7. Herbut, P. A.: Acute Peptic Ulcers Following Distant Operations. Surg., Gynec. & Obst., **80**:410, 1945.
8. Kern, Jud, Jr., G. M. Clark and J. G. Lukins: Peptic Ulceration During Therapy for Rheumatoid Arthritis. Gastroenterology, **33**:25, 1957.
9. Meena, Albert L., J. H. Conn, H. Nauman and J. D. Hardy: Pepsin in Gastric Physiology: Effect of Ulcer Diathesis, ACTH, Histamine, Anesthesia-Operation, Banthine, Pilocarpine, Epinephrine, and Sedation Upon Blood and Urine Pepsin Levels and Upon Gastric Acidity. Surgical Forum, **7**:366, 1956.
10. Sandweiss, David J.: Effects of Adrenocorticotrophic Hormone (ACTH) and of Cortisone on Peptic Ulcers. Gastroenterology, **27**:604, 1954.
11. Schoen, Arthur M. and P. K. Knoefel: The Measurement of Human Gastric Secretion. J. Lab. Clin. Med., **32**:345, 1947.
12. West, Philip M., F. W. Ellis and B. L. Scott: A Simplified Method for Determining the Excretion Rate of Uropepsin. J. Lab. and Clin. Med., **35**:159, 1952.
13. Woldman, E. E.: Acute Ulcers of the Upper Gastrointestinal Tract, Their Relation to Systemic Stress and Adrenal Damage. J. A. M. A., **149**:984, 1952.

Discussion

Dr. Benjamin F. Byrd, Jr.: I rise principally to discuss the papers of Dr. Gilchrist and Dr. Drye. The effect of stress on the stomach is probably the most momentous problem which attracts the gastro-intestinal physiologist at present. The factors of stress that affect peptic ulcer aggravation are still largely unknown, and I simply want to report on an individual who was on the surgical service of Vanderbilt University Hospital some few weeks ago with an example of this variable picture. This woman was 82 years old when she came in with abdominal pain of about four hours duration. She was taken to the operating room and explored and found to have an anterior wall perforated duodenal ulcer. This was closed and Levine tube suction was instituted; she got along very nicely. There were one or two things that worried us. She maintained a packed cell volume of about 61, and she was given serum albumin and intravenous fluids. She went along for two days and still maintained the high packed cell volume. She had had a routine physical examination one week prior to admission and no particular abnormality was found, but she had a hemoglobin of 15 grams. We still were unable to reduce the apparent hemoconcentration after 48 hours. She continued to do fairly well, and on the afternoon of the third day she expired suddenly. The postmortem examination was remarkable for two reasons.

(Slide) Suffice it to say that the anterior wall lesion was closed but she had a posterior wall ulcer that was not closed. She had had *simultaneous* perforation of non-connecting duodenal ulcers, and the posterior wall ulcer had perforated into the peritoneal cavity.

(Slide) This shows the tip of the ulcer perforation in the posterior wall.

(Slide) Here are the two ulcers; the posterior wall ulcer quite separate and distinct from the other.

Then we got to wondering what was going on in the adrenal glands. It just so happened that our assistant resident, Dr. Kenneth Classen, had become curious about her adrenal function 24 hours prior to her demise. This shows the increased 17-ketosteroids and dihydrocorticosteroids. She had an adenoma in her adrenal cortex which again fits in with the picture of functioning benign adrenal tumor.

Thus, we have an 82-year-old woman with two perforated ulcers and with a functioning adrenocortical adenoma, and we can only conclude that the continuity of events between the adrenocortical function and the peptic ulcer must have been the specific factor in the case.

