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The outlook for the patient with leukemia or lymphoma has been improved by the exponential expansion of basic scientific knowledge in physical chemistry and microbiology, added to much new clinical information based on large cooperative group studies. Most of this progress derives, not from a specific treatment for the disease, but from better understanding and use of multiple support measures. These include the availability of blood components, such as red blood cell, platelet and granulocyte concentrates, better protective isolation measures, and greater expertise in the recognition and treatment of bacterial, fungal, and viral infections in immunosuppressed patients. In addition, the management of associated metabolic disturbances, such as hyperkalemia, hyperuricemia, and hypercalcemia, is now based on firm ground. A review of the major progress in these various areas of supportive care comprises this essay.

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Improvement in remission rate and length of survival overall in acute leukemia can be credited in large measure to better management of the hemorrhagic complications and the infections seen in most of these patients. Particularly is this so during the post-treatment phase of cyclic chemotherapy when severe marrow aplasia and peripheral pancytopenia become intense. Today roughly 11% of patients with acute leukemia die of hemorrhage alone, 69% die of infection alone, and the remainder die of both factors or some other cause.[1] This essay will attempt a concise review of current measures and approaches available in support of the patient whose condition is marrow-depressed and immunologically compromised.

1. Blood Cell Component Therapy

The use of *whole blood* should be restricted to episodes of massive hemorrhage. When there is need to support a falling hemoglobin level due to unremitting blood loss and/or marrow hypoplasia, *packed red blood cells* should be the first choice. Advantages over whole blood are less total volume, and less sodium intake. Sodium balance may be critical in the many patients who are receiving, concomitantly, corticosteroids (Na^+ retention) and carbenicillin (high Na^+ content). Furthermore, packed cells contain less alloimmunizing material in the suspending plasma, and, generally, patients tolerate packed cells longer than whole blood before developing pyrogenic

or other reactions. In our experience, increasingly frequent pyrogenic episodes occurring with succeeding packed cell transfusions can often be controlled by removing the buffy coat of the packed cells with a pipette prior to administration. This observation suggests that leukocyte or platelet antigens are responsible for most of these febrile reactions.

Frozen Stored Red Cells

Occasionally, when transfusion reactions are resistant to the above maneuvers, one can use frozen red cells, which are thawed, washed, and resuspended in saline. It is necessary to wash out the glycerol (a cryoprotective agent). These preparations are expensive, and the donor red cells are, per force, somewhat damaged. Therefore, survival in the recipient is shortened. Frozen red cells may be the transfusion method of choice despite the drawbacks, in situations involving very rare blood types and severe alloimmunization reactions to plasma proteins, white cells or platelets.

Platelet Concentrates

It is now practicable to prepare and administer platelet concentrates (generally in numbers equivalent to 4-12 units of donor blood, reduced to a volume of 50-150 cc). The effective functional life of the donor platelet is probably no more than 48 hours, and, with succeeding boli of pooled random platelets, rapid alloimmunization develops in the recipient. Thus, after three to eight platelet transfusions, the progressively more rapid destruction of donor platelets in the recipient makes their value nil. The best practical guide to judging the effectiveness of a given bolus of platelets is performing a post-transfusion count and observing the clinical effect on hemostasis.[2] Some oncologists have recommended giving prophylactic donor platelets daily or every other day, when the platelet count reaches levels below 20,000 per cu mm. Others, including this author, feel it is better to wait for episodes of frank and significant bleeding. In favor of the first position can be cited a study in children by Roy,[3] who observed a 26% incidence of major bleeding at platelet counts below 10,000 per cu mm. This is a significantly greater figure than that seen in children receiving both low and high dose platelet concentrates daily. Furthermore, it cannot be denied that the first manifestation of a severe hemorrhagic complication can be a fatal cerebral or gastrointestinal hemorrhage, occurring too rapidly to be controlled by platelet transfusions "on demand." However, the rapid development of alloimmunization to random donor platelets, coupled with long periods of marrow suppression seen after many courses of chemotherapy, makes the "on demand" use of platelets superior, in my view. There are other hazards in administering platelets besides alloimmunization; such as the transmission of hepatitis virus, cytomegalovirus, or toxoplasmosis. Rarely, the transmission of bacterial contaminants from platelets stored at room temperature as well as graft-vs-host reactions from lymphocytes present in the concentrates have been described in severely immunosuppressed recipients.

