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Staff Meeting Report

Epidemiological Studies on Toxoplasma Antibodies in Obstetrical Patients*†

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Two unusual characteristics of *Toxoplasma gondii* have made it difficult for investigators to elicit the mode of transmission of toxoplasmosis: First, this parasite is remarkably indiscriminate as to its host and host tissue selectivity; and second, it does not often stigmatize the infected host with clinically recognizable disease. The combination of these two characteristics makes toxoplasmosis unique among infections: The infection is very widely distributed both geographically and zoologically, but the clinical disease is relatively rare. Studies on the mode of transmission are thus attempts to elicit the probable important pathways of transmission among many potential pathways, none of which has been delineated by clinical cases with the exception of congenital toxoplasmosis.

The wide variation in percentages of positive tests for toxoplasma antibodies in various areas of the world cannot readily be accounted for, although one can generalize that toxoplasma infection is more prevalent in warm, moist climates and less prevalent in cold climates and in warm but dry climates. Other variations are unexplained, such as a 17 per cent dye test positivity in Portland, Oregon, and a 35 per cent dye test positivity in Pittsburgh, Pennsylvania.[1] Dye test positivity in urban and rural residents has been studied by Gibson[2] and others[3,4,5] and is usually, but not always, higher among rural than among urban residents; the differences, however, are generally too slight to be significant.[2,3,5]

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The assumption that animal contact is important in the transmission of this infection to humans is indirectly supported by several studies.[7–11] Jacobs,[12] in a recent review of the literature on the interrelationship of toxoplasmosis in swine, cattle, dogs, and man, points out the need for further study, particularly in swine and cattle.

Weinman and Chandler[13] have suggested the consumption of insufficiently cooked pork as a source of toxoplasmosis, but this hypothesis is not supported by the work of others. Jacobs reported no significant difference in the percentages of positive dye tests in Orthodox Jews and other residents of New York,[14] and he also noted 25 per cent positive dye tests in vegetarians. Schnurrenberger *et al.*[15] have found a significant association of the percentage of positive skin tests (toxoplasmin) with the consumption of raw eggs but not with the consumption of pork, beef, or raw milk. Skieller and Smetana[16] reported very low percentages of positive toxoplasmin skin tests in residents of the area of Delhi, India (1.2 per cent in children, 5 per cent in adults), but positive tests were observed among vegetarians, meat-eaters who did not eat pork, and meat-eaters who did not eat beef.

In the present study, residence (current and past), history of animal contact (in general and with selected species), and consumption of selected foods of animal origin, are correlated with toxoplasma dye test positivity in three groups of obstetrical patients.

Materials and Methods

The Study Groups

Groups A, B, and C patients were from three areas of Minnesota as shown in Figure 1.

The 327 patients of group A, which has been studied the most intensively, comprised the complete obstetrical practice of one of us (C.G.S.) from May, 1949, through July, 1954. Two or more blood specimens from each of 274 patients in this group have been dye-tested, and the observed changes in titers with time have been published for 272 patients from whom two or more specimens had been obtained prior to February, 1957.[17] The median time elapsing between the collection of first and last specimens tested was 55 months. Current residence by city, village, or, for farm residents, township, was known at the time of each test. Residence of the 274 patients tested two or more times was relatively stable during the period of observation; one change of residence was observed for each of forty-five patients and two changes apiece were noted for eight. Our major in-

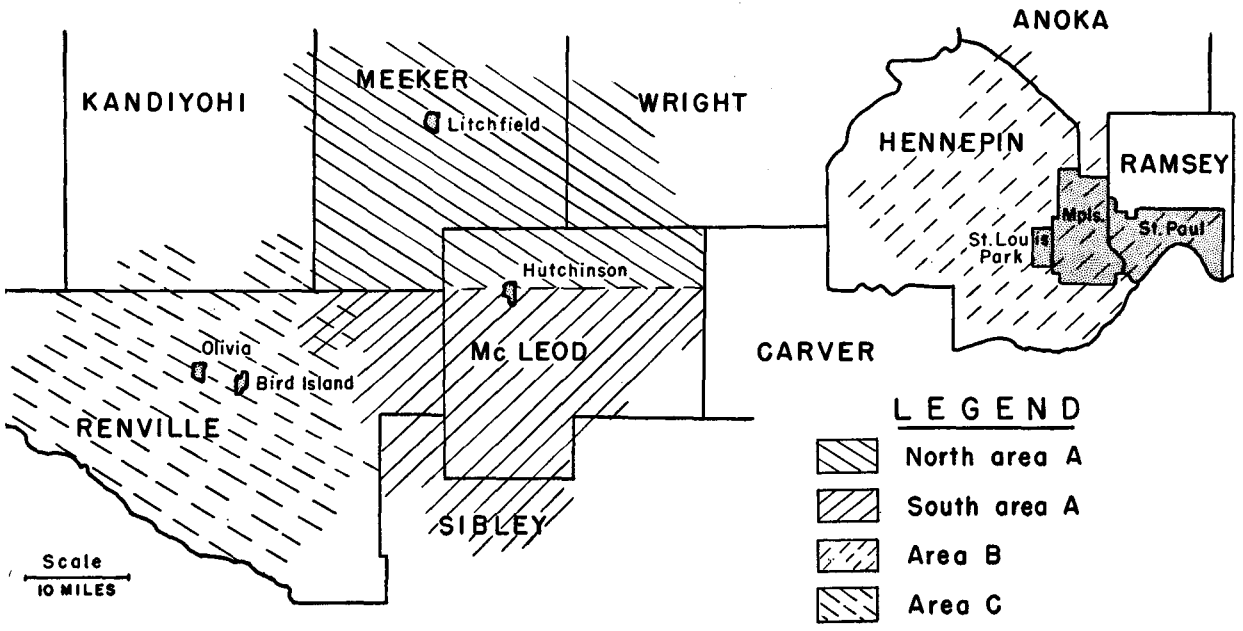

Fig. 1. Map of area, toxoplasmosis studies, Minnesota, 1949–1958

terest in repeated testing was to observe changes from dye-test negative to dye-test positive. Of the 184 patients who were initially dye-test negative, changes of residence were noted for 36.

A questionnaire regarding past residence (farm vs. city or village) and contact with house pets (in general) and farm animals (in general) was mailed to the patients in group A in late 1954. Patients were asked to describe past residence as "on a farm" or "in a city or village" because this differentiation was simpler for patients to make than the classification "urban" vs. "rural." The specific location of the past residence was not requested. Questionnaires were returned by 309 (94.5 per cent) of the total group. These patients comprise group A1.

In August and September of 1956, a random sample of 158 of the 327 group A patients was interviewed for history of contact with cattle, horses, swine, and fowl; consumption of pork, pork products, raw milk, and raw beef; source of pork (home butchered, commercial source, or both) and source of pork products (prepared at home or commercially). The interviews took cognizance of the time of potential exposure, i. e., whether this had taken place before or after the first blood test or both before and after. These 158 interviewed patients are designated collectively as group A2. Contact with cattle, horses, swine and chickens was quantitated on the basis of frequency and type of contact. Contact with ducks, geese, and turkeys was not quantitated, the majority of patients stating only the species of such fowl contacted. The interviewing was done by three senior medical school students* who collected blood specimens at the time of the interview from 149 of the 158 patients. Interviewers were not informed as to the dye-test results on patients.

During the fall of 1957, a new questionnaire was mailed to all group A patients to determine consumption of raw beef and raw eggs, with source of eggs (from the patient's own chickens, from a farm, a store, or other source). Questionnaires were returned by 248 (76 per cent) of the total group; these are designated as group A3. The dye test for toxoplasma antibodies had been performed on 126 (51 per cent) of the group A3 patients within 12 months before or after the return of this questionnaire (the majority of such tests were made in the period 12 months before), and on 199 (80 per cent) of the patients within 24 months.

Selected portions of the study were extended to include group B

*The authors wish to express appreciation for the fine job of interviewing done by Paul Brink, Eugene Muchow, and Barbara Rosine.

and C patients. Group B, consisting of 103 patients, comprised the complete obstetrical practice at one medical clinic in suburban Minneapolis, Hennepin county,* from early December, 1957, through March, 1958. Group C, 103 patients, represented the complete obstetrical practice of two physicians in Olivia, Renville county,† from early June, 1957, through September, 1958. These patients completed a questionnaire regarding current and past residence, contact with cattle and fowl, consumption of raw beef and eggs, and source of the eggs. Questionnaire completion was supervised by previously instructed office personnel. At the time the questionnaires were completed, blood specimens were collected for the toxoplasma dye test.

