

Prophylactic and Adjuvant Use of Nitrogen Mustard in the Surgical Treatment of Cancer *

RUDOLPH MRAZEK, M.D., STEVEN ECONOMOU, M.D., GERALD O. McDONALD, M.D.,
DANELY P. SLAUGHTER, M.D., WARREN H. COLE, M.D.

*From the Department of Surgery, University of Illinois, College of Medicine,
Chicago, Ill.*

THE PURPOSE of this paper is to report the results of prophylactic and adjuvant cancer chemotherapy with nitrogen mustard associated with surgery in the treatment of cancers of the breast, colon and rectum. Nitrogen mustard is being administered with the hope of destroying cancer cells which are liberated into the blood stream at the time of operation or shortly before operation, and are beyond the scope of surgical resection. Cancer has long been known to invade veins.^{3, 6} In 1954, Cole, Packard and Southwick¹ reported that cancer cells could be identified in fluid perfused through the arteries and veins of operative specimens. Further studies by Turnbull⁵ and Engel⁴ demonstrated cancer cells in the blood draining from tumors in from 13 to 28 per cent of the cases. Cancer cells have been demonstrated in the peripheral venous blood by Roberts *et al.*⁷ in 17 per cent of 100 patients with curable cancer, and in 31 per cent of 100 patients with inoperable cancer.

In experimental studies in which suspensions of the Walker 256 rat carcinosarcoma cells were injected into the portal vein of rats there was reduction of tumor "takes" (97 per cent in controls to 19 per cent in treated animals) in the animal's liver when this injection was followed immediately by

injection of nitrogen mustard.² Nitrogen mustard injected before or six, 24 and 48 hours after the tumor inoculation had little prophylactic effect.

In view of the demonstration of free cancer cells in the portal and peripheral blood of cancer patients, and the destruction of injected malignant cells in rats by nitrogen mustard, we began (in March 1956) a program of prophylactic and adjuvant injection of nitrogen mustard immediately after curative resection of carcinoma in the hope of minimizing the incidence of distant metastases.

Method

The series discussed herein includes patients with carcinoma of the breast, colon and rectum. To minimize the danger of drug toxicity we excluded all patients past 70 years of age. Moreover, exclusion of patients past 70 should make the series more valid with a smaller number of cases. Patients with multiple primary tumors, or a previous history of cancer, or in whom the surgeon felt a curative resection had not been accomplished, were excluded. Inflammatory cancer of the breast was excluded. The patients were divided into control and treated groups of equal number by a previously established system of randomization in blocks of two, which determined at the close of each operation whether or not nitrogen mustard should be administered.

A total dose (per course) of 0.4 mg. per kg. of body weight of nitrogen mustard is given. In patients having a mastectomy, all

* Presented before the American Surgical Association, San Francisco, Calif., April 15-17, 1959.

Supported in part by Grant No. CY-3157C2 from the U.S.P.H.S.

We wish to express appreciation to H. C. Batson, Ph.D., for assistance in *statistical design* of the project.

the nitrogen mustard is injected into a peripheral vein; 0.2 mg. per kg., or one-half the total dose, is given immediately after the operation and 0.1 mg. per kg. on each of the two following days. In patients having bowel surgery one-half of the total dose is also given immediately after resection. This is divided into two portions, one of which is diluted with 50 cc. of physiologic saline solution, and injected into a branch of the portal vein; the other is diluted with 400 cc. of saline, and instilled into the peritoneal cavity just as the incision is closed. The remaining portion is given in two equal amounts on the next two days into a peripheral vein. To minimize the danger of overdosage in obese patients the *maximum dose is limited to 30 mg.* To minimize the incidence of infection, which we expected to be high, we give antibiotics as a routine for several days.

Postoperatively, blood counts are taken on the first, fourth, seventh and fourteenth day with close attention paid to the white blood cell and platelet counts and hemoglobin level.

