Family Practice Grand Rounds

Endocrine Effects of Alcoholism

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DR. JOSEPH A. TRONCALE *(Assistant Professor, Department of Family Practice)*: Welcome to Family Practice Grand Rounds. We would also like to welcome those at the outlying hospitals who are listening by telephone hookup. The topic for this morning's Grand Rounds is alcohol and endocrine system interaction. We are privileged this morning to have Dr. Robert Kreisberg, Professor and Chairman of Internal Medicine here at the University of South Alabama Medical Center, visiting with us. He has agreed to attend the conference today as our guest discussant.

Since the beginning of 1983, when the Department of Family Practice began an alcohol detoxification and treatment service, we have taken care of a number of patients. The aim of this service is not only to detoxify the alcoholics but also to begin, in the hospital, the appropriate behavioral and family therapy that is essential to keep the alcoholic from continuing to drink. Our recent experience with several patients on the service prompted interest in the subject being presented today.

DR. PAUL SCHMIDT *(Second-year resident*

in Family Practice): The patient we are presenting today is a 50-year-old white man with a 20-year history of ethanol abuse. He was referred from a nearby town in Alabama for therapy of his alcoholism. Beginning in July 1981, he had noticed increasing inability to function normally as a result of his alcoholism. Over the past several years his average alcohol intake was approximately one-half pint of vodka per day. This amount had increased during the past five months because he had taken an extended vacation and had been laid off from work. Incidentally, this man had been an excellent worker according to his factory supervisors, and one reason he was referred to the alcohol treatment program was that the company was eager to have him back on his regular work schedule. There was no known history of significant medical disease other than that related to alcoholism. Previous hospitalizations included a four-day hospital stay for injury to his back in 1979. In 1981 he had a one-day hospitalization for an alcoholic blackout while on vacation in Tennessee. In addition to his alcoholism, the patient's social history included working 31 years as a foreman for a local manufacturing plant. He is married and lives with his wife and three children. The review of systems was pertinent in that he had complained of impotency for the past several years. He also reported that

his abdominal girth had increased over the past several months.

On physical examination his vital signs included pulse 120 beats/min and blood pressure 140/100 mmHg. His general appearance was that of a tremulous, middle-aged white man in mild distress. He had thinning hair; his pupils were equal, round and reactive to light; his sclerae were slightly icteric; tympanic membranes were clear; lungs were clear; and his heart had a regular rate with a 3/6 systolic murmur heard over the entire precordium at the upper left sternal border. The abdomen was distended with normal bowel sounds, and a fluid wave and shifting dullness were noted. Spider angiomata were present on the skin. Liver span was approximately 15 cm in the midclavicular line and was mildly tender to palpation. The liver edge was firm and extended to the left upper quadrant. He had pitting ankle edema (2+).

Initial chest x-ray films showed bilateral pleural effusion with no infiltrates. An electrocardiogram (ECG) showed sinus tachycardia with nonspecific ST-T wave changes. His initial laboratory test results showed a hemoglobin level of 12.1 g/dL, a hematocrit level of 35.9 percent, and a mean corpuscular volume of 100.7 μm^3 His prothrombin time was 12.8 seconds; partial thromboplastin time was 31.8 seconds. Test results for hepatitis B surface antigen were negative. His alcohol level on admission was 26 mg/dL, uric acid was 3.6 mg/dL, calcium was 7.6 mg/dL, total bilirubin 5.5 mg/dL, direct bilirubin 5.3 mg/dL, total protein 5.6 g/dL, albumin 2.6 g/dL, alkaline phosphatase 481 U/L, serum glutamic-oxaloacetic transaminase (SGOT) 262 U/mL, gamma-GT 1,510 U/L, and lactic dehydrogenase (LDH) 316 U/L.

