Hepatic Lipidosis: Mechanisms, Diagnostics, and Treatments

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Historical Background

Ketosis has been a recognized problem in dairy cattle since the late 1920's when the role of glucose and energy demands were first associated with this condition.[1] Descriptions of a disease syndrome, now thought to be ketosis, characterized by anorexia, decreased milk production, and constipation appeared in veterinary texts 50 years prior to this.[2,3] A more complex type of ketosis was recognized by Sollman[4] and Alston[5] which, unlike simple ketosis, was associated with high mortality and a variety of concurrent disease problems. Morrow[6] called this disease "Fat Cow Syndrome" based on the physical condition of affected cattle. Like simple ketosis, the disease occurred at or around parturtion. The typical histologic lesion common to these affected cows was severe fatty infiltration of the liver (hepatic lipidosis).

This same finding (hepatic lipidosis) is not only found in overly conditioned cattle but also in poorly conditioned animals during the periparturient period. As with the Fat Cow Syndrome cows, these cattle also suffer from a variety of concurrent diseases.

Mechanisms

To understand the mechanisms responsible for hepatic lipidosis, it is important to review the mechanisms brought into play in simple ketosis. Ketosis occurs as a result of high energy demands placed upon dairy cattle in the early stages of lactation in addition to hormonally mediated shifts in lipid metabolism.[7] It has been documented that the oral intake of nutrients in a high producing cow will be insufficient to meet the energy expended for production for approximately 6-8 weeks.[8,9] During this phase the cow is dependent on her body stores of fat and protein to meet this demand. Ketosis occurs when the amount of fat mobilized and sent to the liver exceeds the hepatocytes ability to convert it to energy through the tricarboxylic acid cycle. A relative deficiency of oxalacetic acid [OAA] occurs when large amounts of lipids are presented to the liver. This results in incomplete oxidation of the lipid and the resulting generation of ketone bodies. Ketone bodies perpetuate their own production by acting as appetite suppressants, thus stimulating more fat mobilization into an already compromised liver. By the 6-8th week of lactation, oral intake should meet the lactational demands and so the incidence of clinical ketosis decreases[8].

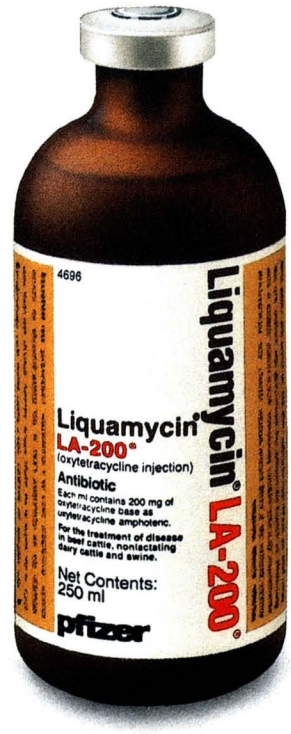
In hepatic lipidosis, the cow not only deals with production of ketone bodies but associated loss of liver function. Normal, healthy cows mobilize fat from body stores to the liver in late gestation.[10] The non-esterified fatty acids (NEFA), actively absorbed by the hepatocytes during this time, can render these cells non-functional (lacking the ability to release the lipid). When large numbers of hepatocytes are involved, liver function is diminished. These functions include detoxification of body waste compounds, synthesis of proteins, and clearance of bacteria via the hepatic reticulo-endothelial system, in addition to the conversion of fats and proteins to energy. The end result is that the affected cow has less ability to fight infection and even mild infections tend to overwhelm the patient.

To state that the mobilization of fat stores to the liver is responsible for hepatic lipidosis is an over simplification. A variety of mechanisms have been or are currently being investigated as to their role in hepatic lipidosis. These include: adrenal insufficiency, carbohydrate deficiency, and selenium deficiency[11] as well as vitamin deficiencies of A and E.[11] In addition, the role of insulin (impaired release) has also been studied[12] The most current research in this area suggests the problem resides in lipid transport and the release of the triacylglycerol-rich lipoproteins from the hepatocytes.[13,14]

Diagnostics

The diagnosis of hepatic lipidosis/fat cow syndrome is most often based on history, physical findings, and failure to respond promptly to what seems appropriate therapy. Laboratory methods are available which can aid the practitioner in accurately assessing the degree of liver lipidosis and lost function. These include non-specific enzymatic tests, specific enzymatic tests, quantitative assays of hepatic lipid content, and function tests of the liver itself.