Dr. Curtis Artz: Dr. Gilchrist has presented an important entity, the so-called "stress ulcer." A similar type ulcer, called Curling's ulcer, is seen in burned patients. During the period of 6½ years from December 1949, through May 1956, one thousand burned patients were hospitalized at the Brooke Army Medical Center. The total number of deaths among these patients was 80 during this period. Gastro-intestinal ulceration was found in 17 of the 80 patients. Three patients survived who were thought to have Curling's ulcer. Seven patients were entirely asymptomatic. Hemorrhage occurred in 10 instances, and 3 patients experienced abdominal pain. The majority of the ulcers occurred in the duodenum. In only seven instances were the ulcerations multiple. Three patients treated medically after severe hemorrhage survived. Two patients with continuing hemorrhage had subtotal gastrectomy and both died. There was complete failure of all incisions to heal. Both

of these patients were extensively burned. In each instance local and systemic infection was present. The cause of the failure of the wounds to heal was not determined.

Dr. Gilchrist has pointed out the advisability of operative intervention in ulcers that develop after the trauma of surgical procedures. Burned patients, however, must be different. The extent of the injury and the infection that is usually present complicate wound healing after gastrectomy. Our experience at the Brooke Army Medical Center leads us to believe that gastro-intestinal ulceration after burns should be treated conservatively, unless operation is absolutely mandatory as a life-saving procedure.

DR. JOHN M. HOWARD: The papers of Dr. Gilchrist and Dr. Drye recall experiences with the problem of acute ulceration in two children within 24 hours after massive burns, where there was spontaneous perforation of the esophagus. Autopsy revealed acute ulceration and perforation of the esophagus. The clinical picture was that of acute ulceration with perforation when vomiting led to an increase in interluminal pressure.

Studies parallel with Dr. Drye's led us to the conclusion that within the first 6 to 24 hours after injury there was a disappearance of hydrochloric acid within the stomach. This was repeated uniformly in our experience among those patients with major external trauma. Coincident with this the injured patient may be quite thirsty. When you see him after injury his stomach may be full although he has not eaten for some hours so there is a decreased gastric motility, a decrease in hydrochloric acid, and studies show a decrease in absorption of water. Putting these observations together, they are very much like the atropine syndrome. Is this nature's method of supplementing the epinephrine response, the autonomic response to injury? This was our line of thinking, and we thought it was a new observation. Dr. Walter Cannon described the same thing in his studies on gastro-intestinal autonomic function. Dr. Cannon put it this way: He said a patient came to Boston to see a gastro-intestinal consultant. She came in for gastric analysis at 9:00 a.m., having taken a test meal. The analysis showed no free hydrochloric acid and the stomach was full of undigested food. Further inquiry revealed that coming to Boston had given the husband an opportunity to go out the night before, get drunk and embarrass his wife who was terribly upset. The tests were repeated and at this time there was normal hydrochloric acid, the stomach was empty, and the food digested. Cannon went on to show that this immediate response of alchlohydria and decreased gastric motility resulted from the administration of epinephrine.

DR. RUDOLF J. NOER: The paper by Drs. Drye and Schoen is the latest in a series relating to the pathogenesis of peptic ulceration from the University of Louisville Department of Surgery. Some years ago Dr. R. Arnold Griswold and Dr. Schoen carried on a series of experiments aimed at predicting which patients might more logically benefit from vagotomy and which from gastric resection, depending upon predominance of vagal or hormonal influences in their secretory patterns. Unfortunately, they were able to predict this in only a relatively small number of patients, though their findings were most interesting.

The work which Drs. Drye and Schoen have reported was stimulated first by a court case relating to a man who fell from a scaffold and later bled to death from a peptic ulcer; testimony at that time was that there could be no likely relationship between the ulceration and the injuries. However, sometime thereafter Dr. Griswold had a patient who bled from a peptic ulcer following an abdominoperineal resection. Then, two patients at the Louisville General Hospital bled severely from duodenal ulcers, one following operative treatment for diverticular hemorrhage, the other following severe femoral fractures. It was this series of cases which stimulated the present study as to the relation of trauma to gastric secretion in the hope of more clearly delineating the factors responsible for the behavior of these ulcers following unrelated trauma.