When it is possible, there is a greater advantage in using HL-A matched donors for platelets, matched at least at the four major loci.[4] These donors are generally siblings of the patient. Parents and children of the patient will have two matched loci, rarely more, but are better donors than random donors. The chances of finding a four antigen HL-A match from an unrelated donor is one in 10,000 or 20,000. Non-HL-A platelet specific antigens can produce sensitization even in matched siblings. And, there is the further problem of "locking in" a donor to a protracted, tedious regime, once he or she is identified.

Platelets may be stored at 4°C or 22°C. Those at the colder temperatures require warming before administration. Platelets at 4°C do not survive as well in the recipient as

platelets at room temperature, but they appear to respond to aggregating agents in vitro better than those at room temperature. In vivo studies also show correction of bleeding times by 4°C platelets immediately after infusion, but not by 22°C platelets, although the latter seem to regain their hemostatic properties after a few hours. We are currently using 22°C platelets routinely.

Theoretically, the use of autologous platelets collected from the recipient at a previous time in anticipation of later need, is the best source. In a few investigative studies, these autologous platelets have indeed demonstrated their effectiveness.[5] However, long term preservation, using either 5% DSMO or 5% glycerol as cryopreservatives, has not been entirely satisfactory. Thawing of platelets and washing out of the preservatives prior to administration damage the platelets. Current investigative work concerns finding optimum rates for freezing, optimum freezing temperature, best volume of concentrate, best cryopreservative, and its best concentration, etc. Precollected autologous platelets are not a practical tool, at present.

The use of fresh frozen plasma and prothrombin complex concentrates, such as Konyne, have no place in the management of leukemic patients. The former might be used to correct one or more clotting factor deficiencies, should they occur *not* as a result of disseminated intravascular coagulation, but this situation must be rare. Prothrombin complex concentrates should probably be used only to treat patients with Christmas disease. This material probably contains a thromboplastic contaminant, and its use has produced intravascular coagulation and large vessel thrombosis.[6,7] It also is a common source of hepatitis virus.

The disseminated intravascular coagulation (DIC) syndrome occurs commonly as a complication of progranulocytic leukemia. Evidence for it, such as decreased fibrinogen and increased fibrin split products, should be routinely sought in this disease. Because thrombocytopenia may well be drug- or leukemia-related, low platelet counts may not be a helpful diagnostic sign, but, when present, prolongation of the prothrombin time, partial thromboplastin time, and decreased factor VIII and V assays are indicative of the condition. The syndrome occurs frequently as a result of coincident septicemia during the course of leukemia. In this situation, prompt and vigorous treatment of the infection (to be discussed later) is more helpful than is heparin. If severe and generalized bleeding is due to DIC, the administration of heparin (starting with low doses—10,000-15,000 u/d—and increasing cautiously, if necessary) is an accepted maneuver. Obtaining serial serum fibrinogen and fibrin split product assays is the best way to monitor the response to heparin, in addition to observing clinical control of bleeding.

Granulocyte Transfusions

Some institutions involved in the aggressive treatment of acute leukemia and the lymphomas are coming to the use of granulocyte concentrates in the management of the neutropenic and septic patient. Although our own experience with donor granulocytes has been small and disappointing, there is clear evidence of benefit in the hands of others.[8] One observation seems clear: random donor granulocytes have a poor record. One should obtain relatives, preferably siblings, as donors. At times the urgency of the clinical situation may preclude an HL-A matching, at least until after the first collection and administration. The two methods of collection are by 1) differential centrifugation and 2) continuous flow filtration leukopheresis (CFFL). The first method involves the use of a blood cell separator, and 100% increase granulocyte yields from the donor can be procured by administering etiocholanolone 12 hours prior to donation. Further increases in yields can be obtained by using hydroxyethyl stars (HES), a glucopyranone polymer derived from waxy sorghum cornstarch. This material, introduced into the separator,