The patient was admitted to the hospital and placed on an alcohol withdrawal protocol. He was started on chlordiazepoxide (Librium) 25 mg three times a day and on a 40-g protein, 2-g sodium diet. Initially he showed signs of acute alcoholic hepatitis and encephalopathy, which cleared with cessation of chlordiazepoxide, controlled protein diet, and lactulose. Paracentesis was performed and revealed transudative acidic fluid with no evidence of malignancy on cytology. During his hospitalization he received extensive counseling with Dr. Wil Baker, our staff psychologist, concerning his alcoholism. His liver function studies remained markedly abnormal at the time of discharge, but his encephalopathy had cleared by the time of discharge. He was discharged on a 60-g protein, 2-g sodium, 2-g potassium diet.

DR. TRONCALE: It has been said that if you know syphilis, you know medicine. It can also be said that if you know alcoholism, you know endocrinology. There is evidence that the entire endocrine system is affected by chronic alcoholism. As Marks and Wright[1] have said, "There is no shortage of literature on the effects of alcohol on endocrine function, the only difficulty is to know what to make of it." A number of endocrine functions are affected by alcohol.

It has been recognized for centuries that alcohol has a definite effect on sexual function, perhaps best expressed in an often-quoted conversation between Macduff and the porter in Shakespeare's *Macbeth* in which Macduff asks, "What three things does drink especially provoke?" The porter replies: "Marry, Sir, nose-painting, sleep and urine. Lechery, Sir, it provokes and unprovokes; it provokes the desire, but it takes away the performance."[2] This problem with gonadal function has been in the past associated with alcoholism, particularly with patients who had alcoholic, or Laennec's, cirrhosis; consequently, liver dysfunction was thought to affect gonadal function somehow. More recently it has been found that not only those with cirrhosis have problems with gonadal function. Alcohol has been shown to have a direct toxic effect on the male gonad. Vitamin A metabolism in the testes is thought to be inhibited by alcohol, which in turn inhibits steroid production in the testes. Moreover, alcohol accelerates the rate of testosterone degradation in the liver. Not only is testosterone production affected; other feedback loops are similarly affected, and it is difficult to ferret out which system is responsible for which abnormality. Alcoholics are also noted to have decreased or absent libido, and they are frequently feminized. As you know, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secreted by the pituitary gland usually provide hormonal feedback with testosterone. In alcoholics one would expect high levels of LH in response to the gonadal failure secondary to the testosterone decrease; however, it has been shown that in chronic alcoholics LH and FSH levels are lower than would be expected for the amount of testicular failure.[3,4]

When one peruses the literature on feminization in male alcoholics, an invariable finding is reference to the estrogen-testosterone ratio. Gynecomastia, changes in body hair distribution, and development of cutaneous vascular abnormalities are thought to be caused by hyperestrogenation, but exactly how this occurs is not clear. There are other confounding hormones circulating as well, such as prolactin, progesterone, estrone, and estradiol. Even more confusing is the increased binding of estrogens in the liver of alcoholics. Once this sensitivity to estrogens occurs in the liver, supplemental administration of testosterone does not displace estradiol, for instance, from the hepatic cytoplasmic receptor. One might wonder whether administration of testosterone to male alcoholics might correct this problem; however, testosterone administration is not without the complication of further depressing testosterone production by the testes. So there are no easy answers to the question of feminization of male alcoholics except, of course, their ceasing to drink.[5]

In women, chronic alcoholism has been studied less extensively in terms of its relationship to sexual function; however, it is associated with hypofertility, loss of libido, irregular menses, and amenorrhea. A number of alcoholic women in France were studied in a recent paper by Hugues et al.[6] A smaller group of these women had disturbed sexual function compared with male alcoholics. It was felt that the dysfunction occurred at the hypothalamopituitary level rather than at the level of the ovary.