During the first follow up year nitrogen mustard is given in similar doses at four month intervals to all patients whose white blood counts are above 5,000. However, bone marrow depression becomes more severe after each succeeding dose, and of 30 patients treated over one year ago only 23 received a second course, 16 a third course, and four a fourth course. In the second follow up year we planned to give thio-TEPA at monthly intervals to the patients whose white blood count was above 5,000. However, only nine patients have qualified for this routine. The patients were divided into a young group (under 50) and an older group (over 50). The formal series of treated and control patients was started in March 1956. Up to March 1959 there are 136 patients in the series, half being treated and half controls.

Complications

There is no question that the administration of nitrogen mustard, a powerful alkylating agent, has a chemically "toxic" effect on the patient already burdened by major surgery. This deleterious effect might be expected to be reflected by bone marrow depression and resultant leukopenia, poor wound healing, more severe and frequent infections, depressed vital functions and an increased need for blood transfusions. These effects might be expected to be more severe in older patients. In patients treated before the current series was begun, several serious complications were encountered. The danger of overdosage in obese patients was demonstrated by a 79-year-old obese white female in whom a full course of nitrogen mustard following a radical mastectomy for cancer of the breast was followed by leukopenia, septicemia and death. This patient was one of our very early cases, treated before we started our formal series, and was responsible for our rule to exclude all patients past the age of 70, and to limit the total dosage to 30 mg. regardless of weight. This precaution has been proved valid because our most serious complications have occurred in obese patients, particularly in the breast series. We lost another patient who had a Miles operation for carcinoma of the rectum and one dose (7.5 mg.) of HN_2 at the end of the operation. Early the next day she developed a severe diarrhea (pseudomembranous colitis type with staphylococcus predominating) and was given no more HN_2 . She had been on cortisone for nearly a year and had neomycin for four days preoperatively. We had previously decided to include in the HN_2 series only patients receiving at least half the course dose. Theoretically, then, she should be classed as a control case, but to be more than fair we chose to discard her from the series. If she were included, the operative mortality rate for the controls would be increased accordingly.

Leukopenia (below 3,000) was encountered after 12 (32.4%) of the radical mastectomies, after two (12.5%) of the anterior resections and after five (33%) of the abdomino-perineal resections. The count returned to normal in all cases, perhaps aided by transfusions. In current prophylactic and adjuvant series a constant finding has been that of an increased need for blood in the HN₂-treated patients; 2,040 cc. compared to 1,715 cc. in the controls after mastectomy, 1,125 cc. compared to 708 cc. in the controls after anterior resection, and 3,107 cc. compared to 1,375 cc. in controls after abdomino-perineal resection. Difficulties in wound healing or infection occurred in 17 treated breast cases and in 16 controls, in one treated colon cancer and two controls, and in four treated rectal cancers and two controls. These complications were not significantly increased HN₂ therapy, but as discussed later two or three were much more severe. The only other infection observed was pneumonia which occurred in two treated and two control patients. Three of these patients responded to antibiotics and recovered; the fourth, an HN₂ treated case, died of hepato-renal failure with a terminal bronchopneumonia. With the aid of antibiotics we have not found infection to be a serious complication in either the postoperative or follow up period. Liver function studies revealed increased BSP retention in only one patient. In another patient liver biopsy taken during closure of a wound dehiscence was normal. In one patient a skin slough developed after HN₂ infiltrated subcutaneously and later closure with a skin graft was necessary.

Cancer of the Breast. Since March 1956, 74 patients have undergone radical mastectomy for cancer of the breast, one-half receiving operative nitrogen mustard and one-half serving as controls. There have been no operative deaths. The average postoperative stay for all patients treated with HN₂ was 21.3 days as compared with 14.6 for all controls.

Leukopenia. Leukopenia of a slight degree has been an almost constant finding following HN₂ administration; the white blood cell count of all but four of the patients fell below the preoperative level. The average white blood count before surgery was 7,018 cell per cubic mm. while the average lowest count for all treated cases after therapy was 3,904. In six patients (16.2%) the lowest post HN₂ count was above 5,000; in 19 (51.4%) the count fell to a level between 3,000 and 5,000; in 12 patients (32.4%) the count fell below 3,000 (Table 1). This fall occurred as early as the fifth and as late as the twenty-seventh postoperative day; the average lowest count was seen on the twelfth day. In one case leukopenia was not observed until after the patient had left the hospital after an uneventful recovery. The lowest count averaged 2,020 in patients over 50 years of age, and 2,090 in those 50 and under. Recovery from the leukopenia (count rising to above 5,000) occurred as early as the twenty-second and as late as the two hundred and fortieth postoperative day, and averaged 41 days in the young patient group. In two patients, both in the young group, the white blood counts have not as yet returned to 5,000, one after one year, the other five months. The incidence of leukopenia was similar in the old and young group of patients and the speed of recovery of the count could not be correlated with age.