*The authors wish to express appreciation to the Obstetrical and Gynecological Section of the St. Louis Park Medical Center (Drs. A. Barno, T. P. Bellville, and D. W. Freeman) for their assistance in supplying data and blood specimens from group B patients.

†The authors wish to express appreciation to Drs. J. A. Cosgriff (Sr. and Jr.), Olivia, Renville county, for their assistance in supplying data and blood specimens from group C patients.

TABLE 1

SOURCES OF INFORMATION FROM PATIENTS
STUDIES ON TOXOPLASMOSIS, MINNESOTA, 1949–58

Group	Dates	Source	Information Sought	No. of patients	Positive Dye Test Initially No.	%	Later spec. No.
A	May, '49 through July, '54	Data card	Age, current residence	327	103	31.5	15
A1	late 1954	Questionnaire, mailed	Past residence, contact with farm animals, history of pets in the home	309	98	31.7	15
A2	Aug., Sept., 1956	Interview, (random sample)	Contact with cattle, horses, swine, chickens and other fowl. Consumption of pork, raw beef, raw milk	158	49	31.0	12
A3	late 1957	Questionnaire, mailed	Consumption of raw beef, source and consumption of raw eggs	248	77	31.0	12
B	Dec., '57 through Mar., '58	Questionnaire, completed with supervision	Age, current and past residence; contact with cattle, chickens and other fowl; consumption of raw beef; source and consumption of raw eggs	103	21	20.4	
C	June, '57 through Sept.,'58	Same as for group B	Same as for group B	103	31	30.1	

Table 1 summarizes the sources of information from the three groups of patients, the numbers of patients who supplied the information, and the number of patients who were dye-test positive when first tested. Note that the range of dye-test positivity for groups A, A1, A2, and A3 is 31 per cent to 31.7 per cent. This close agreement gives assurance that dye test positivity and any bias that may have influenced the return of questionnaires or availability for the interview are independent variables.

Questionnaires from A1, B, and C patients and interview records (group A2) were, for the most part, satisfactorily completed. Most of the questions were answered by all patients, although the question regarding the consumption of raw beef was unanswered on 15 questionnaires, and other questions were unanswered on, at the most, 8. Questionnaires from A3 patients were also satisfactorily completed, but 61 did not answer the question regarding the consumption of raw eggs.

When a patient had omitted data on a given item, he was excluded from the presentation of results.

Laboratory Methods

The Sabin-Feldman dye test,[18] slightly modified,[19] was performed on all blood specimens collected from patients. Dye-test positive specimens were titrated to the end point in fourfold dilution, 1/1, 1/4, 1/16, etc.

*Description of the Areas**

The areas in which these three groups of patients resided are shown in Figure 1.

Criteria of Dye-Test Positivity

When data from questionnaires were correlated with laboratory results, the percentages of positive dye-tests in the pertinent categories included all positive titers rather than higher titers only. This procedure gives greater assurance that the dye test negative patients have not been infected with *Toxoplasma gondii* than would be the case if the "positive" group included only the higher titered positives. This procedure has been discussed in a previous publication.[17]

When the dye-test positivity of group A patients was compared with that of group B and C patients, the results of the initial dye-test specimens were used. As later specimens from group A patients were

*Description of the areas is omitted for this preliminary publication. One noteworthy characteristic observed is that the surface area north of Hutchinson is 7 per cent lakes, dry meandered lakes (subject to flood) and marshes, as compared to 2.5 per cent in the area south of Hutchinson.

tested, nine patients whose blood had been dye-test negative had converted to dye-test positive in a dilution of 1/4 or higher. These patients were regarded as dye-test positives only if the conversion to positive had occurred during a period of exposure to the potential factor under study. In addition, six group A patients on whom the initial dye-test was negative were later dye-test positive in a dilution of 1/1. These six patients are grouped as dye-test positive (except when initial test results are being compared) on the assumption that such variations in test results (negative vs. positive 1/1) may occur in patients who formerly had higher dye-test titers. This classification also gives better assurance that the dye-test negative patients have not been infected with *Toxoplasma gondii.* In Table 1 the number of initial specimens that were initially dye-test positive and those that were later positive are shown separately for group A patients. Group B and C patients have been tested only once; test positivity in group B and C patients was therefore not compared with dye-test positivity of group A patients when positive results on later specimens in this latter group were used.

In the presentation of results, differences in dye-test positivity are considered significant only if the difference could have occurred by chance 5 or less times out of 100.*

Results

Dye-Test Results on the Initial Blood Specimens

In Table 1 results of positive dye tests for toxoplasma antibodies among the 533 initial blood specimens is shown by patient group. The percentage of positives (20.4 per cent) observed in group B is significantly lower than the percentage of positives (31.5 per cent) in group A ($P = .03$) but not significantly lower than the percentage of positives in group C (30.1 per cent).

Current Residence

In Table 2, the percentages of dye-test positives are correlated with the residence of patients by area as well as by urban vs. rural classification. Of patients who resided in the greater metropolitan area (including all of Hennepin, Ramsey, and Anoka counties), 21.7 per cent were dye-test positive. Residents of Hutchinson, residents of Olivia (and environs), and residents of the southern part of area A had slightly higher percentages of dye-test positive results than did metropolitan residents, but difference among the 4 groups was not

*The availability and the value of consultation with members of the biostatics section of the School of Public Health, University of Minnesota, is gratefully acknowledged.

TABLE 2

POSITIVE TOXOPLASMA DYE TEST RESULTS ON INITIAL BLOOD SPECIMENS BY RESIDENTIAL CLASSIFICATION

Residential Classification	Tested No.	Positive No.	Positive %
Greater metropolitan area	106	23	21.7
Olivia and environs	103	31	30.1
Hutchinson, McLeod County	132	34	25.8
South of Hutchinson (Group A)	99	29	29.3
North of Hutchinson (Group A)	93	38	40.9
Total	533	155	29.1

significant. Residents of the northern part of area A were 40.9 per cent dye-test positive; this was significantly different ($P = < .01$) from the 21.7 per cent positives observed in residents of the greater metropolitan area and from the 28.1 per cent ($P = < .02$) positives among the total residents of the 3 other residential groups; but it was not significantly different from the 29.3 per cent ($P = < .10$) positives observed in the residents of the southern part of area A.

In Table 3, dye-test conversions observed during the period of serological follow-up (median: 55 months) of group A patients are shown by residential classification. Details of all serological tests on these 9 patients have been published.[17] Changes from negative to

TABLE 3

TOXOPLASMA DYE TEST CONVERSION AMONG GROUP A PATIENTS ACCORDING TO RESIDENCE

Residence during the period of serological follow-up	Initial test Negative No.	Later test Positive in dilution 1/4 or higher No.	%
Hutchinson	64	1	1.6
South of Hutchinson	50	2	4.0
North of Hutchinson	41	5	12.2
Residential area changed during study period	29	1	3.4
Total	184	9	4.9

positive in a dilution of 1/4 or higher represented 1.6 per cent of the negative Hutchinson residents, 4 per cent of the negative rural residents of the southern part of area A, and 12.2 per cent of the negative rural residents of the northern part of area A. The percentage of change from negative to positive observed in the rural residents of the northern area is significantly larger ($P = < .02$) than the change observed in the total of the other two groups. Of the 29 patients who had changed residence during the period of serological follow-up 1 showed a change from negative to positive in a dilution of 1/256. This patient had moved from one village to another and was 1 of 7 patients who had moved from the southern to the northern area.

Past Residence

Dye-test positivity as associated with the percentage of life spent on farms is shown in Table 4. Of patients who had never lived on a farm, 21.2 per cent were dye-test positive, and of those who had spent all of their lives on farms 43.8 per cent were dye-test positive—a significant difference ($P = < .001$). For patients who had spent part (but not all) of their lives on farms, an increasing percentage of dye-test positivity was not associated with an increasing percentage of life spent on farms; the percentage varied from 31.1 per cent to 35.6 per cent. The specific location of past residence was not known, but the high positivity of current residents of the northern part of area A markedly increases the differences shown in Table 4. For example, 29 patients who had lived on farms all their lives were residents of the northern part of area A during the entire study period, and 17, or 58.6 per cent, of these had positive dye-tests. Among the 27 comparable residents of the southern part of area A, 44.4 per cent were positive.