It was formerly thought that hypothyroidism was common in patients with chronic alcoholism. Modern analytical techniques, however, have not given credence to this belief.[1] Paradoxically, some investigators felt that there was a great deal of similarity between delirium tremens and the symptoms seen in hyperthyroidism. If one begins to look at thyroid function tests in chronic alcoholics, the situation becomes even more confused. Alcoholic hepatitis or cirrhosis causes liver dysfunction, which impairs liver deiodinization of free thyroxin (T_4) to free tri-iodothyronine (T_3). It is also believed that more physiologically inactive reverse T_3 is synthesized. Since T_3 is a potent stimulator of the pituitary, its decrease stimulates the production of TSH, and an increase of TSH causes the thyroid to increase its output of T_4 and T_3. This situation is also complicated by patients with alcoholic liver disease having reduced serum thyroid hormone-binding.

A paradoxical situation ensues. If one looks only at TSH in an alcoholic, one would expect hypothyroidism. If one looks only at T_4 radioimmunoassay (RIA), one might suspect hyperthyroidism. *Annals of Internal Medicine* reported in October 1978 a case in which a patient was thought to be clinically hyperthyroid, but with normalization of his liver function, his T_4 RIA dropped from 14.3 μg/dL to 9.2 μg/dL and his TSH dropped from a high of 14.4 μg/dL to 1.4 μg/dL over the course of about two months. These changes occurred with cessation of drinking and adherence to a regular diet only.[7]

The adrenal gland also reacts paradoxically to the effects of alcohol. On one hand it has been shown that about one fourth of patients with chronic alcoholism have a reduced plasma cortisol response to insulin hypoglycemia. This result, however, is not considered clinically significant; consequently, corticosteroids are believed to be of no benefit to patients with chronic alcoholic liver disease. On the other hand, there is a condition seen in alcoholics known as pseudo-Cushing's syndrome, with the classical clinical features of plethoric facies, truncal obesity, thin skin, and a tendency to bruise easily. This pseudo-Cushing's syndrome, shown to resolve with the cessation of drinking,[8] was at first thought to be due to hypersecretion of the adrenocorticotrophic hormone (ACTH). More sophisticated studies seem to point to the stimulatory effect of acetaldehyde, a byproduct of ethanol metabolism on the adrenal glands.

Both hyperglycemia and hypoglycemia can be seen with chronic alcoholism. Hypoglycemia in alcoholics can indeed be very serious. As all of us who have worked in the emergency room know, alcoholics brought in with high ethanol levels must also be carefully screened for hypoglycemia and acidosis. It should not be taken for granted that because someone presents with alcohol on his breath, alcohol intoxication is the sole cause for mental status dysfunction.

Alcohol inhibits gluconeogenesis. Four types of hypoglycemia are recognized in alcoholics. First, there is fasting hypoglycemia. Fasting hypoglycemia usually develops within six hours of ingestion of large amounts of alcohol by malnourished or

fasting subjects. Associated with lactic acidosis, fasting hypoglycemia is thought to be caused by inhibition of gluconeogenesis and to be augmented by the inability of many chronic alcoholics to release ACTH, which may also be due to direct effects of acetaldehyde on the adrenal gland. The next type of hypoglycemia is ethanol potentiation of drug-induced hypoglycemia, seen with concomitant use of insulin or propranolol. Fasting hypoglycemia is thought to cause interference with glucose homeostasis. Its mechanism is not thought to involve decreased cortisol or growth hormone but perhaps inhibition of adrenergic release. The last type of hypoglycemia described in alcoholics is alcohol-induced hypoglycemia, in which alcohol may promote increased response of insulin release at the beta cell level.[1]

On the other hand, chronic alcoholism is thought to be diabetogenic in susceptible individuals. In a paper from the University of Toronto, Sereny and Endrenyi[9] showed that there was a significant decrease in insulin secretion in alcoholics. A number of authors have reported that cirrhosis is positively correlated with diabetes. A number of factors, including pancreatitis and insulin resistance, have been suggested as factors contributing to the development of diabetes in cirrhotic patients. However, it is not known exactly why alcoholics also become diabetic.