Wound Complications. Minor wound complications (Table 2) such as seroma, hematoma and superficial infection occurred in nine patients (24.4%) in both the treated and control groups. In the older patients four treated and one control patient had these complications and there was an associated leukopenia (below 3,000) in one case. In those under 50, five wound complications with two associated leukopenias occurred in the treated group while eight complications occurred in the controls. The postoperative stay in these patients was not appreciably lengthened.

TABLE 1. *Leukopenia Associated with HN₂ Therapy After Radical Mastectomy*
(37 Patients)

| | Age: Over 50 14 Patients | Age: Under 50 23 Patients |
|--|-----------------------------|------------------------------|
| Number with WBC below 3,000 | 5 (35.6%) | 7 (30.4%) |
| Average lowest WBC | 2020 | 2090 |
| P.o. day of lowest WBC | 12 | 12.3 |
| Range | (7-20) | (5-27) |
| P.o. day of recovery of WBC to over 5,000 | 118 | 41.0 |
| Range | (22-240) | (8-90) |

Major wound complications (Table 3) such as wound necrosis or separation, graft loss or abscess occurred in eight treated patients and seven controls. There was associated leukopenia (below 3,000) in only one instance. These wound complications occurred slightly more frequently in the older patients: five (35.7%) in the treated and four (28.6%) in the controls. Only three (13%) were seen in both treated and control younger groups. The average postoperative stay for the older treated patients was greatly lengthened, being 54 days as compared to 29.2 days for their controls. One patient, an obese 60-year-old, developed a pseudomonas wound infection. After debridement, three skin grafts failed to take and she was discharged after 91 days with the wound still open. She had received 32 mg. of HN₂ and by her seventh postoperative day had a leukopenia of 1,550 cells per cubic mm. Her white blood count recov-

ered to 5,250 by the twenty-second day. She received a total of 5,000 cc. of blood during this episode. A second patient, an obese 64-year-old, received 30 mg. of HN₂. On the eight postoperative day she developed a wound abscess which subsequently made skin grafts necessary and delayed her discharge until the eighty-third day. Her lowest white blood count was 3,750 cells per cubic mm. on the eighth day. This patient ultimately required 5,000 cc. of blood. The danger of relative overdosage in obese patients and the importance of a dosage ceiling must be emphasized. The hospital stay in these two treated patients was so prolonged that they alone increased the average hospital stay of the treated series considerably.

Major or minor wound complications occurred in 17 treated patients (46%) and 16 controls (43.3%). The occurrence of wound complications was not increased in

TABLE 2. *Minor Wound Complications Following Radical Mastectomy*
(Seroma, Hematoma, Superficial Infection)

| | HN ₂ Treated | Control |
|--------------------------|-------------------------|-----------|
| Age: Over 50 (14 cases) | | |
| Minor complications | 4 (28.5%) | 1 (7.1%) |
| Associated leukopenia | 1 | 0 |
| Average p.o. stay | 21 days | 18 days |
| Age: Under 50 (23 cases) | | |
| Minor complications | 5 (21.8%) | 8 (34.8%) |
| Associated leukopenia | 2 | 0 |
| Average p.o. stay | 21.4 days | 15.4 days |

those patients with leukopenia. In the 12 treated patients who developed leukopenia four complications occurred, an incidence of 33 per cent (Table 4). In the 25 who did not develop leukopenia 13 complications occurred, an incidence of 52 per cent. In two instances, both in older treated patients, wound complications led to greatly prolonged postoperative stays.