promotes rouleaux of red cells and thereby delineates better the granulocyte layer. By use of these techniques, 2.73 x 10^9 granulocytes per litre of donor blood processed was obtained by McCredie et al.[9] In contrast, Djerassi,[10] using two nylon fiber filters in parallel to collect granulocytes and then eluting them off the filters in a continuous flow system, processed 10-18 litres of blood in three hours. The granulocyte yield is much greater than by differential centrifugation, averaging 37.5 x 10^9 cells. These granulocytes have been shown to retain normal function, ie, ingestion of bacteria and latex particles, and migration to sites of infection. However, pyrogenic reactions are increased in the recipient as compared to separator prepared cells even in HL-A matched donors. In favor of CFFL is the relatively low cost, and the ease of re-using the same donor, since only 30 cc of red cells are sacrificed at each donation. As methods are refined, we can reasonably expect to have useful granulocyte transfusions as adjunctive support to the leukemic patient in a few years.

Plasmapheresis

Although not strictly pertinent to the topic of supportive management of the leukemic patient, it is probably valid to mention the proven value of plasmapheresis in myeloma and lymphoma patients with extreme levels of serum globulin. The occurrence of a hemorrhagic state due to impairment of platelet function or fibrinogen conversion by excess globulin and/or manifestations of the hyperviscosity syndrome both can be satisfactorily controlled with this technique.

II. Infection

It is a rare patient with acute leukemia who does not become "infected" by bacterial or fungal organisms. Often infection produces the initial awareness of illness which leads to medical care and the diagnosis of the leukemia. At other times infection occurs during the course of early chemotherapeutic efforts at attaining remission. As a rule of thumb, an absolute neutrophil count below 500/cu mm, certainly below 200/cu mm, carries with it almost sure promise of bacterial invasion of the host. Furthermore, neutropenic patients may fail to elicit the expected signs of local inflammation at infected sites, and may not necessarily have significant fever. On the other hand, a leukemic patient who suddenly shows a fever of 38.5°C (101°F), or more, surely has an infection and should be treated as such with all urgency. Acute leukemia per se may produce a low-grade fever, but never as high as 101°F. Drugs sometimes produce this high fever and cause confusion in the patient already receiving antibiotics or antileukemic agents. Sites of trauma, such as the mouth and anal region are frequently the portal of entry for infecting agents, as is the respiratory tract and skin. Local lesions should be sought, since their presence may suggest the most likely infecting organism(s). For example, *E coli,* and *P aeruginosa* are often cultured from perirectal and rectal abscesses; gram negative bacteria and fungi from pharyngitis; *Klebsiella sp* organisms, and fungi from pneumonia; *E coli* from urinary tract infections; and *S aureus* from skin lesions.

In 90% of cases sepsis was due to either *P aeruginosa, E coli,* or *K pneumonia* in a 1968 study at M.D. Anderson Hospital[11] (see table 1). Other institutions vary somewhat as to which are the most prevalent organisms causing septicemia. The clinician should be familiar with the local current experience in this regard. It is noteworthy in a given patient that once an organism produces clinical disease which responds to treatment, a second episode of infection is very likely to be due to this same organism. Unfortunately, there are too many exceptions to this rule to be useful in the overall therapeutic plan. Acknowledging that it may be difficult to recognize sepsis in this group of patients, nonetheless, the pro-

Table 1

BACTERIAL ORGANISMS PRODUCING SEPSIS IN LEUKEMIC PATIENTS

1) Pseudomonas aeruginosa	40%
2) Escherichia coli	30%
3) Klebsiella pneumoniae	20%
4) Staphylococcus aureus	3%
5) Proteus vulgaris	2%
6) Others	5%

Data is derived from unpublished observations by GP Bodey, M.D., Houston, Texas, in 1968.

phylactic use of antibiotics is unwise. It has been clearly shown that the longer such a patient receives antibiotics, the greater his chances of acquiring an infection due to resistant organisms. Greene et al reported superinfections in patients taking a three-drug antibiotic treatment, ie, 12%, 25%, and 50% after 6, 12, and over-12 days respectively.[12] On the other hand, delay in starting treatment of septicemia until there is cultural proof will result in a high percentage of failure.