Animal Contact—General

Dye-test positivity was significantly associated with contact with farm animals in general ($P = < .01$), but not with a history of pets in the home. Of group A1 patients who frequently worked with farm animals, 43.7 per cent were dye-test positive; among those who sometimes worked with farm animals, 35.7 per cent were positive; and among those who never worked with farm animals, 19.4 per cent were positive. Of the patients who almost always had pets in their homes, 26.8 per cent were dye-test positive; of those who sometimes had pets, 36.8 per cent were positive; and among those who never had pets in their homes, 36.5 per cent were positive. These data are presented in Figure 2 in a "correlation square." Within each square

TABLE 4

TOXOPLASMA DYE TEST POSITIVES ACCORDING TO PERCENTAGE OF LIFE SPENT ON FARM GROUP A1, B AND C

% of Life on Farm	Tested No.	Positive No.	Positive %
0	146	31	21.2
5 to < 25	45	16	35.6
25 to < 50	61	19	31.1
50 to < 75	85	28	32.9
75 to < 100	98	33	33.7
100	80	35	43.8
Total	515	162	31.5

the numerator is the number of dye-test positive patients and the denominator is the number of patients tested who had answered the questions relating to contact with farm animals and pets in the home. Thus it can be noted that the association between dye-test positivity and frequency of farm-animal contact is significant ($P = < .01$), whereas that for frequency of pets in the home is not. These differ-

Work with farm animals	Pets in the Home			Total	Positive Dye Test %
	Never	Some-times	Almost Always		
Never	4/ /19*	8/ /38	1/ /10	13/ /67	19.4
Sometimes	16/ /41	24/ /64	1/ /10	41/ /115	35.7
Frequently	22/ /55	24/ /50	9/ /21	55/ /126	43.7
Total	42/ /115	56/ /152	11/ /41	109/ /308	35.4
Positive Dye Test %	36.5	36.8	26.8	35.4	

*Numerator: number of positive dye tests; denominator: number of patients tested

Fig. 2. Dye test positivity as associated with contact with farm animals and with pets in the home, 308 group A1 patients

TABLE 5

TOXOPLASMA DYE TEST POSITIVE RESULTS AS ASSOCIATED WITH CONTACT WITH CATTLE, GROUP A2, B AND C PATIENTS

Cattle Contact	No. of Patients	Dye Test Positive No.	Dye Test Positive %
None	199	47	23.6
Moderate	95	38	40.0
Marked	64	24	37.5
Total	358	109	30.4

ences or lack of differences respectively are maintained in all categories of the correlation square.

Contact With Various Species of Farm Animals

Dye-test positivity was significantly associated with contact with cattle ($P = < .002$), chickens ($P = < .002$), ducks ($P = < .002$) and geese ($P = < .001$) but was not significantly associated with contact with swine and horses.

Cattle. Among patients who reported that they had not worked with cattle, 23.6 per cent were dye-test positive; whereas among patients who reported having worked with cattle to a moderate or great extent, 40 per cent and 37.5 per cent, respectively, were dye-test positive. The number of patients tested and the number who were dye-test positive in each group of patients as well as among the combined groups are shown in Table 5, according to the extent of contact with cattle.

Chickens. Among patients who had not worked with chickens, 20 per cent were dye-test positive, whereas among patients who had worked with chickens to a moderate or marked extent, 34.9 per cent and 38 per cent, respectively, were dye-test positive. Similarly, Table 6 presents the dye-test data among the several groups according to extent of contact with chickens.

Cattle and chickens. A high proportion of patients had no contact with either cattle or chickens, and a similarly high proportion had contact with both. As is shown in Table 7, 134 patients had had contact with neither cattle nor chickens, and 17.2 per cent of these were dye-test positive; 147 patients had had contact with both cattle and chickens, and 38.8 per cent of these were dye-test positive. Of six patients who had had contact with cattle and not chickens, 50 per cent were dye-test positive. Contact with chickens but not cattle was

TABLE 6

TOXOPLASMA DYE TEST POSITIVE RESULTS AS ASSOCIATED WITH CONTACT WITH CHICKENS, GROUP A2, B AND C PATIENTS

Chicken Contact	No. of Patients	Dye Test Positive No.	%
None	135	27	20.0
Moderate	146	51	34.9
Marked	79	30	38.0
Total	360	108	30.0

TABLE 7

TOXOPLASMA DYE TEST POSITIVE RESULTS AS ASSOCIATED WITH CONTACT WITH CATTLE AND CHICKENS, GROUPS A2, B AND C

Contact			Tested	Positive	
Cattle	Chickens		No.	No.	%
No	No		134	23	17.2
Yes	No		6	3	50.0
No	Yes		69	25	36.2
Yes	Yes		147	57	38.8
		Total	356	108	30.3

reported by 69 patients, and 36.2 per cent of these were dye-test positive; this percentage is significantly higher than the 17.2 per cent with positive tests among those who had reported no contact with cattle or with chickens ($P = < .003$).

Other fowl. Contact with *ducks* was reported by 85 of 346 patients in groups A2, B, and C, and 37 of these (43.5 per cent) were dye-test positive as compared to 65 (24.9 per cent) among the 261 patients who had not had contact with ducks. Contact with *geese* was reported by 48 of the 346 patients, and 27 (56.3 per cent were dye-test positive as compared to 74 (24.8 per cent) among the 298 patients who had not had contact with geese. These percentages of positive dye-test results are significantly associated with contact with ducks ($P = < .002$) and geese ($P = < .001$). Table 8 presents the dye-test results according to the number of species of fowl contacted. The percentage of positives increases with an increase in the number of species of fowl contacted, although the number tested among those having contact with four species is small.

TABLE 8

TOXOPLASMA DYE TEST POSITIVE RESULTS AS ASSOCIATED WITH CONTACT WITH ONE OR MORE SPECIES OF FOWL GROUPS A2, B AND C

No. of Species of Fowl Contacted	Tested No.	Positive No.	Positive %
None	136	24	17.6
One	110	39	35.5
Two	52	18	34.6
Three	43	19	44.2
Four	6	5	83.3
Two to Four	9	4	44.4
Total	346	109	31.5

Swine and horses. Contact with swine and horses was not significantly associated with dye-test positivity in the group A2 patients. Contact with *swine* was reported by 107 patients, 44 (41.1 per cent) positive as compared to 26 per cent among the 50 patients who reported no contact with swine. Contact with *horses* was reported by 110 patients, 38 (34.5 per cent) of them positive as compared to 37.5 per cent among the 48 patients who reported no contact with horses.

Food Consumption

There was no significant variation in percentage of dye-test positivity according to total pork consumption or to source of pork (home-butchered vs. commercially-butchered). Interview records (group A2) indicated that for 30 patients, pork constituted up to one-third of the meat eaten; for 97 patients, it constituted about half of the meat eaten, and for 26 patients, it constituted about three-quarters of the meat eaten. Percentages of dye-test positives among these three categories of pork consumption were 46.7, 37.1, and 30.8, respectively. Among the 153 patients who consumed pork (three consumed none at all) 70 patients reported that at least part of the pork was home-butchered, and 29 (41.4 per cent) of these were dye-test positive as compared with 29 (34.9 per cent) positives among the 83 patients who reported consuming only commercially-butchered pork.

There were no significant differences in percentages of dye-test positive results in accordance with the consumption of various *pork products* (head cheese, blood sausage, unsmoked and smoked liver

sausage, summer sausage, fresh pork sausage, and home cured ham), nor with the consumption of home made (all or part) vs. commercially prepared pork products. The data for consumption of pork sausage are given as an example: Among 62 patients who did not eat pork sausage 21 (33.9 per cent) were dye-test positive as compared to 36 (37.9 per cent) among the 95 patients who reported eating pork sausage. Among the patients who ate pork sausage 39 reported that at least part of it was prepared at home; 18 of these (46.2 per cent) were dye-test positive. Differences in the percentage of dye-test positivity associated with the consumption of pork sausage are not significant.

Dye-test positive results were not significantly associated with the consumption of *raw milk.* Interview records (group A2) indicated that 12 (32.4 per cent) of the 37 patients who had not consumed raw milk were dye-test positive. Raw milk had been consumed by 121 patients, of whom 44 (36.4 per cent) were dye-test positive. Raw milk had been consumed for long periods of time (median 17 years) by many of these patients and was currently being used by 30.

