with two exceptions. The introduction of whole blood and plasma on a liberal scale in 1941

following establishment of a hospital blood bank was associated with an increased incidence of septic complications in Group D. This paradox is logically explained by noting a decline in mortality due to septic causes at the same time. Thus patients were surviving due to the beneficial effect of whole blood and plasma in the treatment of appendicitis and associated peritonitis, and these survivors then developed septic complications. The technic of intestinal intubation and skillful use of intravenous fluids undoubtedly contributed to these changes as well although these important aids were not introduced abruptly in 1941.

The second exception is the significant improvement in mortality due to sepsis in Group E. The favorable influence of antibiotics in aiding localization of large abscesses most likely accounts for the improvement seen in these cases since 1945 as well as in Group D where the sepsis tended to remain more confined.

There is no general agreement as to the value of antibiotics in the treatment of appendicitis. Some recent reports flatly assert that they have been responsible for improved results.[1, 10] Others limit the role of these drugs. Gilmour and Lowdon in comparing two equal series of 535 patients treated in 1930–31 and 1948–50 stated the improvement in their mortality rate was traceable to the introduction of antibiotics.[8] Yet the number of residual abscesses was essentially the same in the two series, being nine and seven, respectively. The seven residual abscesses in the second series developed while antibiotics were given in the postoperative period.

Cantrell and Stafford have reported that antibiotics are of limited value since increasing the dosage did not decrease the morbidity or mortality, that the incidence of complications following perforated appendix was not changed by their use, and that the incidence of complications follow-

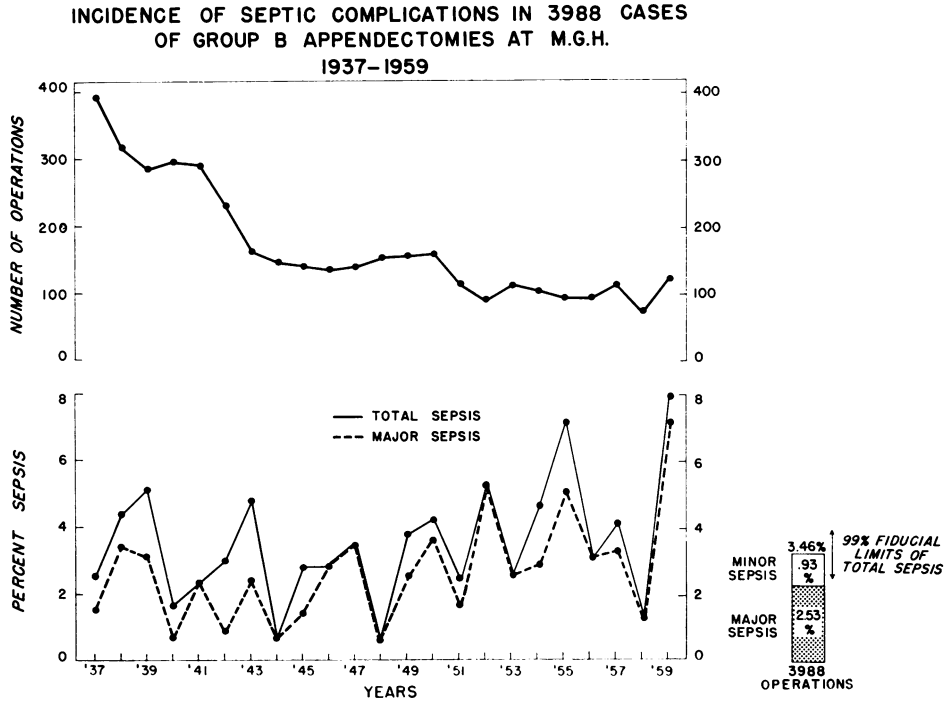

FIGURE 3.

ing removal of a nonperforated appendix was likewise unaltered.[7] However, they mention a reduction of secondary abdominal abscesses as seen in Groups D and E of the present report.

An interesting Cabot Case gives a striking example of the ineffectiveness of antibiotics in preventing appendicitis.[9] A 17-year-old boy was admitted to the emergency ward of the Massachusetts General Hospital with symptoms and signs consistent with meningococcal or pneumococcal meningitis. He promptly was given 500,000 units of penicillin every two hours and 0.5 Gm. chloramphenicol every six hours intramuscularly. Intravenously, 2.5 Gm. of sulfadiazine was given every six hours in 5.0 per cent dextrose and water. The sulfadiazine level in the blood was 10.3 mg.% on the second hospital day. The signs of meningitis cleared, but on the sixth hospital day while on this intensive routine he developed acute appendicitis and had an appendectomy.

Conclusions

1. A review of appendectomy and appendicitis in 7,810 cases established the incidence of postoperative septic complications as varying between 1.7 and 25 per cent depending on the stage of appendicitis.

2. These rates have been constant over a 23-year period with two exceptions.

3. The introduction of whole blood and plasma and the introduction of antibiotics have influenced in a limited way the appearance of septic complications.

4. Interpretation of the data is facilitated if the cases of appendicitis are classified according to stage of the disease.

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