The non-specific tests are those that measure enzymes of possible hepatic origin such as asparate amino transferase (AST), commonly referred to as SGOT, and lactic de-



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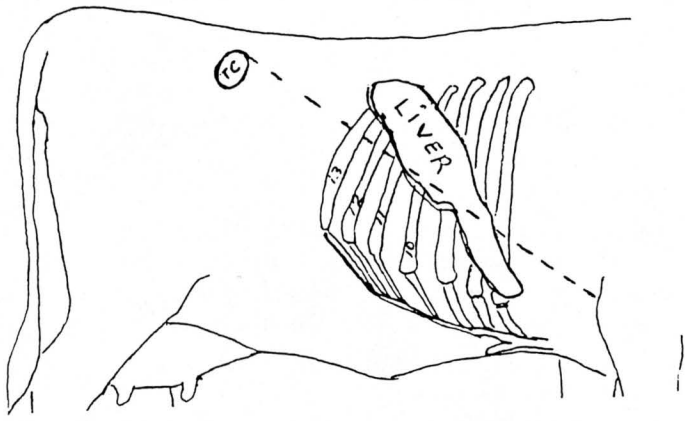
hydrogenase (LHD). Both these enzymes are found in tissues other than liver and thus have limited usefulness. AST and LDH are derived from muscle as well as liver and, since cows with hepatic lipidosis frequently spend more time down due to infection, it may be difficult to determine the origin of the rise. AST rises slowly following injury to hepatic cells, reaching peak values in about 3 days. The decline of the enzyme is even slower and may take 2 weeks to return to normal values. LDH can be used as a liver specific enzyme if isoenzymes are measured; otherwise, the determination is no more specific than AST.

Liver specific enzyme tests are available. These include sorbitol dehydrogenase (SDH), ornithine carbamyl transferase (OCT), and glutamate dehydrogenase (GDH). Like AST, these enzymes are associated with cell injury. The magnitude of the rise does not necessarily correlate with the amount of liver involved. In fact, focal lesions such as actively enlarging liver abscesses would be more likely to cause a large rise in these enzymes than would fatty infiltration. Roberts and Reid[15] have reported these laboratory determinations are poor indicators of hepatic lipidosis. Our experience with SHD in cases of severe fatty infiltration would support their findings.

Quantitative determinations of hepatic lipid content can be done by several methods, all of which require a bioposy. Percutaneous biopsying of the liver has been performed thousands of times with minimal complications. The site for the biopsy can be located by drawing a line from the right tuber coxae to the right elbow. The intersection of the line and the 10th intercostal space is the location for the insertion of the biopsy needle (fig.1).

FIGURE 1



The biopsy needle should be inserted perpendicular to the skin and advanced through the muscles and peritoneum. Once the peritoneum has been punctured, the needle is advanced slowly until resistance is encountered (liver). A sharp stab is made with the needle to puncture the liver's capsule. The biopsy portion of the needle is then opened and the biopsy cut. If correctly done, approximately 40-50 mg of liver will be obtained.

The simplest quantitation procedure can be done on the fresh sample using a buoyancy test.[16] This involves dividing the biopsy into thirds and placing the samples into solutions with specific gravities of 1.000, 1.025, and 1.055. The solutions are made from distilled water (1.000) and copper sulfate. The amount of fat present can be roughly determined based on whether the samples float or sink in the various solutions(table 1).

Table 1. Liver Specific Gravity Test

% Fat Content	Interpretation	1.000	1.025	1.055
34	Severe	Floats	Floats	Floats
25-34%	Moderate	Sink	Floats	Floats
13-24%	Mild	Sink	Sink	Floats
13%	Insignificant	Sink	Sink	Sink

As many as 30% of all freshening dairy cattle may have hepatic lipid content in excess of 34% so interpretation of this test must be made in light of the clinical signs of the cow.

The more sophisticated methods involve chemical assay for triglycerides or point count determination of lipid content based on histologic sections. The histologic determinations can be done on either frozen or fixed tissue. These tests are likely more accurate but are not readily available outside academic institutions.

Liver function tests are not diagnostic for hepatic lipidosis, however, they are useful in prognosing individual cases. About the only function test used in large animals is the BSP dye excretion tests. This involves the intravenous injection of the dye (1 mg/lb) and the collection of 2-3 heparinized blood samples timed between 5 and 12 minutes post injection. The dye is handled much the same as bilirubin and is normally rapidly excreted by the liver. The half-life of the dye is calculated. The normal value is T1/2 = 3.3+/-0.5 minutes. Most dairy cows at partrition will have elevated dye half-lives but still are unlikely to have clinical signs of hepatic lipidosis. In our experience, the prognosis for cattle showing signs of fatty livers, based on BSP clearance, is:

BSP half-life (minutes)	Prognosis
5	EXCELLENT
5-8	GOOD (may require tx)
9-12	GUARDED (requires aggressive tx)
12	POOR (unlikely to respond)

Another possible test of liver function presently being investigated is the quantitation of serum bile acids (SBA).[17] Bile acids, synthesized by the liver and excreted in bile, facilitate the digestion and absorption of fats. Bile acids are absorbed from the intestinal tract and taken up by the liver and re-excreted in bile. This is a very efficient

process with little loss through the gut. In hepatic dysfunction in man, SBA's elevate due to impaired hepatic uptake. In patients with cirrhosis, SBA elevated even when enzymatic values were normal. Work by Dr. Frank Garry[a] however, indicates this test is no more accurate than BSP at prognosing outcome in hepatic lipidosis.