With these considerations in mind, the following *modus operandi* seems most logical in the management of the acute leukemic patient: At the first clinical clue that sepsis is present, cultures of blood, sputum, throat, and urine are taken, along with a chest x-ray. A three-drug antibiotic regimen, consisting of gentamicin, carbenicillin and cephalothin is given via a parenteral route. There is evidence that carbenicillin is more active in the presence of neutropenia than the other agents. Furthermore, carbenicillin and gentamicin seem to be synergistic in *Pseudomonas* infections. Gentamicin and cephalothin probably work synergistically in *Klebsiella* infections, and all common infecting bacteria are "covered" by these three drugs. This program is followed for eight days unless a specific organism is recovered which would dictate an appropriate change in the regimen. For example, recovery of an anaerobic *Bacteroides* resistant to penicillin might warrant a change to clindamicin.[13] If the organism is not recovered, and the patient remains clinically septic, all antibiotics are discontinued around the eighth day, and additional cultures obtained after 48 hours. However, many patients respond promptly to this program. Others survive long enough so that neutrophils repopulate the circulation if marrow recovery occurs. Frequently, all signs of sepsis disappear when the polymorphs return. Relapses, occurring with subsequent vagaries of the disease or with cyclic chemotherapy require repetition of the same prompt attack.

Because of the frequency of monilial stomatitis, pharyngitis, and esophagitis, particularly in neutropenic patients receiving corticosteroids, mycostatin oral suspension is prescribed prophylactically during the periods of risk. This practice does not seem to create any new problems and is effective in controlling and/or eradicating oral candidiasis. Other important preventive measures include avoidance of intravenous catheters, changing intravenous needles every 48 hours, and changing intravenous tubing daily. Also, one should avoid using urinary catheters or any other invasive procedure not clearly of ultimate benefit to the patient. Skin care is of unusual importance in this clinical setting. Prompt attention to even the most innocuous-appearing lesion, trimming finger and toe nails, regular bathing, avoiding wetness and maceration of skin, all must be included in the nursing regimen. The bacterial burden to the patient can be reduced to a significant degree by a private room and by practicing a simple form of reverse isolation. We require personnel attending the patient to use gown, mask, and gloves. Potential sources of pathogens such as respiratory equipment, ice machines, bath tubs, etc., should be monitored by periodic culturing.

Table 2

NON-BACTERIAL INFECTIONS SEEN IN LEUKEMIC PATIENTS

Candidiasis
Aspergillosis
Mucormycosis
Varicella-Zoster
Cytomegalovirus disease
Pneumocystis Carinii Pneumonia
Toxoplasmosis
Viral hepatitis
Cryptococcal meningitis

Fungal and Protozoal Infections

Table 2 is an incomplete list of nonbacterial causes of infection seen with increasing frequency in immunosuppressed patients. These include fungal, protozoal and viral organisms.

Candidiasis in pharynx and urine generally represents superficial infection, but substernal pain and dysphagia may indicate invasive esophagitis. These symptoms in the presence of other evidence of oropharyngeal thrush should virtually establish the diagnosis, although esophagograms, esophagoscopy, and biopsy are decisive in questionable cases. In the immunosuppressed neutropenic patient with acute leukemia, late stage chronic leukemia or lymphoma, *Candida* organisms, (ie, *albicans, tropicalis,* and other species) are the most common fungal offenders. Their presence should be suspected if a patient fails to recover satisfactorily from antibacterial therapy or has a late febrile relapse. Since the advent of aggressive chemotherapy in acute leukemia, candidiasis has strikingly increased. Pseudomycelial forms of *Candida* in the urine suggest the presence of the disseminated form of the disease while finding *Candida* in blood or marrow cultures, in the absence of indwelling intravenous catheters, virtually establishes the diagnosis. Despite its toxicity, amphotericin B should be used in this latter circumstance. 5-Fluorocytosine, a new oral antifungal agent, has been disappointing in disseminated candidiasis in the compromised host, although synergism with amphotericin B has been described.[14]

The second most common fungus invader in the leukemic patient, also with increasing incidence is *Aspergillus,* rarely recognized ante-mortem and even less often treated successfully. This species generally attacks the respiratory tract. Chest roentgenograms show a variety of pulmonary abnormalities in already severely ill patients. At autopsy, widespread involvement of the gastro-intestinal tract, brain, liver and kidney is often found. More aggressive diagnostic efforts, such as bronchial brushing, closed needle aspiration, or even open lung biopsy, may make it possible to recognize invasive disease in time to render effective antimycotic therapy with amphotericin B.