The observations of Dr. Griswold, of Drs. Drye and Schoen, and of many others leave little doubt that patients do actually develop activation of peptic ulcers following severe trauma and after operative procedures unrelated to the stomach. It is important that we all recognize this, for if there be any history of previous duodenal ulcer we should be well advised to take measures to control these patients' gastric acidity following severe trauma and during the early days subsequent to elective surgery.

These studies have shed some light on the problem, but unfortunately the pathogenesis of this ulcer activation has not been greatly clarified. The authors have proposed an explanation which is interesting but not clearly established. It may be true, as they suggest, that the ulcer is prevented from healing rather than caused by the physiologic response to stress. Certainly, the suggestion they make as to study of traumatized patients who had previously undergone vagotomy is an excellent one. Such a study would be a further valuable contribution to our understanding of this situation. Until the picture is further clarified, it is of paramount importance that we all bear in mind that gastric hyperacidity so commonly follows trauma and that we be prepared to meet the complications which may be associated with this phenomenon.

DR. R. K. GILCHRIST: (closing) I should like to thank all the discussers. I have certainly enjoyed these other two papers. I might say that in our cases, none of these patients had reactivation of old ulcers; these were all new acute ulcers. Only one patient had any kind of ulcer history and he

had a scar from an ulcer and that scar had probably been present for many years. It was perfectly obvious that these acute ulcers had something to do with stress. We have had no luck at all in predicting which ones would bleed, and we have attempted to neutralize acidity in the postoperative period, especially in those who are apprehensive. The third patient was one of the most nervous patients I have ever seen; he had seen five or six very good surgeons before he would decide which one he would have operate on him, and fortunately he is well.

It is my impression that the situation in Curling ulcer is different for a good many reasons, one being that the stress is so much greater and so much more prolonged, since you have a wide open wound for so long. It is not like an operative wound with healing within a few days. These people have loss of all sorts of fluids for a long time. We have had no experience with these acute ulcers which follow burns.

DR. ARTHUR M. SCHOEN: (closing) The experiments reported by Dr. Drye this morning confirm our earlier, less detailed, work carried out in the same laboratory showing that trauma in persons with and without history of duodenal ulcer is followed after 12 to 24 hours by an increase in gastric acidity. These experiments also show that gastric secretion was not increased in dogs or men during a period of several months in which Cortisone was given intramuscularly in doses equal to those commonly used clinically. This later observation may appear contrary to the report of S. J. Gray and L. Dragstedt, but it should be noted that published data of Dr. Gray's suggest that gastric acidity in the person receiving daily doses of Cortisone or Corticotropin may remain unchanged until after peptic ulcer develops, at which time acidity may be increased and remain so until the ulcer heals. In Dr. Dragstedt's report of the effect of ACTH on four pouch dogs, it was shown that gastric acidity was not increased in one animal during the daily intramuscular administration of this hormone. The data of B. I. Hirschowitz suggest that intramuscular ACTH gel does not stimulate gastric acidity in normal persons, but that gastric acidity may be increased following development of peptic ulcer during a period of daily ATCH administration. It is my belief that we do not have sufficient evidence to show that Corticotropin or adrenal steroids, per se, stimulate gastric secretory activity.

Our data agree with those of others who have shown that the renal excretion of uropepsin cannot be relied upon to reflect the secretory activity of the stomach with regard to volume, pepsin or acid output. The endocrine and exocrine functions of the stomach are not necessarily related by a simple constant, but conceivably bear a complex relationship to one another.

The etiology of peptic ulcer is still undetermined but acidic gastric juice is unquestionably a sine qua non. For this reason, most studies of the pathogenesis of this disease have concerned themselves with gastric secretory mechanisms or changes in gastric juice associated with ulcer. Very few studies have attempted to learn something of local mucosal changes which may predispose to ulceration. I would like to suggest that more work be done investigating the pre-ulcer site in human beings, this to include a study of the local mucosa, its blood and nerve supply, sensitivity to allergens, the local response, both motor and secretory, to humoral and nervous stimuli, and to any other characteristic or change which may be present in the ulcer diathesis. I believe such studies would be fruitful and may give us the key to the pathogenesis of peptic ulcer.