The breast patients treated with HN₂ required an average of 2,040 cc. of blood, the controls 1,715 cc. In these patients with breast cancer there was no unusual operative bleeding. The increased need for blood reflected marrow depression and resultant leukopenia and, to a lesser extent, anemia. Significant thrombocytopenia was not encountered.

Repeated Courses of HN₂. During the first follow up year, repeated courses of HN₂, in a dose of 0.1 mg. per kg. body weight per day for four days, were given every four months (for one year) to those patients whose white blood counts remained above 5,000 cells per cubic mm. (Table 5). Twenty-three of the group were able to receive the first follow up course of HN₂ and nine (39%) developed leukopenia. Sixteen were able to receive the second follow up course of HN₂ and eight (50%) developed leukopenia which was also seen in 50 per cent of the four patients who received the third follow up course of HN₂. In the second follow up year nine patients so far have received Thio-TEPA and three have become leukopenic. We adopted the rule of withholding or delaying further courses of either drug until a stable white blood count of at least 5,000 cells per cubic mm. existed. In those in whom this recovery was delayed into the second follow up year fewer than the usual three follow up courses were given. The incidence of leukopenia increased with each succeeding course of HN₂ until finally only four of the original 30 patients were able to receive the third follow up course. Almost all of these pa-

TABLE 3. *Major Wound Complications Following Radical Mastectomy*
(Wound Necrosis or Separation, Graft Loss, Abscess)

| | HN ₂ Treated | Control |
|---------------------------|----------------------------|-----------|
| Age: Over 50 (14 cases) | | |
| Major wound complications | 5 | 4 |
| Associated leukopenia | 1 | 0 |
| Average p.o. stay | 54 days | 29.2 days |
| Age: Under 50 (23 cases) | | |
| Major wound complications | 3 | 3 |
| Associated leukopenia | 0 | 0 |
| Average p.o. stay | 30.3 days | 26.3 days |

tients experienced nausea and vomiting several hours after the injections; this was alleviated by chlorpromazine. Two of these patients required blood transfusions because of the treatment. One, unknown to us, was pregnant at the time of HN₂ administration, aborted, and required 500 cc. of blood. Her white blood count, which was normal after her surgical course of HN₂, fell to 2,000 cells per cubic mm. after the first follow up course and abortion, and has remained below 5,000 for two years. The count in a second patient dropped to 1,600 with a hemoglobin of 5.9 Gm. after her third follow up course of HN₂. She responded to 1,800 cc. of blood. Her last white blood count was 5,200 cells per cubic mm. and her hemoglobin 14.7 Gm. Since then she has received Thio-TEPA without further depression. Except for the early postoperative period anemia has not been prominent in the treated patients; the average latest hemoglobin in all the treated

TABLE 4. *Association of Leukopenia and Wound Complications After Radical Mastectomy and Nitrogen Mustard*
(37 Patients)

| | | |
|-------------------------------|----|-----|
| WBC depression below 3,000 | 12 | |
| Associated wound complication | 4 | 33% |
| WBC not depressed | 25 | |
| Associated wound complication | 13 | 52% |

TABLE 5. *Leukopenia Associated with Followup Nitrogen Mustard Therapy of Breast Carcinoma (30 Patients, all over one year postop.)*

| | | *Leukopenic After Therapy |
|--------------------------------------|----|---------------------------------|
| Operative HN ₂ | 30 | 9 |
| First follow up HN ₂ | 23 | 9 |
| Second follow up HN ₂ | 16 | 8 |
| Third follow up HN ₂ | 4 | 2 |
| Thio-TEPA in second post-op. year | 9 | 3 |

patients is 12.9 Gm., that of the controls 12.8 Gm.

Recurrences. To date five of the HN₂ treated and 12 of the control patients have developed recurrences of their breast cancer (Table 6). The average time of these recurrences was 11.2 and 11.8 months postoperatively respectively; they were noted in the axilla, at the drain site, in supraclavicular nodes and in bone, liver and the lungs. All were proved by biopsy or x-ray. One treated and seven control patients have died from cancer, an average of 28 and 21.3 months postoperatively. An additional control patient died of a heart attack while clinically free from cancer. Thirty-two treated and 24 control patients are living free from cancer. All patients developing recurrences had axillary metastases at the time of surgery. Nitrogen mustard does not seem to have delayed the time of recurrence. Since only one death has occurred in the treated cases, no comparison can be made in the time of death.