Mucormycosis should be considered in chronically ill, neutropenic, immunologically deprived individuals who demonstrate in addition the triad of orbital cellulitis, sinusitis, and diabetes mellitus (generally poorly controlled). Diagnosis requires a biopsy of infected tissue from skin, palate, or lung since ordinary fungus cultures are rarely positive.

Cryptococcosis and histoplasmosis are rarely seen in acute leukemia, but continue to occur in the late stages of chronic leukemia and lymphoma. Patients who seem to be failing in a nondescript way, with or without fever, and without obvious progression of their basic hematologic disease, may have one of these latter two fungal diseases. In addition, disseminated toxoplasmosis or

Pneumocystis carinii pneumonia are occasionally responsible for the same clinical picture, although *Pneumocystis* is almost always accompanied by dry cough, tachypnea, and objective signs in the chest.

Cryptococcus neoformans meningitis, when present, only yields a 50% positivity on India ink preparations of the cerebrospinal fluid. One should always culture the spinal fluid as well as the sputum and urine in suspected cases. Complement fixation or latex agglutination tests of the spinal fluid are also helpful. Histoplasmosis, of all the fungi, is most successfully cultured from blood or bone marrow with positive results in 50% of disseminated cases.[15] Should the signs of Addison's disease occur during the course of chronic leukemia or lymphoma, the most likely causes are histoplasmosis or myleran toxicity. Disseminated or adrenal tuberculosis has become less common in recent years. Biopsy of oral ulcers may disclose the presence of the typical-appearing fungus. The combination of amphotericin B and 5-Fluorocytosine is occasionally successful against cryptococcosis and histoplasmosis.

Toxoplasma gondii disseminates in immunodepressed hosts, producing a serious preterminal condition. Because of central nervous system (CNS) involvement, mental symptoms, cranial nerve palsies and motor paresis occur. Although rising titres of *Toxoplasma* antibodies are diagnostic, it may be quicker to obtain a biopsy of a lymph node, where typical pathologic changes can be recognized. Treatment currently given is the combined use of pyrimethamine and sulfadiazine for four weeks.

To recover the organisms of *Pneumocystis carinii,* one must generally perform open lung biopsy although a few reports of success with bronchial brushings and tracheal aspirations are available. Treatment for this protozoan organism in established cases is pentamidine isethionate for two weeks. Experience at the National Cancer Institute indicates about a 50% clinical recovery overall, and 80% in patients who received treatment for 7 days or more.[1]

Viral Infections

Chronic lymphocytic leukemia and lymphoma patients are particularly prone to some, but not all, viral disease. The predominant culprits are herpes viruses, including varicella-zoster, simplex, and cytomegalovirus. In addition, vaccinia and measles produce more severe clinical disease in these patients. As a general rule it is wise to avoid using any vaccine which contains live and/or attenuated virus in potentially immunosuppressed subjects.

Varicella-zoster either in its typical dermatome or disseminated distribution is easily recognized. If deemed necessary, a Tzank test can be performed to confirm the etiology. This consists of finding, under light microscopy, intranuclear inclusions in multinucleate giant cells from scrapings taken from the base of vesicles, stained by the Giemsa method. Both the local and disseminated (chicken pox) form of the disease are more severe, the latter being life-threatening, as is the pneumonic form. ZIG (zoster immune globulin) is an effective passive suppressant of varicella in exposed children, but it must be given within 72 hours of exposure. Since zoster is thought to be a reactivation of a dormant varicella virus in adults and, clearly, prophylaxis is not feasible, ZIG would appear to be useless in the latter. Furthermore, the large dose (0.5 ml/kg) is impracticable. In adults who develop severe herpes, the use of adenine arabinoside (Ara-A) has recently shown promise. Cytosine arabinoside (Ara-C) and idoxyuridine (IUDR) have not been effective, although the latter (IUDR) is of proven value in herpetic keratitis. Ara-A in the recommended dosage, 10 mg/kg/day x 5 days in continuous intravenous drip, is less toxic to marrow and immuno-suppressive than Ara-C and other antimetabolites.