Osteomalacia occurs in patients with alcoholic liver disease and is thought to be due to vitamin D deficiency. Osteoporosis occurs in alcoholics as well. Once again, the only known cure for this condition is stopping alcohol intake as well as ensuring an adequate diet and increasing mobility. Sodium metabolism disturbances are also noted in alcoholics, and sodium retained as a result of cirrhosis is a factor in the development of ascites. Hypoalbuminemia and portal hypertension contribute to ascites as well. In cirrhosis reduced effective blood volume causes reduced juxtaglomerular apparatus flow and increased plasma renin. This process, in turn, causes hyperaldosteronism and accounts for some, but not all, of the sodium retention.

Growth hormone is found to be increased in alcoholics with liver disease. This increase in growth hormone may also contribute to hyperglycemia. Prolactin is also found to be elevated in chronic alcoholics, which may contribute to the feminization discussed earlier.[10]

Another fertile area for discussion in those having cirrhosis with ascites is the hepatorenal syndrome. Its cause is not known, and the kidneys are normal at autopsy. During life, however, the renal vasculature basically shuts down as a result of mechanisms that have not been fully elucidated. I would like now to turn the discussion over to Dr. Kreisberg for his comments.

DR. ROBERT KREISBERG (*Professor and Chairman, Department of Internal Medicine*): Dr. Troncale has covered a very large area. As you can see, each of the endocrine disorders that he summarized could alone provide enough information for a single conference.

I would like to amplify the earlier discussion of gonadal dysfunction that occurs in alcoholics. It is quite clear now that both liver disease and alcohol are responsible for the gonadal dysfunction. That this is true has been demonstrated by study of patients who have chronic liver disease not related to alcoholism compared with those that have chronic liver disease due to alcoholism. Alcohol itself in some way augments the tendency for feminization in men and interferes with pituitary-ovarian function in women. In men the problem is a direct toxic effect of alcohol on the testicular synthesis of androgen. We know that alcohol is metabolized primarily in the liver, where the enzyme systems are present for its degradation to acetaldehyde, an acetic acid. The testes were not felt to have this enzymatic machinery, but recently they have been shown to have alcohol dehydrogenase; consequently, many of the metabolic disturbances in liver function that are attributed to the metabolism of alcohol may also occur in the testes. As a consequence, there is interference and inhibition in testosterone synthesis.

You would expect the pituitary gland to respond with increased release of gonadotropin, but gonadotropin release is inhibited, so that the patients behave as though they have a hypothalamic-pituitary disorder with ineffective release of trophic hormones in the presence of reduced secretion of testosterone by the testes. With time there is going to be testicular atrophy, together with the signs of feminization or demasculinization that occur in men, as well as the complaints of impotency. The literature suggests that if there

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to Motrin Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use Motrin Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If Motrin Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with Motrin Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with Motrin Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of Motrin Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when Motrin Tablets are added.

The antipyretic, anti-inflammatory activity of Motrin Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), Motrin should be discontinued.

Drug interactions. Aspirin: used concomitantly may decrease Motrin blood levels.

Coumarin: bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness;* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

*Incidence less than 1%–Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

*Incidence less than 1%–Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with Motrin. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under "Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under "Causal Relationship Unknown" if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

is testicular atrophy in an alcoholic, it is very unlikely that a substantial return of gonadal function will occur even though the patient withdraws from alcohol.

If this patient's testicles were of normal size at the time he discontinued drinking, even though he may have had some signs of feminization and some complaints of impotency, the expectation would be that he would recover full function. If he already had testicular atrophy, the cessation of alcohol would not be expected to reverse any of the symptoms. If he continues to be impotent, it would be useful to check for testicular atrophy on his next visit. As you know, however, impotency does not have to be related to either vascular, neurogenic, or endocrine disorders; it can be psychogenic. There may be psychogenic factors in this man's background we are not aware of that are responsible for his impotency.