The proportion of patients who reported consuming *raw beef* and the association of dye-test positive results with the reported consumption differed with the method used to obtain the information and also differed between group A and groups B and C (see Tables 9 and 10). Of the 158 interviewed (A2) patients, 19 (12.2 per cent) reported consuming raw beef; but when 130 of these patients (part of A3)

TABLE 9

VARIATION IN REPORTING OF CONSUMPTION OF RAW BEEF WITH PATIENT GROUP AND THE METHOD USED TO OBTAIN THE INFORMATION

Group	Source of Information	Total No.	Raw Beef Consumption "Yes" No.	%
A2	Interview, 1956*	158	19	12.0
A3, part	Questionnaire only	114	22	19.3
B	Questionnaire only	101	9	8.9
C	Questionnaire only	94	4	4.3
Total A2, A3, B, C	Inter. and Quest.	467	54	11.6
*A3, part	Questionnaire 1957, following 1956 interview	130	29	22.3

TABLE 10

VARIATION IN ASSOCIATION OF POSITIVE DYE TEST RESULTS WITH CONSUMPTION OF RAW BEEF WITH THE PATIENT GROUPS AND THE METHODS USED

Group	Source	Consumption of Raw Beef —"Yes"— No.	—"Yes"— % D.T. Positive	—"No"— No.	—"No"— % D.T. Positive
A 2 + 3	Questionnaire and interviews	58	44.8*	214	33.6
B, C	Questionnaire only	13	23.1	182	25.3
A2	Interview, 1956	19	63.2*	139	35.3
A3, part	Questionnaire following interview	29	55.2*	101	34.7
A3, part, B, C	Questionnaire only	35	28.6	274	27.8

*Significant

later returned questionnaires, 29 (22.3 per cent) reported consumption of raw beef; questionnaires from 114 patients who had not previously been interviewed (part of A3) indicated that 22 (19.3 per cent) had eaten raw beef. Questionnaires from 101 group B patients showed nine (8.9 per cent) and from 94 group C patients showed four (4.3 per cent) consumed raw beef. Dye-test positive results were significantly associated with the consumption of raw beef in the total for group A2+3 patients (regardless of whether interview or questionnaire responses are considered) but not for group B and C patients (see Table 10). Also, dye-test positive results were significantly associated with consumption of raw beef for two parts of group A patients (interview data from group A2 patients and questionnaire data from previously interviewed, part of group A3) but not for questionnaire data from patients not previously interviewed (remainder of group A3). Therefore, dye-test positivity did not correlate with consumption of raw beef when data were obtained exclusively by questionnaire (part of group A3, group B and C).

Dye-test results according to the consumption of *raw eggs* and the dominant source of eggs are shown in Table 11. The percentages of positive dye-test results were 30.5 per cent among the 95 patients who reported eating raw eggs and 31.5 per cent among the 293 patients who reported not eating raw eggs. If raw egg consumption is also

TABLE 11

TOXOPLASMA DYE TEST RESULTS AS ASSOCIATED WITH THE CONSUMPTION OF RAW EGGS AND SOURCE OF EGGS, GROUPS A3, B AND C

Consumption of Raw Eggs	Dominant Source of Eggs — Store, or Other *	% Pos.	Farm or Own Chickens *	% Pos.	Total	
Yes	12/53	22.6	17/42	40.5	29/95	30.5
No	36/120	30.0	55/173	31.8	91/293	31.1
Total	48/173	27.7	72/215	33.5	120/388	30.9

*Numerator: number positive; denominator: number tested

**Question regarding consumption of raw eggs was not answered by 61 group A3 patients, 4 group B patients and 1 group C patient. Dye test results were positive on 21 (31.8 per cent) of these 66 patients.

related to the dominant source of eggs, the patients who consumed raw eggs from a farm or from their own chickens were 40.5 per cent dye-test positive as compared to 31.8 per cent of patients who used only cooked eggs from these same sources. The patients who used eggs dominantly from a store or other sources showed a lower percentage of dye-test positive results if they consumed raw eggs (22.6 per cent) than if they did not (30 per cent). Also dye-test positivity was not significantly associated with dominant source of eggs in the group as a whole. None of the differences in percentages of dye-test positivity as associated with consumption of raw eggs or source of eggs are significant.

DISCUSSION

Residence

Results of a number of studies in several different geographic areas disagree as to whether urban residents differ significantly from rural residents in the percentage showing toxoplasma antibodies.[2–5] Although our study is limited to a sample of residents in a relatively small area of Minnesota (approximately 70 by 30 miles), it contributes to the lack of agreement. The rural residents (obstetrical patients) of the northern part of area A included a significantly higher proportion of dye-test positives than did the remainder of the patients; but the percentages of dye-test positives among rural residents of area C and of the southern part of area A were not significantly higher than among urban residents. The patients residing in the northern part of area A who were dye-test negative when first tested converted to dye-

test positive at a significantly higher rate (12.2 per cent) during the period of serological follow-up than did the residents of the remainder of area A (2.6 per cent). Therefore, the factors which contributed to the more rapid spread of toxoplasma infection in this limited area *before* this study, were apparently also functioning *during* the study.

An investigation of several of the cultural and environmental characteristics of these areas did not reveal any striking difference in the northern part of area A as compared to the other areas. The only noteworthy difference was that the northern part of area A has a larger percentage of water area (7 per cent) than does the southern part of area A (2.5 per cent) or area C ($<$ 1 per cent) in which there are no lakes. The import of this difference with respect to the more rapid spread of *Toxoplasma* cannot be evaluated, but on a smaller scale, the differences in dye-test positivity among these areas are comparable to the differences reported by Feldman and Miller[1] between residents of a moist area (Tahiti, 68 per cent) and residents of a dry area (Navajo Indians in Arizona, 4 per cent).

When the proportion of dye-test positive patients among those who always lived on farms (44 per cent) was compared with the proportion among patients who never lived on farms (21 per cent) the difference was significant. These data, however, do not refute Gibson's conclusion that ". . . factors responsible for human toxoplasmosis are common to both environments rather than peculiar to one or the other."[2] The significantly higher dye-test positivity associated with rural residence, as reported in our study, suggests that the transmission of toxoplasmosis to humans is more efficient in rural environments but is not limited to rural residents. Additional factors may contribute, or the same factors may combine more often to facilitate transmission in a rural environment.

Animal Contact

Although the observed associations of dye-test positivity with cattle and chicken contact are not clearly separable, the data suggest that the contact with chickens may be more important than the contact with cattle. The highest proportion of dye-test positivity was associated with the larger degree of contact with chickens (Table 6) but with the smaller degree of contact with cattle (Table 5), although the values for each category of degree of contact were of the same order respectively for chickens and cattle and the differences were not significant. Furthermore, patients who had contact with chickens but not cattle were significantly higher in dye-test positivity than those

who had contact with neither; unforunately, too few patients (only 6) had contact only with cattle to permit separate evaluation of cattle contact, but for the 147 patients who had had contact with both species the dye-test positivity was only slightly higher than that observed for the 69 patients who had had contact only with chickens (36.2 per cent vs. 38.8 per cent, see Table 7).

Indirect support for the thesis that contact with chickens may be more important than contact with cattle is supplied by the data for contact with other fowl. The percentages of positive dye-test results on patients who reported contact with ducks and with geese were also significantly higher than the percentage of positives observed among patients who had not had such contact. Also, the progressively increasing proportion of dye-test positivity observed in patients who had had contact with from one to four species of fowl supports the thesis that all domestic fowl may be important in transmission (see Table 8).

Food Consumption

Evaluation of the data on the consumption of raw beef is difficult because the results have varied with the methods used to obtain these data, or with the groups of patients observed, or both. Although it was not possible to determine conclusively which method gave the more accurate information, the interview method is generally held to be more effective than the questionnaire technique. Also, it is worth noting that group A patients and their private physician (C.G.S.) had been involved in this study for some time, and as a result these patients may have given more thought to their answers in interviews and on questionnaires than did the patients in groups B and C, who were invited to participate only recently. If these intangibles are important, they support the results from group A which showed the consumption of raw beef to be associated with dye-test positivity.