With regard to herpes simplex (hominis) infection, suffice it to say that the local skin or mucous membrane lesion may develop an extensive area of cellulitis in compromised hosts. Occasionally, one of these patients will develop an atypical indolent encephalitis which mimics progressive multifocal leukoencephalopathy. Brain biopsy is required to establish the etiology of the CNS symptoms. A study to evaluate treatment with Ara-A is underway,[16] but the problem of securing a patient population with proven herpes encephalitis is obvious. IUDR has been found unacceptably toxic in this condition.[17]

The occurrence of clinical symptoms due to cytomegalovirus does not seem to be more prevalent in leukemia and lymphoma patients. However, the manifestations are so variable that the present status of this entity is vague at best. A prospective study at the National Cancer Institute tried to clarify points regarding the significance of virus excretion in throat or urine in relation to cryptogenic fever, rash, or pneumonitis, and also evaluate the presence of hemagglutinating antibody and complement-fixing antibody.[18] Patients with severe pneumonitis, rash and fever, with demonstrated virus in throat or urine, and a fourfold antibody rise should probably receive antiviral agents, such as Ara-A or IUDR.

Because of the likelihood of severe local reaction or generalized dissemination, smallpox vaccination should be avoided in patients with chronic lymphocytic leukemia or lymphoma. Nonetheless, despite this admonition, vaccinia gangrenosa, eczema vaccinatum, or generalized vaccinia will continue to occur among the unwary. VIG (vaccinia immune globulin), in 0.6 ml/kg intramuscular dosage, is sometimes successful in controlling these often fatal manifestations.[19] Marboran, a thiosemicarbazone, has also been shown to be effective. The drug is taken orally in doses of 200 mg/kg/daily for four days.

The immunosuppressed patient, if infected with rubeola virus, may succumb to a severe pneumonic process. This virus, which can be recovered from normal individuals only up to 48 hours after disappearance of the rash, has been shown to persist in leukemic patients' respiratory tracts for long periods. Successful passive immunization with commercial gamma globulin in a dose of 0.25 ml/kg can be accomplished if given within 48 hours of exposure, and modification of the severity if given within five days of exposure.

Hepatitis B is an on-going problem in the management of leukemia and lymphoma patients, because of the usual high transfusion requirement. The incidence decreases if only healthy, Australia antigen-negative volunteers are used as a source of blood for transfusion in contradistinction to commercial donors. Although gamma globulin intramuscularly can protect against hepatitis A, it is not predictably effective against type B exposures. Furthermore, it is impracticable to carry out long term prophylaxis with this passive immunization method. Current research is pointing the way toward inactivation of the virus in the donor blood prior to its administration. A 75% reduction in the incidence of icteric hepatitis has been described by incubation of donor blood with gamma globulin.[20] Also, active immunization with a vaccine consisting of a heat-inactivated Australia antigen is under trial. In treating the patient with viral hepatitis, it is best to refrain from the use of corticosteriods early in the clinical course, since this therapy has been shown to be associated with an increased incidence of chronic sequelae and the Australia antigen carrier state.

III. Metabolic Abnormalities

In acute leukemia, the most common metabolic disturbances are shown in Table

Table 3

METABOLIC DISORDERS ASSOCIATED WITH LEUKEMIA AND LYMPHOMA

1) Positive Na^+ balance, fluid overload

2) Hyperkalemia and Hypokalemia

3) Hyperuricemia

4) Hypercalcemia

3. The occurrence of hyponatremia and hypochloremia as a result of excessive losses in the gastrointestinal efflux requires appropriate replacement by parenteral fluids. However, conversely, one often sees hypernatremia and/or vascular congestion from excessive sodium intake, associated with large doses of carbenicillin in conjunction with the need for blood products and intravenous chemotherapy.

Hyperkalemia and Hypokalemia

Recently the findings of hyperkalemia[21] and hypokalemia[22] have been described during the course of acute leukemia. The hyperkalemic state has been explained, at least theoretically, by the release of potassium from leukemic cells but, paradoxically, hypokalemia has also been found in the presence of high total body potassium.[23] A renal tubular defect, possibly associated with excess lysosyme excretion seen in monocytic and myelomonocytic leukemia may account for a high potassium excretion rate and a consequent low serum level but the explanation is almost certainly more complex. The antibiotics gentamicin and carbenicillin may induce urinary potassium loss. By altering cell membranes, cytotoxic drugs may be responsible for significant ionic shifts. For the present, it is well to realize that, although hypokalemia may be present before any treatment of the leukemia is begun, most often it appears sometime during the complex post-treatment period. It makes a major contribution to the patient's morbidity. The condition is generally slow to respond to potassium replacement, but obviously the attempt should be made, if renal function is grossly satisfactory.