TABLE 6. *Recurrences and Deaths in the Breast Series (74 Patients, half treated, half control)*

| | HN ₂ Treated | Control |
|------------------------|-------------------------|-----------|
| Recurrences | 5 | 12 |
| Average time p.o. | 11.2 mos. | 11.8 mos. |
| Dead of ca. | 1 | 7 |
| Average time p.o. | 28 mos. | 21.3 mos. |
| Dead—free of ca. | 0 | 1 |
| Living—free of disease | 32 | 24 |

Two of the treated patients who developed recurrences received the operative and two follow up courses of HN₂, and revealed recurrences two and four months after their last treatment. The third and fourth patients who developed recurrences received HN₂ only at the time of operation because their white blood cell counts postoperatively hovered below 5,000 cells per cubic mm. Tumor recurred 11 and 15 months postoperatively. The fifth patient received operative HN₂, two follow up courses of HN₂ and three injections of Thio-TEPA. Recurrence became evident two months after the last injection.

Types of Cases. The treated and control groups were selected at random and from the clinical standpoint are comparable. As seen in Table 7, there is no marked difference in the groups in age, duration of tumor, tumor size, the presence of axillary nodes and the menopausal state. The distribution into stage 1, 2 or 3 in the Portman system of classification, revealed 40.5 per cent of the treated and 35.2 per cent of the control patients to be in stage 1, 46 per cent and 54 per cent respectively in stage 2, and 13.5 per cent and 10.8 per cent respectively in stage 3.

Carcinoma of the Colon. Thirty-two patients with carcinoma of the colon have undergone colonic resection; one-half of this group has received intra-peritoneal and intravenous adjuvant HN₂, the other half is serving as controls. In all cases radical excision was carried out and the principles of preliminary ligature with occlusion of the bowel lumen and early ligation of the veins draining the tumor were followed. There were two operative deaths in this group, one in a HN₂-treated patient who died of hepato-renal failure and pneumonia, the other in a control patient from a pulmonary embolus. Two (12.5%) of the treated patients developed leukopenia. One developed a severe staphylococcal pneumonia, and the white blood count fell as low as 2,400 cells per cubic mm. The count had

risen to 15,200 by the time she was discharged. The second patient with leukopenia developed a severe ileus which responded to conservative therapy. As seen in Table 8, pneumonia, wound dehiscence or infection, ileus or entero-colitis were seen in both treated and control groups. Phlebitis occurred in two control patients. One treated patient had a transfusion reaction. The average postoperative stay was 13 days in the treated group and 14 in the control. The treated patients received an average of 1,125 cc. of blood, the controls 708, a difference of 417 cc.

To date one recurrence with death later from cancer has occurred in the treated colon group (Table 9). This occurred in a patient who received both operative and one follow up course of HN₂. This patient had an advanced carcinoma of the ascending colon which had to be "shaved off" the duodenum and kidney. Death was due to massive local recurrence five months post-operatively. One control patient died of a coronary heart attack while apparently free of cancer. Fourteen patients are living free of disease in both the treated and control groups.

Carcinoma of the Rectum. Thirty patients have undergone abdomino-perineal resection for cancer of the rectum and one-half of these have received intraperitoneal and intravenous HN₂, the other one-half are serving as controls. There has been one operative death in this series in a control patient who had a perforated peptic ulcer (Table 10). Five (33%) of the treated patients developed leukopenia (below 3000) and two of these had no further complications. The third patient, whose white blood count fell as low as 1,400 cells per cubic mm., developed a mild perineal infection which cleared up readily. A fourth patient whose count fell as low as 2,550 had unusually brisk bleeding during the perineal dissection which was about 30 minutes after the intraperitoneal HN₂ had been given. The fifth patient through error received one