The suggestion originally made by Muhlpfordt[20] that *Sarcocystis* and *Toxoplasma* cross-react, while it has not been substantiated by others,[1,21,22] cannot be completely excluded. Since cattle in Minnesota are infected with *Sarcocystis*,[23] the association of dye-test positivity with consumption of raw beef may be derived from false-positive results due to *Sarcocystis* antigen present in beef, as suggested by Garnham.[24]

None of the present data indicated that the consumption of raw eggs was significantly associated with dye-test positivity (see Table 11). When considering potential transmission of *Toxoplasma*, the consumption of raw eggs might well be of great importance; Schnurren-

berger *et al.*,[15] using the toxoplasmin skin test, have reported a significant association of positive tests with the consumption of raw eggs. Information on the source of eggs was also sought, on the assumption that patients consuming eggs from their own chickens, a farm, or a store, would, on the average, be consuming eggs of progressively increasing age. Dye-test positivity was higher among patients who consumed raw eggs predominantly from their own chickens or from a farm (40.5 per cent) as compared to those who used cooked eggs from these sources (31.8 per cent), but the differences were not significant. Since all these data were obtained by questionnaire only, these associations should probably be explored further with more definitive interview techniques.

Domesticated Fowl or Birds in General as the Reservoir for Human Toxoplasmosis

The most significant result obtained in this study was the association of dye-test positivity with contact with domesticated fowl. Even if the consumption of raw beef and contact with cattle were proved to be important in the transmission of toxoplasmosis in Minnesota, cattle could not be important in transmission on a world-wide basis. For toxoplasmosis is frequently observed in areas (e. g., Tahiti) where beef is not part of the diet and cattle are not kept.[25] Domesticated fowl, which are far more widely distributed than cattle, may account for transmission in areas such as Tahiti. However, contact with domesticated fowl does not account for the transmission of all toxoplasmosis. In the present study 17.6 per cent of 136 patients who reported no contact with fowl were dye-test positive. This leads to the consideration not only of domesticated fowl but of all birds as sources of human toxoplasmosis.

The following studies, briefly summarized with emphasis on the recent literature, have dealt with toxoplasmosis in birds: Frenkel[26] reports that adult chickens are comparatively resistant to symptomatic experimental toxoplasmosis but that they do develop infection and antibodies. Toxoplasmosis in chickens was reported by Fankhauser,[27] and endemic toxoplasmosis in chickens has been observed in Denmark by Biering-Sørenson.[28] Erichsen and Harboe[29] reported an epizootic in Norway, with isolation of the organism from three of six chickens; they also observed gliomas in one of six spontaneously infected and two of 25 experimentally infected chickens, and cautiously suggested that *T. gondii* may be one cause of gliomas in chickens.[30] Jackson[31] had previously questioned the neoplastic nature of gliomas in chickens. If future studies prove that naturally occurring gliomas rep-

resent a chronic form of toxoplasmosis in chickens, further consideration of chickens must be given in the epidemiology of human toxoplasmosis; this may provide another example of an animal reservoir in which clinical evidence of disease is infrequently associated with infection.

Cases and epidemics of toxoplasmosis in wild birds have been reported infrequently.[32–34] Isolation of *T. gondii* from "normal" wild birds has been attempted for several species,[11,35–40] and the organism has been isolated from one crow,[38] from sparrows,[40] and from pigeons,[11,35–37] including two wild pigeons with negative dye tests.[35] Experimental toxoplasmosis has been studied in several species,[26,30,36,41–49] but notably in pigeons.[26,36,41,44,46,47,49] In general, the disease is more chronic in birds than in mice, guinea pigs, or rabbits. In experimentally infected pigeons, the dye test becomes negative when the organism can still be isolated from the tissues;[46] these experimental data augment the evidence of isolation of the organism from dye-test negative wild pigeons.[35]

No single mode of transmission from birds to humans has been strongly suggested by the experimental evidence or the epidemiological studies available at present. The eye has been reported to be involved in experimental toxoplasmosis in chickens[42] and in pigeons, and the organism has been isolated from exudates from the eye,[49] but the disease has not been transmitted to normal cage mates. Furthermore, infected pigeon hens have not infected their young, which have later proved susceptible to infection by inoculation.[47] Mites have been suggested as possible vectors in an epidemic in pigeons in Stanleyville, Belgian Congo.[32] The parasitemia in experimental toxoplasmosis in pigeons has been shown in one study to last for 35 days[36] and in another, for 44 days;[46] therefore, vector transmission is a possibility in pigeons and perhaps in other birds. The extent to which the mite could be a vector in transmission from birds to humans requires further study.

Because birds have not been suspected until recently, reporting of contact with birds has not been frequent. For example, a very detailed study of animal contacts associated with a congenital case of toxoplasmosis was made by Gibson and Eyles[11] in which cats, dogs, mice, chickens, ducks and pigeons from the vicinity of the infected mother's home were shown to be infected.[11] Kayhoe *et al.*[51] have reported toxoplasmosis in a patient who was pecked by a parakeet prior to the onset of the disease.

Human toxoplasmosis may not be derived from one source only, and different sources and modes of transmission may be dominant in

different areas of the world and in peoples with varying habits. Further experimental and epidemiological studies are needed in order to interpret fully even the more closely significant findings presented in this report and to show how these findings will yield an understanding of the source and mode of transmission of toxoplasmosis.

Summary

Toxoplasma dye-test results were correlated with data obtained by interview and questionnaire on three groups of obstetrical patients from area A (Hutchinson, McLeod county, and environs), area B (suburban Minneapolis), and area C (Olivia, Renville county and environs). Group A (327) patients were studied more intensively, and parts of the study were extended to groups B (103) and C (103) patients.

I. *Residence*
   - A. Dye-test positivity was significantly higher in residents of the northern part of area A as compared to all other patients or groups of patients, urban or rural.
     1. A significantly larger percentage of dye-test negative patients in the northern part of area A converted to dye-test positive compared to other residents (urban and rural) in area A.
     2. Of the area characteristics, cultural and environmental, only one attribute was found to be associated: a larger percentage of the surface was water (lakes, etc.) in the northern part of area A than in the two other rural areas (the southern part of area A and area C).
   - B. Among patients who had always lived on farms 44 per cent were dye-test positive, and among patients who never lived on farms 21 per cent were dye-test positive.

II. *Animal Contact*
   - A. Dye-test positivity was significantly associated with contact with farm animals (in general), cattle, chickens, ducks and geese.
   - B. Patients who had contact with chickens but not cattle had a significantly higher percentage of positive dye-tests (36 per cent vs. 17 per cent) than patients who had had contact with neither.
   - C. Dye-test positivity was not associated with contact with swine or horses or with a history of pets in the home.

III. *Food Consumption*

A. Dye-test positivity was significantly associated with the consumption of raw beef in group A patients and in patients who supplied this information in an interview (random sample of group A); but it was not associated with consumption of raw beef in group B and C patients nor in patients who supplied this information only by questionnaire (groups B and C, and part of group A).

B. Dye-test positivity was not significantly associated with the consumption of pork, pork products, raw eggs, or raw milk.

It is suggested that domesticated fowl, and possibly birds in general may be an important source of human toxoplasma infection, and an appeal is made for further studies, both experimental and epidemiological, in this area.

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Staff Meeting Report

Benign Ulcer of the Colon and Rectum*†

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The occurrence of solitary benign ulcers in the colon and rectum has been reported in the medical literature for more than 100 years. The earliest description of the disease appears to have been made by the French pathologist Cruveilhier[1] in 1832. By 1928, Barron[2] had been able to collect a total of 53 cases from the literature, and the most recent reviews indicate a total of nearly 90. The many terms used to describe what appear to be closely related pathological entities include: (1) simple ulcer of the cecum or colon; (2) solitary benign ulcer of the cecum; (3) Barron's ulcer; (4) nonspecific ulcer of the colon; (5) acute solitary ulcer of the cecum. All these terms reflect the two most basic characteristics of this pathological entity: (1) its simple or benign nature and (2) its most characteristic site—the cecum.

Ulcers of the cecum or colon have been called simple, or benign, or nonspecific when they are not associated with tumors, chronic ulcerative colitis, generalized arteriolar disease of the gastrointestinal tract, or infection by specific organisms. The specific infections that are known to cause ulcerative lesions of the gastrointestinal tract include: (1) Endamoeba histolytica; (2) Balantidium coli; (3) Actinomycetes; (4) tubercle bacilli; (5) dysentery-typhoid and paratyphoid bacilli. Infection of the small intestine and colon by beta hemolytic streptococcus has been reported; it may result in a suppurative process. The pathologist usually makes the diagnosis of acute or simple ulcer of the colon after the aforementioned conditions have been definitely excluded.

This paper will review the medical literature on nontraumatic benign ulcer of the colon and rectum, and will also describe three cases of this disease which have been seen and treated here at the

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University Hospitals. To permit an analysis of the clinical features of the disease, 31 cases have been collected from the literature since Barron's extensive review of the subject in 1928. The three cases from this hospital have been added to the series, bringing the present total to 34 cases. Various aspects of this more recent survey will be compared with the earlier review by Barron.