Hyperuricemia

Hyperuricemia occurs frequently in patients with both chronic and acute leukemia of all cell types. The serum uric acid level fluctuates with disease activity and with the state of renal function. Treatment with radiation or cytotoxic drugs, particularly in the presence of a high tumor cell mass, can be expected to produce an increase in the serum level. It is also a burden on the renal mechanism for excretion of urates, whether the pretreatment serum uric acid level was elevated or not. The development of acute renal failure as a result of uric acid nephropathy is an acknowledged and dreaded complication of this urate overload. Yet, despite its documentation in the literature, it must be quite rare, judged by the author's experience. Nonetheless, it is accepted practice to give allopurinol to the patient with elevated serum uric acid or to the patient with high tumor cell mass in whom one anticipates a rapid cell kill. An inhibitor of xanthine oxidase, allopurinol protects the serum and kidneys from a large urate load. But, it is still wise to alkalinize the urine and push fluids in conjunction with radiotherapy and/or chemotherapy since there is the possibility of producing xanthine calculi with these treatment modalities. Allopurinol is excreted by the kidney and the dose should be reduced in the presence of renal failure. The average dose of 300-600 mg/day is reduced to 200 mg for a

creatinine clearance of 10 ml/min. High doses (600-800 mg) are given just prior to major treatment thrusts. One should also be aware that the interaction of allopurinol with some chemotherapeutic agents, eg, cyclophosphamide, results in greater marrow depression than with the latter alone.[24]

Obviously, the occurrence of renal shutdown, in a clinical setting which suggests uric acid nephropathy, would be managed by the measures usually employed, no matter what the underlying cause; ie, fluid intake adjusted to maintain normal hydration (insensible losses plus urine output), allopurinol in reduced dosage to adjust for impaired output, and alkalinization. Hemodialysis would be preferable to peritoneal dialysis, should uremia supervene.

Hypercalcemia

Acute and chronic leukemia are rarely, if ever, accompanied by a pathologic degree of hypercalcemia. On the other hand, the condition occurs fairly commonly in uncontrolled myeloma (10%-20%), and occasionally in lymphomas or other malignancies in which bony involvement is a clinical feature. Indeed, the presence of hypercalcemia may alert the clinician to an otherwise silent spread of disease to the bones. The symptoms of hypercalcemia are nonspecific, but they are suggestive to the alert physician: lethargy, depression, constipation, anorexia, and even nausea and vomiting. The patient is generally dehydrated and shows obtunded or absent deep tendon reflexes. Frequently, there is an associated hyperuricemia with or without variable degrees of azotemia. Measures directed toward correction of the hypercalcemia can render a very gratifying improvement in the patient's well-being as well as in other biochemical abnormalities. On the other hand, untreated prolonged hypercalcemia leads to irreversible renal failure, metastatic calcifications, cardiac arrhythmias, shock and death. Therefore, we should consider hypercalcemia (above 11.5 mg %) as a medical emergency, requiring the following corrective measures in decreasing order of priority.

1) Rehydrate with adequate fluid replacement to yield a daily urine output of 3 to 4 litres.

2) Administer furosemide (Lasix) following initial rehydration. This agent is particularly effective in inducing calcium excretion, since it acts to block tubular reabsorption of sodium (and therefore, calcium at the same site).

3) Give high dose corticosteriods which promptly lower the serum calcium in multiple myeloma patients, less predictably so in other cancer patients. The mechanism of action is thought to be through decreasing bone absorption.

4) If the first three measures are ineffectual, one should use mithramycin in a single intravenous injection of 25 ug/kg.[25] This is far below the anti-tumor dose and should not significantly affect marrow function. It also acts by inhibiting bone absorption, and a favorable change in serum calcium is generally observed within 24 to 48 hours.

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