TABLE 7. Comparison of Clinical Data (Excluding Therapy) in the Breast Carcinoma Series (74 Patients)

| | HN ₂ | Control |
|-------------------------|-----------------|------------|
| Age | 49.7 years | 47.1 years |
| Known duration of tumor | 7.4 mos. | 6.6 mos. |
| Size of tumor | 4.1 cm. | 4.2 cm. |
| Positive ax. nodes | 54% | 62% |
| Premenopausal | 48.6% | 56.7% |
| Portman grading: | | |
| Stage 1 | 40.5% | 35.2% |
| Stage 2 | 46% | 54% |
| Stage 3 | 13.5% | 10.8% |

extra dose of HN₂, a total of 37.5 mg., and developed a white blood count as low as 800 per cubic mm. He was placed on 20,000,000 U. of Penicillin daily and with the aid of a total of 8,000 cc. of blood was discharged on the twenty-third postoperative day after an otherwise uneventful convalescence. Wound infection or dehiscence occurred in four treated patients, one of whom had leukopenia, and in two control patients. Pneumonia and bacteremia were seen only in control patients. Colostomy necrosis and dysuria occurred in both groups only once. The average postoperative stay of the treated patients was 21.9 days, that of the controls 22 days. (This includes one prolonged stay of 73 days by a control patient.) The treated patients required an average of 3,107 cc. of blood and

TABLE 8. Hospital Complications in 32 Patients with Cancer of the Colon (½ HN₂-Treated, ½ Control)

| | HN ₂ Treated | Control |
|-------------------------------|----------------------------|-------------|
| Operative death | 1 (hepato-renal failure) | 1 (embolus) |
| Leukopenia | 2 | 0 |
| Pneumonia | 2 | 1 |
| Wound dehiscence or infection | 1 | 2 |
| Phlebitis | 0 | 2 |
| Ileus or entero-colitis | 2 | 1 |
| Miscellaneous | 2 | 1 |

TABLE 9. *Tumor Recurrences and Deaths in the Colon Series (32 Patients)*

| | HN ₂ | Control | |
|--------------------|--------------------------|-----------------------|---|
| Recurrences of ca. | 1 | 0 | |
| Months p.o. | 4 | 0 | 0 |
| Dead from ca. | 1 | 0 | |
| Dead without ca. | 0 | 1 | |
| Operative deaths | 1 (hepato-renal failure) | 1 (pulmonary embolus) | |
| Living—free of ca. | 14 | 14 | |

the controls 1,374, a difference of 1,732 cc. The high figure of 3,107 cc. in the treated cases is caused in part by the 8,000 cc. given the patient who was given an extra dose of HN₂ by error, and another patient who bled postoperatively.

To date there have been three recurrences and subsequent deaths due to cancer in the treated patients and five recurrences and three subsequent deaths in the controls (Table 11). The recurrences came at an average of 23.5 months postoperatively in the treated and 19.0 months in the control patients. The deaths occurred on a average of 24.5 months postoperatively in the treated and 18.0 months postoperatively in the control patients. One control patient died of a coronary heart attack apparently free of disease. Twelve treated and eight control patients are living free of disease.

Discussion

The longest observation following mustard therapy in the series is three years and

TABLE 10. *Hospital Complications in 30 Patients with Cancer of the Rectum (½ HN₂ Treated, ½ Control)*

| Complications | HN ₂ | Control |
|-------------------------------|-----------------|-----------------|
| Op. death | 0 | 1 (perf. ulcer) |
| Leukopenia | 5 | 0 |
| Wound infection or dehiscence | 4 | 2 |
| G-I (Ileus) | 1 | 2 |
| Pneumonia | 0 | 1 |
| Excessive op. bleeding | 1 | 0 |
| Miscellaneous | 2 | 2 |

the shortest three weeks. Accordingly, valid conclusions cannot be drawn, particularly since the colon and rectum series are very small. There are 74 patients in the breast series, half being controls and half treated. The recurrence rate of 12 and five and one respectively are not statistically significant because of the small series. The time for development of the recurrence and death is slightly longer in the treated group than in the controls, but not significantly so.