Etiology

Attention has been focussed on etiological factors which could explain the fact that the majority of these ulcers are located in the cecum or the proximal ascending colon close to the ileocecal valve. Barron's series revealed that 30 per cent of the total number of lesions reported occurred in the cecum. More than 50 per cent of his cases could have been assigned to this location if the area of the ascending colon just proximal to the ileacecal valve had been included with the cecum. Barlow,[3] reviewing the literature 1941, also found that more than half of the cases of simple ulcers of the colon appeared in this location. Almost 80 per cent of the lesions in the present series of cases from the literature were located within a 10-centimeter radius of the ileocecal valve (Table 1). Two general theories have been evolved to explain this observation:

1) The first theory postulates that benign ulcer of the colon is a disease similar in many respects to peptic ulcer. Many observers have correlated the various anatomical and chemical characteristics of peptic ulcer with those of benign ulcer of the colon. The most striking anatomical similarity is the frequent occurrence of the latter in the cecum just opposite a sphincter mechanism, i.e., the ileocecal valve, as compared with the high rate of occurrence of peptic ulcers in the duodenum opposite the pylorus. According to this thesis, the terminal ileum and the main body of the stomach correspond to one another, while the ileocecal valve and the pylorus represent corresponding autonomicaly innervated sphincter mechanisms. This analogy to acid peptic disease of the stomach is further strengthened by the observation that the fecal material leaving the terminal ileum is slightly acid in reaction.

A modification of this viewpoint was set forth by Wilkie,[4] who claimed that the cecal ulcer is more analogous to the simple gastric ulcer which occurs most frequently on the lesser curvature of the stomach. He compared the human cecum and ascending colon to those of lower animals, especially of birds and rodents. In these lower evolutionary forms the cecum and colon are distinct anatomical

structures, with a sphincter mechanism in the proximal colon which prevents a too rapid emptying of this part. Although no similar sphincter muscle tract has ever been observed in man, Wilkie has asserted that the corresponding area of the ascending colon is often found in spasm. He has compared the proximal colon to a second stomach, the ileum to the esophagus, and the cecum to the cardia. In his view the cecal or proximal colon represents the body of the stomach, and the ileocecal tract compares with the pyloric antrum and pylorus. By this anatomic analogy, the simple ulcer of the stomach usually occurring in the lesser curvature is comparable to the benign ulcers of the colon occurring just distal to the ileocecal valve in the cecum or proximal ascending colon.

The pathologic findings in benign ulcers of the colon are less striking in their similarity to peptic ulcers. Ulcers of the colon are conspicuous by the relative absence of the fibrosis that is so characteristic of stomach and duodenal ulcers. Usually inflammatory cell invasion is more pronounced in colonic ulcers. In summary then, the two disease states are similar, but, as in so many biological analogies, they are also disturbingly different.

2) The other theory about the high occurrence rate of these lesions in the cecum emphasizes the role of colonic distention as a result of

TABLE 1

LOCATION OF LESION IN PATIENTS WITH BENIGN ULCER OF THE COLON

Location	Barron's Series 1837–1928 Total No. Cases: 53		Present Series 1928–1957 Total No. Cases: 34	
	Number	Per Cent	Number	Per Cent
1. Cecum	15	28.4	17	50.0
2. Ascending Colon	12	22.6	12	35.0
3. Ascending Colon or Cecum within 10 cm. of ileocecal valve	28	53.0	27	79.5
4. Hepatic Flexure	3	5.7		
5. Transverse Colon	0	0	0	0
6. Splenic Flexure	5	9.4	0	0
7. Descending Colon	2	3.8	0	0
8. Sigmoid Colon	11	20.8	1	2.9
9. Rectum	4	7.5	3	8.8
Total	53		34	

constipation. Prutz and his associates[5] postulated that constipation, obstruction, or impaction of feces can produce colonic distention which results in a venous stasis. Other investigators have shown that following venous distention, ecchymosis and desquamation of the poorly nourished epithelium could easily occur, resulting in superficial ulcers. Von Greyerz and von Schimodeira[6] brought forth experimental evidence on this point in a series of experiments on dogs showing that gaseous distention of the bowel clearly reduces the arterial blood flow to the distended segment. Wangensteen and his associates,[7] in a study on the effect of sustained intraluminal pressure on the appearance of bowel, showed that a pressure of 40 cm. did in some instances produce petechial hemorrhages on the antimesenteric border of the bowel. But histologic studies of segments of colon subjected to chronic distention did not reveal any erosion of the mucosa in segments of the bowel which remained viable. These studies, however, amply proved that distention of any segment of the bowel will produce serious alterations in its vascular supply.

An alternative explanation of the role of constipation in the pathogenesis of this disease has been offered by Rankin.[8] According to his view, hardened masses of feces form in the colon and become agglutinated to the mucosa; when they are finally pushed along, these agglutinated fecal masses tear off small pieces of mucosa, and ulceration quickly follows through secondary infection which attacks the denuded bowel wall. While this theory could explain the occurrence of ulcers in the sigmoid colon or rectum, where the fecal masses are often exceedingly hard, it can hardly apply to the cecum, where the contents are normally fluid.

A number of writers have stressed the importance of foreign bodies in the pathogenesis of these ulcers. Some authors have felt that the lesions occur more frequently among populations whose diet consists predominantly of grains. A few cases have been reported in which fruit pits and stones have been lodged in the gut or have actually penetrated the bowel wall. Rosenow[9] of the Mayo Clinic advocated the bacterial theory, which was based on specific affinity of certain organisms for certain parts of the digestive tract. He claimed to have demonstrated that specific bacteria, when injected into the blood stream of a rabbit, could cause ulcers in the cecum. Boss[10] has stated that ulcers occurred not as primary lesions but as secondary manifestations due to embolism or thrombosis of the arteries of the mesentery. Most pathologists have felt that changes in the arteries represented a secondary manifestation of these lesions.

Clinical Features of Benign Ulcer of the Colon

The total incidence of this type of lesion is reasonably low. To date, less than 90 documented cases have been reported in the literature. In 1957 Parker[11] stated that he had counted only 66 reported cases of solitary ulcer of the cecum. (He excluded the broader category of solitary or benign ulcer of the colon.) Since various studies have indicated that approximately 50 per cent of all benign ulcers of the colon are located in the cecum or ascending colon, this calculation would hardly put the total number above 130. According to nearly all published case reviews, the disease appears to occur almost twice as frequently in men as in women. Thus, in Barron's series, out of a total of 53 patients, 34 were men and 17 were women (Table 2). Barlow recorded that 60 per cent of lesions of the right colon occurred in men, and that men accounted for nearly 80 per cent of lesions of the descending colon and sigmoid colon. The various surveys in the literature also reveal that this is a disease of the younger age group (Table 3). Almost half of the patients in Barron's review were under the age of 50, whereas only 20 per cent were over 60, with an average age of 41 years and the highest incidence in the age group between 40 and 50. In the present study of 34 cases, 68 per cent of the patients were male, and the average age was 44. Other studies have substantiated these general findings regarding the age and sex incidence.

Symptomatology

A review of published case reports reveals that the symptom complex is dependent largely on the complications of this disease. Apparently the simple ulcer in the cecum is seldom if ever diagnosed

TABLE 2

Sex Incidence of Patients With Benign Ulcer of the Colon

Sex Distribution	Barron's Series 1837–1928 Total No. Cases: 53		Present Series 1928–1957 Total No. Cases: 34	
	Number	Per Cent	Number	Per Cent
Men	34	64.0	23	68
Women	17	32.0	11	32
Unspecified	2	4.0	0	
Total	53		34	

TABLE 3

AGE INCIDENCE OF PATIENTS WITH BENIGN ULCER OF THE COLON

Age Distribution	Barron's Series 1837–1928 Total No. Cases: 53		Present Series 1928–1957 Total No. Cases: 34	
	Number	Per Cent	Number	Per Cent
15—20	2	3.8	2	5.9
20—30	8	15.0	4	11.8
30—40	4	7.5	9	26.4
40—50	11	21.0	3	8.8
50—60	8	15.0	11	32.4
60—70	6	11.3	3	8.8
70—80	4	7.5	2	5.9
No age specified	5	9.5	0	0.0
Total	53		34	

before surgery. The chief complications appear to be: (1) hemorrahge; (2) acute perforation with development of generalized peritonitis; (3) subacute perforation or so-called penetrating perforation, with the formation of a localized abscess; and (4) stenosis of the cecum with partial bowel obstruction.