The feminization that occurs in alcoholics can be attributed to a number of different changes. First, a drop in testosterone level, leaving the estrogen level unchanged, would result in demasculinization, or feminization. It appears that the ability to convert androgens to estrogens is increased in patients with alcoholism, perhaps because this process is augmented in the liver, or because the estrogen precursors ordinarily detoxified by the liver are not in alcoholics. In men, one estrogen precursor is androstenedione, an adrenal steroid normally extracted by the liver. If the liver does not extract androstenedione, it then reaches peripheral tissues, where it is converted to estrogen. Estrone levels are therefore high in alcoholics. Estradiol levels can be normal or elevated, and testosterone levels are low; consequently, the substrate is present for demasculinization and feminization. In women the same types of changes occur, but these changes are more difficult to quantitate because, as is commonly known, women have menstrual disturbances. One can demonstrate, however, that alcohol will interfere directly with ovarian function as well as depress the hypothalamic pituitary response to reduced estradiol. As a result women develop oligomenorrhea or amenorrhea as a consequence of their impaired ovarian function. Women also show increased conversion of peripheral androstenedione to estrone. Such women have excess

estrone, which leads to a hyperplastic endometrium with withdrawal or acyclic bleeding; therefore, you can expect to see menstrual disturbances in female alcoholics. Unfortunately, it is much more difficult to evaluate sexual dysfunction in women, and it is difficult to know whether there is a female counterpart to the male problem of impotency.

In a small proportion of men, impotency is now recognized to be related to hyperprolactinemia. It is currently thought that in a manner similar to alcohol prolactin interferes with the pituitary-testicular axis. Hyperprolactinemia in men causes low androgen production and an ineffective release of gonadotropins. The result is high prolactin, low gonadotropin, and low testosterone levels. These men, comparable to women who have microprolactinomas of the pituitary glands, may complain of impotency. When they are treated with testosterone so that their serum testosterone levels are restored to normal, they still complain of impotency. However, when their prolactin levels are reduced by the use of bromocriptine (Parlodel, the same drug used to treat hyperprolactinemia in women), their potency returns. It would appear that although androgens are important in regulating potency, prolactin also has an effect in men that is not fully understood. The hyperprolactinemia that exists in some male alcoholic patients may contribute directly to the problems of impotency. This is a fascinating and complex area in which multiple endocrine deficiencies are induced by chronic alcoholism.

Another area warranting discussion is the relationship between chronic alcoholism and sodium and water disturbances. The mechanism of the hepatorenal syndrome is not well understood, but as Dr. Troncale indicated earlier, there are no morphologic abnormalities of the kidney. So the hepatorenal syndrome is a functional disturbance of renal function, the proof of which is that the kidneys can be successfully transplanted to normal recipients. It is now known that when there is ineffective blood volume, maintenance of glomerular filtration is dependent upon renin and angiotensin. We also know that ineffective blood volume will stimulate renin, angiotensin, and aldosterone. The angiotensin originally was considered to be a stimulating factor for aldosterone, but it has function in and of itself. Angiotensin is a potent vasoactive substance, and it causes vaso-

constriction. The ability to maintain normal or near-normal glomerular filtration in the presence of ineffective blood volume is a renin-angiotensin dependent response. Anything that interferes with the secretion of renin (and therefore the secretion of angiotensin) is likely to adversely affect the glomerular filtration rate. It is known that renin release in the kidney is prostaglandin dependent. As a result, the ability to maintain relatively normal renal function depends upon having normal renal prostaglandins, normal renin release, and normal angiotensin. Anything that interferes with prostaglandin synthesis in the kidney is likely to precipitate renal failure. Consequently, the nonsteroidal anti-inflammatory drugs, of which indomethacin is the prototype, have virtually all (except sulindac) been demonstrated to reduce glomerular filtration rate and to produce acute renal failure when there is ineffective blood volume.