We are of the opinion that the repeated courses extending over a maximum of two years are an important item in minimizing the recurrences and deaths in the treated series, but we have no proof of this. We were a bit concerned lest repetitive courses would result in a carcinogenic effect, but we have observed no evidence whatever that this is true. Because of these repetitive courses we have chosen to classify our series as prophylactic and adjuvant. We have joined the adjuvant series sponsored by the NCI with our patients having carcinoma of the stomach and lung, but did not join the adjuvant group with the patients having carcinoma of the breast, colon and rectum because our series was two years old when the adjuvant series was formed, and we did not want to discard them to start a new group.

We are convinced, but again have no proof, that our principle of transfusing all treated patients exhibiting even slight anemia has been a very important factor in keeping our operative mortality rate down to the rate sustained in our controls. In the entire series of 136 patients there have been two operative deaths in the 73 control patients, and one operative death in the 73 treated patients. There were no operative deaths in the breast series. It is barely possible that our routine use of antibiotics in the treated series is also a factor in preventing a higher incidence of operative deaths in the treated series. Since the start of our series we have excluded all patients over

70 years of age because we feared serious reactions from the HN₂ in the aged; moreover, since so many of these patients would be expected to die of natural causes it would appear that dilution of the series with this group would obscure effects of the procedure. Also from the start of our series we have limited the maximum dose to 30 mg. per adult patient. The large incidence of serious infections and wound complications in our obese patients suggests that this precaution was a wise one.

The number of complications in the treated and control groups is just about equal, but the complications (particularly of wounds) seem definitely to be more severe in the treated series. We actually expected a *higher* incidence of complications, but as yet this difference has not revealed itself in the figures. We have used transfusions freely (Table 12), and have a definite opinion that if the hematocrit and hemoglobin are below normal, free use of blood tends to minimize some of these complications, some of which are related to bone marrow depression.

Even though the recurrence rate and follow up death rate are greater in the controls than the treated cases, we still do not advise this prophylactic and adjuvant therapy for routine use. We would prefer to wait longer, particularly since the longest observation in our series is three years, and only a few patients have been observed that long. Moreover, it would be important to find out whether or not the differences in results would duplicate themselves in another series of patients.

Admittedly, nitrogen mustard and Thio-TEPA are not very effective drugs in solid tumors, although as expressed previously in this paper, we believe these drugs may be active against loose cells or cells recently implanted. With better drugs, we believe the difference in the treated and control cases would be more significant.

It appears that the procedure is going to be effective in patients with cancer of the

TABLE 11. *Tumor Recurrences and Deaths in the Rectum Series*
(30 Patients)

| | HN ₂ | Control |
|--------------------|-----------------|---------|
| Recurrence of ca. | 3 | 5 |
| Months p.o. | 23.5 | 19.0 |
| Dead from ca. | 3 | 3 |
| Months p.o. | 24.5 | 18.0 |
| Dead without ca. | 0 | 1 |
| Operative deaths | 0 | 1 |
| Living—free of ca. | 12 | 8 |

breast, but perhaps slightly so or not at all in patients with cancer of the rectum. There is only one recurrence in the colon series so it is impossible even to detect a trend in this group. We would expect that the prophylactic and adjuvant therapy would be effective with one drug in a given type of cancer, *but not in another*, i.e., one drug might be effective in cancer of the breast, whereas another drug might not. In other words, we believe ultimately numerous drugs must be tried, utilizing some type of assay, so that the best drug will be used for each patient.

Summary

The principle of adjuvant and prophylactic cancer chemotherapy associated with surgery is being studied in a group of 136 patients with cancer of the breast, colon and rectum. One-half of these patients are receiving nitrogen mustard immediately after surgery; the other half serve as controls. This administration has resulted in bone marrow depression and resultant leukopenia of varying intensity in the majority of patients, particularly those who

TABLE 12. *Blood Transfusion Requirements*

| | HN ₂ Treated | Controls | Difference |
|------------|----------------------------|----------|------------|
| Breast ca. | 2040 cc. | 1715 cc. | 325 cc. |
| Colon ca. | 1125 cc. | 708 cc. | 417 cc. |
| Rectal ca. | 3107 cc. | 1375 cc. | 1732 cc. |

are obese. The leukopenia has responded to transfusions and the treated patients have required a significantly greater volume of blood transfusions postoperatively. Other complications such as wound infection or pneumonia have not been increased in frequency, but in a few instances may have been increased in severity. There was no correlation between postoperative complications and leukopenia. The postoperative stay was longer in the treated breast cancer group than in the controls, but no difference was seen in the colon and rectal groups. No postoperative deaths can be attributed directly to nitrogen mustard administration in this series. The operative mortality rate has been the same in the two groups.