The simple uncomplicated cecal ulcer has been discovered occasionally as an incidental finding during exploratory laparotomy, and a subsequent review of the symptoms has in two or three instances revealed constipation and vague pains on the right side of the abdomen.

Hemorrhage is a fairly rare complication. In only five cases was it a prominent feature of the disease. Wilkie[4] reported a case of simple ulcer of the ascending colon in which the patient had passed about an ounce of bright red blood from the rectum about a week before being admitted to the hospital. Barron[2] reported four cases of hemorrhage, three of them located in the rectum.

Acute perforation of the cecum or colon is the most serious and most frequent complication. Barlow[3] recorded that 66 per cent of ulcers of the right side of the colon and 81 per cent of those of the left are perforated when first seen. He also stated that nearly half of the perforated ulcers of the right side have free gas either intraperitoneally or extraperitoneally when first seen. In Barron's[4] series, 42 out of a total of 53 lesions had perforated by the time they were

first seen (Table 4). In the present review, 35 per cent were found to have free perforation at the time of medical attention. The occurrence of free perforation almost invariably gives rise to generalized peritonitis.

"Subacute perforation" is a term which is applied when the ulcer has penetrated the bowel wall but apparently under conditions where a localized reaction has taken place which prevents the widespread dissemination of fecal material throughout the peritoneal cavity. In a number of cases neigboring structures have been involved in this inflammatory process, resulting in the production of an inflammatory mass which has been mistaken for a neoplasm even at operation. In other cases a localized abscess cavity has formed, often mistaken for an appendiceal abscess. In Barlow's[3] study, 4 out of a total of 52 patients had a preoperative diagnosis of carcinoma of the cecum based in each case on the presence of a mass in the right lower quadrant. These patients also gave evidence of a more chronic disease pattern based on a long history of recurrent episodes of pain on the right side of the abdomen.

In a few cases the ulcers have given rise to a dense fibrous reaction which has led to an actual stenosis of the cecum. Wilkie[4] reported a case in which the patient gave a 10-year history of dragging pain in the lower right side of the abdomen. Preoperative x-ray studies revealed a distended cecum with delayed emptying time, the cecum retaining a residual amount of barium long after the rest of the colon had cleared. At operation a dense band of adhesions was found which was constricting the ascending colon just above the ileocecal valve. When these adhesions were divided, a fibrosed stellate scar was found marking the site of a healed ulcer half an inch

TABLE 4

PRESENCE OF PERFORATION AT TIME OF EXPLORATORY LAPAROTOMY OR AUTOPSY IN PATIENTS WITH BENIGN ULCER OF THE COLON

	Barron's Series 1837–1928 Total No. Cases: 53		Present Series 1928–1957 Total No. Cases: 34	
	Number	Per Cent	Number	Per Cent
Perforation	42	79.0	12	35
No perforation	11	21.0	22	65
Total	53		34	

above and slightly in front of the ileocecal valve. Surgical release of the adhesions resulted in a complete disappearance of the symptoms.

Diagnosis

The diagnosis of the vast majority of these lesions is made at exploratory laparotomy. Indeed, only one case is recorded in the literature in which the correct preoperative diagnosis was made by a barium x-ray study (Bombi[12]). An analysis of the cases in the literature reveals that in the greater percentage of cases a preoperative diagnosis of acute appendicitis is usually made. The very frequent location of these ulcers near the ileocecal valve and the inflammatory nature of this disease make this confusion a most understandable one.

In the present study of 34 cases, acute appendicitis was considered as the preoperative diagnosis in 15 of the cases (Table 5). The second most frequent was ulcer of the rectum in 3. Cameron[13] has recorded that acute appendicitis was the working diagnosis in 9 out of a total of 21 cases, and Barlow[3] listed the following preoperative diagnoses in a series of 52 cases: (1) appendicitis in one form or another, 36.6 per cent; (2) carcinoma of the cecum or colon, 7.7 per cent; and (3) peritonitis, 3.8 per cent.

TABLE 5

Preoperative Diagnosis of Patients With Benign Ulcer of the Colon

Preoperative Diagnosis	Barron's Series 1837–1928 Total No. Cases: 53		Present Series 1928–1957 Total No. Cases: 34	
	Number	Per Cent	Number	Per Cent
1. No diagnosis listed	20	38.0	9	26.4
2. Acute Appendicitis	12	22.6	15	44.0
3. Peritonitis due to Intestinal Perforation	8	15.1	0	0.0
4. Intestinal Obstruction	5	9.4	1	2.9
5. Carcinoma of Cecum	2	3.8	2	5.9
6. Ulcer of the Rectum	2	3.8	3	8.8
7. Appendiceal Abscess	1	1.9	1	2.9
8. Miscellaneous Diagnosis	3	5.6	3	8.8
Total	53		34	

The history is seldom helpful, and the sudden onset of abdominal pain which usually localizes in the right lower quadrant suggests appendicitis. The physical findings are those of acute inflammatory disease with a maximum of tenderness over McBurney's point. When actual free perforation has occurred, there is usually generalized abdominal tenderness, often with pronounced rigidity in the right side of the abdomen. A review of the laboratory findings reveals that a fairly high percentage of these patients may have elevated white blood counts, often above 20,000. Taken as a whole, these findings most often suggest the appendix as the site of the inflammatory lesion.

Treatment

The treatment is always surgical, and indeed, the diagnosis itself is almost always made at exploratory laparotomy. There is no record of any patient recovering without an operation. The type of surgical procedure elected depends largely on whether or not perforation has occurred. If the ulcer is small and perforation has not occurred, most surgeons feel that the ulcer can be oversewn by drawing the surrounding edges of the serosa together. Some surgeons suggest the local excision of the ulcer, while a few clinicians advise a local resection of the proximal colon. Rabinovitch and his co-authors[14] have expressed the belief that when the bowel is inflamed and edematous, oversewing is frequently difficult and hazardous, and they advise a resection of the entire segment of the ulcerated bowel.

In the case of perforation with a generalized peritonitis, Barron[2] has recommended that the perforation should be sutured without any attempt to excise the edges. This should be followed by a general abdominal lavage and adequate drainage. Barron has also stated that a resection is contraindicated in the face of a generalized peritonitis. Most surgeons feel that the safest way to handle a perforated colon or cecum in the face of generalized peritonitis is to exteriorize the involved segment and later to perform a resection.

In the event of a localized abscess, the surgical treatment is also more conservative, with most authors recommending an incision and evacuation of the abscess, and a suturing of the perforation to the abdominal wall in continuity with the outside. An alternative method in the case of a localized inflammatory mass is a bypass procedure, that is, an ileocolostomy. In the event that the ulcer has produced an obstructive mass, most patients have had a right hemicolectomy. In the majority of these cases, the surgeon, under the impression that he was dealing with a neoplasm, undertook the more extensive opera-

tion. In the cases of ulcer in the rectum where hemorrhage is the chief problem, most authors recommend the use of cautery and a tamponade if necessary.

The mortality rate is directly related to the presence of perforation. In Barron's[2] series the overall mortality was nearly 68 per cent (Table 6); in the group which had sustained a perforation, the mortality was 74 per cent, whereas the rate in the nonperforating group was 55 per cent. In the present review, the overall mortality was 26 per cent. Here, too, the difference in mortality of the two groups was very apparent. Over 56 per cent of the group with perforating ulcers died, whereas less than 10 per cent of those with nonperforating ulcers died. The lower mortality figures in this later series probably reflects the wider extent of surgical intervention in acute abdominal disease during the last 20 years.

Pathology

The lesion may occur as a single ulcer or as multiple ulcers. In Barron's[2] series of 53 cases the ulcer occurred as a single lesion in 37. In 16 cases the ulcers were multiple; these were generally close

TABLE 6

Mortality Rate of Patients With Benign Ulcer of the Colon

	Barron's Series 1837–1928 Total No. Cases: 53		Present Series 1928–1957 Total No. Cases: 34	
	Number	Per Cent	Number	Per Cent
Overall Mortality				
Deaths	36	68.0	9	26.0
Cured	17	32.0	25	74.0
Total	53		34	
Mortality in group with perforation				
Deaths	31	74.0	7	58.0
Cured	11	26.0	5	42.0
Total	42		12	
Mortality in group without perforation				
Deaths	5	45.0	2	9.0
Cured	6	55.0	20	91.0
Total	11		22	

together, and there were never more than six. The location, as stated elsewhere, was most often in the cecum or ascending colon. The ulcers may vary a great deal in size—ranging in diameter from only 3-4 mm. to 3-4 cm. Often the ulcer is oval or round with sharply cut edges, and the mucosa in the neighboring area usually appears completely normal. The ulcers show all stages of acute inflammation, destruction, and repair. Sections taken through these lesions usually show the typical findings of acute inflammation associated with local tissue necrosis. The inflammatory cell exudate consists largely of polymorphonuclear leukocytes and to a lesser extent of lymphocytes. The fibroblastic reaction is usually poor and quite unlike that seen in the case of peptic ulcer, where fibrous formation at the base of the ulcer is most pronounced.