The important clinical implication is that such drugs as acetaminophen, indomethacin, and most of the new nonsteroidal anti-inflammatory drugs have the potential to cause renal failure in patients who have ineffective blood volume. One possible explanation for the hepatorenal syndrome is that for reasons not particularly clear certain chronic alcoholics with tense ascites lose their capacity to maintain renal prostaglandin synthesis and renin release. As a result there is a redistribution of blood away from the glomerulus, thereby creating a functional, rather than a morphologic or anatomic, abnormality, which probably explains why the kidneys work when transplanted into normal recipients. We recommend using the nonsteroidal anti-inflammatory drugs with great caution in patients who have left ventricular dysfunction and ascites.

DR. H. C. MULLINS *(Professor and Chairman, Department of Family Practice)*: What is the difference between acute alcoholism, chronic alcoholism, and casual alcohol use with regard to metabolic and endocrine defects?

DR. KREISBERG: Interestingly, casual alcohol use is just as potent as chronic or acute alcohol ingestion with regard to some metabolic abnormalities. The reason that such patients seldom get into any difficulty is that it is short lived. In other words, you can demonstrate in vitro the acute toxic effects of alcoholism on testicular function

(ie, testosterone synthesis). When individuals drink casually, they are probably experiencing some of the same reactions, but the effects are self-limited, and when the alcohol is metabolized, testicular function returns to normal. It is only in the presence of chronic alcoholism that one is likely to encounter the types of complaints or problems that we have touched upon briefly today.

An additional point worth mentioning, however, is that alcohol has been known for centuries as a precipitant of gout. The ability of alcohol to elevate the serum uric acid is equally present in individuals who drink only one or two cocktails at a party as it is in a chronic alcoholic. Studies done in the cocktail party setting show that there is a significant transient increase in the plasma urate concentration in individuals who are having only one or two drinks. The ability of alcohol to produce hypoglycemia is not seen in casual drinking, but casual drinking will block gluconeogenesis. Casual drinkers do not become hypoglycemic because they have 12 to 18 hours' worth of glycogen stored in the liver; as glucose synthesis from precursors is blocked, they buffer a falling glucose concentration by mobilizing preformed glycogen. Alcoholic patients often have not eaten and are glycogen depleted; consequently, when they drink alcohol, it interferes with gluconeogenesis, and having no glycogen stores to buffer a falling glucose concentration, they become hypoglycemic.

DR. TRONCALE: I do not understand why, in chronic alcoholics with liver damage, either estrogen production is increased or there is lack of degradation. Estrogen sits on receptors in the liver, and testosterone is not able to displace the estradiol that is in the liver. Are those separate receptors?

DR. KREISBERG: There is no doubt that estrogen binds to a specific cell; however, the major problem in alcoholics with chronic liver disease is deficient androgen production and increased sex-hormone binding globulin that reduces free testosterone levels more than free estradiol levels.

DR. TRONCALE: Are there too many estrogens, or is there not enough testosterone?

DR. KREISBERG: I don't think it is the amount so much as it is the balance between estrogens and testosterones. Let me give you an example. A young man who for some particular reason has no testicular development and, therefore, is deficient in testosterone is also somewhat deficient in estrogen, because the testes are responsible for 50 percent of the estradiol synthesis in the man. So in a hypogonadal male, testosterone levels are reduced by about 90 percent or even more, but estrogen levels are reduced by only about 50 percent. The net effect of that difference, however, is a relative estrogen excess. The result is a lack of masculinization or signs of feminization (eg, gynecomastia).

DR. TRONCALE: In summary, this discussion has shown us that practically no endocrine system is left unaffected by alcoholism. Many of the signs and symptoms of the endocrinopathies associated with alcoholism such as feminization and impotence are common. Others, such as thyroid dysfunction and menstrual irregularities, are less well known. We hope that some light has been shed on this interesting and complex subject.

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