To date five recurrences and one death from cancer have occurred in the treated breast cancer patients, compared to 12 recurrences and seven deaths in their controls. As yet recurrences in the colon-rectal group are too few to compare.

DISCUSSION

DR. JOHN PAUL NORTH: This work which Dr. Mrazek has presented, from Dr. Cole's group, is certainly very stimulating, and the results seem promising.

I wish to enter one brief word of caution arising from findings which have developed in a co-operative study of adjuvant chemotherapy that has been conducted over the past few months in twenty Veterans' hospitals.

For a long time it has been recognized that when nitrogen mustard or other alkylating agents are used in close proximity with x-ray therapy the action of these drugs seems to be potentiated. It has not been suspected that the same effect may be encountered when the drugs are given concomitantly with a serious major surgical procedure.

In our original program, we gave nitrogen mustard in cases of resection for lung cancer, and thiotepa in resections of the stomach or colon-rectum, in the identical dosage outlined by Dr. Mrazek a few moments ago, and with the same schedule of dosage on the day of operation and upon the two succeeding days.

After a few months it became apparent that there was at least a two-fold increase in the body

References

1. Cole, W. H., D. Packard and H. W. Southwick: Carcinoma of the Colon with Special Reference to Prevention of Recurrence. *J. A. M. A.*, 155:1549, 1954.
2. Cruz, E. P., G. O. McDonald and W. H. Cole: Prophylactic Treatment of Cancer: The Use of Chemotherapeutic Agents to Prevent Tumor Metastases. *Surgery*, 40:291, 1956.
3. Dukes, C. W.: Surgical Pathology of Rectal Cancer. *Proc. Roy. Soc. Med.*, 37:131, 1944.
4. Engel, H. C.: Cancer Cells in the Circulating Blood: A Clinical Study on the Occurrence of Cancer Cells in the Peripheral Blood and in Venous Blood Draining the Tumor Area at Operation. *Acta Chir. Scandinav. Suppl.*, 201:1, 1955.
5. Fisher, E. R. and R. B. Turnbull, Jr.: The Cytologic Demonstration and Significance of Tumor Cells in the Mesenteric Venous Blood in Patients with Colorectal Carcinoma. *Surg., Gynec. & Obst.*, 100:102, 1955.
6. Grinnell, R. S.: The Spread of Carcinoma of the Colon and Rectum. *Cancer*, 3:691, 1950.
7. Roberts, Stuart, Alvin Watne, Ruth McGrath, Elizabeth McGrew and Warren H. Cole: Technique and Results of Isolation of Cancer Cells From the Circulating Blood. *A. M. A. Arch. Surg.*, 76:334, 1958.

mortality of the treated cases as opposed to randomized controls or the early mortality in the same hospitals prior to the study. A few cases obviously had profound bone marrow depression. More generally they showed simply a lack of the anticipated postoperative leukocytosis.

We were unable, after very careful analysis, to determine any cause for the increased postoperative mortality in treated cases except for the administration of the drug. Accordingly we cut this study off last July and have been proceeding, using a 3-quarter dosage scale compared with the previous conventional level. It is too early to know what our results may be.

DR. WARREN H. COLE: The first point I wish to make in my discussion is that even though these figures with breast carcinoma may appear favorable, we are still not advising this procedure as a routine method. It is still experimental.

I have seen so many strange, inconsistent figures and data appear in experimental and clinical studies that I am becoming a great skeptic when studying figures; yet in the long run we must admit that figures are much better than impressions, because impressions are so often wrong.

One of the reasons I feel cautious is the pos-