The three cases summarized below represent benign ulcers of the rectum which have been seen here at the University Hospitals. A careful survey of the records at this hospital has not revealed a single case of benign ulcer of the cecum. Since more than 50 per cent of the cases of benign ulcers of the colon which have been reported in the medical literature were located in the cecum, this absence of cecal ulcers in our three cases warrants an explanation. The most obvious is a possible defect in the coding system resulting in incorrect coding of these lesions through the years. But in view of the rarity of these lesions, on the other hand, it is entirely possible that no cecal lesions have actually been seen in this hospital.

Case Review

Case 1

A 49-year-old woman entered the hospital with a nine-month history of intermittent episodes of rectal bleeding associated with bowel movements. The physical findings at the time of admission were negative.

Laboratory studies revealed a hemoglobin of 13.5 gm. a white cell count of 6,050, with a normal differential. A barium study of the colon was negative. Proctoscopy under anesthesia revealed an ulcerating lesion at about the 8 cm. level. The lesion was on the lower valve of Houston, and the valve itself was soft and movable. Repeated biopsies showed that the ulcer was a chronic benign ulcer of the rectum. The lesion was removed surgically through a proctoscope.

The pathologist reported that the lesion showed a normal histologic structure with no inflammatory reaction in the underlying tissue. The surface of the mucosa in some areas was covered with a thin layer of exudate containing many polymorphonuclear leukocytes.

A follow-up proctoscopic examination six months later showed that the area was still red and swollen, with two areas of polypoid changes. Biopsy specimens of these areas revealed that the polyps were benign.

Case 2

A 59-year-old man entered the hospital with a one-month history of episodes of rectal bleeding. The patient was obese with a yellow, follicular eruption over the arms, hands, and belt line of the abdomen. A digital rectal examination revealed an ulcerating lesion just inside the anal canal. Anoscopic examination showed a shallow ulcer 1 cm. in diameter with raised edges; the ulcer was located in the anal canal about 2 to 3 cm. from the pectinate line. Proctoscopic examination was negative to 25 cm. On repeated biopsies, this lesion proved to be a chronic benign rectal ulcer. The patient underwent a cryptectomy and a papillectomy, the postoperative course was smooth, and the ulcer cleared up in a few weeks.

The pathologist reported that the tissue showed a superficial exudate with an infiltration with leukocytes and chronic inflammatory cells. There were areas which also revealed a lymphocytic infiltration of the connective tissues.

Case 3

A 72-year-old man entered the University Hospital with a one-year history of bowel disturbances, with several episodes of diarrhea associated with bowel incontinence but without bleeding. The patient had suffered a nervous breakdown and had been treated with 100 mg. of thorazine twice daily. Digital examination of the rectum revealed a questionable mass at the tip of the finger. Repeated biopsies were reported as indicating chronic benign ulcer of the rectum. But because the proctologist felt that this was a neoplastic process, the patient underwent an exploratory laparotomy and had a segmental resection of part of the descending colon, sigmoid colon, and rectum with a low anastomosis. Examination of the surgical specimen revealed numerous small ulcerations in the distal 12 centimeters of the rectum. The largest ulcer, which was also the most distal, measured 3.5 cm. in diameter. The more proximal ulcers measured 5 to 8 mm. The ulcer margins were not raised. Microscopic sections revealed that the normal mucosa in the ulcerated areas was replaced by a thin layer of exudate of granulation tissue. A few glands deep in the mucosa adjacent to the ulcer were filled with a purulent exudate. The base of the ulcer showed some increase in fibrous tissue in the submucosa. No organisms were seen. The pathologist reported the lesion as a chronic benign ulcer of the rectum. The patient had an uneventful recovery, and no follow-up has been made.

SUMMARY

1. The cases of benign ulcer of the colon and rectum which have appeared in the medical literature since 1928 have been reviewed. These have included three cases of benign ulcer of the rectum seen at the University Hospitals.

2. This appears to be a disease of the middle decades of life with an average age incidence of 44, occuring nearly twice as often in men as in women.

3. Over half the reported lesions are located in the cecum or ascending colon within 10 cm. of the ileocecal valve.

4. The most serious complication of the disease is caused by acute perforation, which occurs in approximately one-third of the cases. Perforation is generally diagnosed at surgery, the patient having undergone an exploratory laparotomy for what is usually diagnosed as an acute appendicitis. Surgical intervention represents the only successful treatment. In recent years the mortality rate from perforated cecal ulcers has been greater than 50 per cent.

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Medical School Activities

DR. HERBERT M. HIRSCH, Division of Cancer Biology, gave a lecture on January 21, 1959, before the University of Pittsburgh School of Medicine; he also presented a lecture on February 10 to the University of North Dakota School of Medicine. One of Dr. Hirsch's publications will be included in the 1959 volume of "Yearbook on Cancer;" its title is "Can the Inbred Mouse be Immunized Against Its Own Tumor?"

DR. DENNIS W. WATSON, Department of Bacteriology and Immunology, has been appointed to the Graduate Training Grant Committee of the National Institute of Allergy and Infectious Diseases, United States Public Health Service.

Guests of the Department of Bacteriology and Immunology for lectures and seminars were: DR. WILLIAM HOYER, National Microbiological Institute, Rocky Mountain Laboratory, Hamilton, Montana, who spoke on "Cellulose Ion Exchange Chromatography of Viruses" on February 17 and 18; DR. PETER S. OLMSTED, Biochemistry Department, University of Pittsburgh, School of Medicine, who talked on "An ADP Specific Polynucleotide Phosphorylase" on February 18 and 19; DR. SEYMOUR S. COHEN, Charles Hayden American Cancer Society Professor of Biochemistry, University of Pennsylvania School of Medicine, Philadelphia, who discussed "Virus-Induced Acquisition of Metabolic Function and Thymine Deficiency in Induction of Unbalanced Growth and Cell Death" on February 19 and 20.

PROFESSOR JAMES FREDERIC DANIELLI, of Kings College, London, an English physiologist who specializes in the chemistry of cells, will lecture at the University of Minnesota on Thursday, March 5, on "Designing of Drugs for the Chemotherapy of Cancer." Professor Danielli's talk is sponsored by the University's Department of Continuation Medical Education and the Centennial Lecture Committee of the Squibb Institute for Medical Research.

Faculty Publications

BRADLEY, S. G.: Effect of Nystatin on *Candida stellatoidea,* Antibiotics and Chemotherapy 8:282, 1958.

BRADLEY, S. G.: Interactions Between Phosphate and Nystatin in *Candida stellatoidea,* Proc. Soc. Exp. Biol. & Med. 98:786, 1958.

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LEE, H. W.; HINZ, R. W.; and SCHERER, W. F.: Porcine Kidney Cell Cultures for Propagation and Assay of Japanese Encephalitis Virus, Proc. Soc. Exp. Biol. & Med. 99:579, 1958.

WATTENBERG, LEE W.: A Histochemical Study of Five Oxidative Enzymes in Carcinoma of the Large Intestine in Man, Am. J. Path. 35:113, 1959.

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday,	9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
	12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
	4:00 to 6:00 P.M.	ANESTHESIOLOGY Classroom 100 Mayo Memorial
Tuesday,	12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Thursday,	11:30 A.M. to 12:30 P.M.	TUMOR Todd Amphitheater University Hospitals
Friday,	7:45 to 9:00 A.M.	PEDIATRICS McQuarrie Pediatric Library, 1450 Mayo Memorial
	8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
	9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater, University Hospitals
	1:30 to 2:30 P.M.	DERMATOLOGY Eustis Amphitheater University Hospitals
Saturday,	7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
	9:15 to 11:30 A.M.	SURGERY Todd Amphitheater, University Hospitals

For detailed information concerning all conferences, seminars, and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospitals, and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minnesota.