Other laboratory tests useful in evaluating affected cows would include the hemogram and the chemistry profile. As already mentioned, affected cattle have impaired responses to infection. This can often be manifested by low leukocyte counts (3000). The hemogram allows the practitioner to monitor the cow's response to treatment. Cattle which fail to mount a neutrophilic response despite appropriate antimicrobial therapy are unlikely to survive.

A serum chemistry profile would be useful in directing appropriate therapy (electrolytes, fluids). Many profiles incorporate CPK as one of their tests. This may be useful in determining the origin of elevations in AST.

Therapy

The standard treatment for the fatty liver cow revolves around meeting her energy needs and, thus, preventing continued fat mobilization. Since the most readily detectable sign is ketosis, the standard treatment is intravenous **glucose** therapy. The big problem is that 250 g of glucose given by rapid IV administration will only keep the cow's glucose level up for 1-2 hours. This is because the cow can only utilize approximately 60 g/hour.[18] The remainder is spilled into the urine and lost. The severely affected cow needs a steady flow of dextrose to avoid the peaks and valleys that result in additional fat mobilization. Valuable cows deserve slow intravenous drips of glucose for at least 24 hours. This gives the liver a chance to clear whatever fat it can from the functioning hepatocytes and will hopefully improve the liver's ability to metabolize fat. Maintenance of cows on continuous glucose therapy has been done for up to 3 days with good success.

Glucocorticoids have been advocated in the treatment of ketosis but careful thought should be given before they are used in animals with clinical hepatic lipidosis. While it is true that these compounds will increase blood glucose[19], they may do so without benefit to the cow. One side effect of glucocorticoid therapy is to decrease the release of insulin. It is already well documented that insulin levels are low at parturition, and lowered further by ketosis[12,20], thus the elevated blood glucose may reflect impaired peripheral tissue utilization.[19] Additionally, these compounds reduce the animal's immune response. In cases with infectious processes, the use of these products may be detrimental to the cow. If infections are not a problem, the positive effects of glucocorticoids (decreased milk production, elevated blood glucose, generalized euphoria) may warrant their use.

Anabolic steroids have been advocated as efficacious in preventing further depletion of protein and fat in cattle with hepatic lipidosis.[15] The use of trienbolone acetate has been advocated for cattle.[15] There is logic to this treatment but few reports of its use under field situations.

Protamine zinc insulin has been given to affected cattle with good results.[21] It is known that one effect of insulin is to inhibit lipolysis.[22] It has also been shown that ketotic cows in the early stages of lactation have lower than normal circulating insulin levels so glucose utilization may be affected. Protamine zinc insulin (PZI) has been selected because of its slow rise (peaks about 18 hours post administration) and long duration of effect (36 hours). The dose used (100-200 units SQ) has been arrived at empirically but appears to be adequate based on clinical response.[21] The possibility of creating a hypoglycemic crisis at the peak effect of the insulin should be considered in those cows not receiving continuous glucose therapy; however, this dosage is small enough that this problem has infrequently been observed.

The use of **choline** in fatty liver cows has been an area of much debate. The controversy arises from the use of this drug in man where some beneficial effects have been reported. Work done by Reid et al suggests that choline may be a useful adjunct to treatment; however, it must be given parenterally. Orally administered choline will be destroyed by the rumen flora. **Methionine,** at 40 g/day for 7 days has some limited benefit in cows with subclinical ketosis.

Propylene glycol, sodium propionate, and **glycerol** have been recommended as ketosis treatments. All these sustances supply substrate to the TCA cycle resulting in increase glucose production. An inherent drawback to their use is that they require a functioning liver for conversion. Left unmetabolized, these products act as appetite suppressants. Propylene glycol is most often used because it is both more economical and more palatable than either of the other products. These products have been most effective when used in cattle that are still eating some roughage (hay).

Adjuncts to treatment:

A variety of drugs have been used in cows with fatty livers. These include ACTH, vitamin E-Se products, and nicotinic acid. ACTH has been used to induce the endogenous production and release of glucocorticoids. Postiive effects have been reported, but have no identifiable advantage over exogenously administered gluocorticoids. **Vitamin E-Se** preparations may be useful because of their roles as antioxidants. Since fat metabolism produces oxide radicals within the cell, the administration of vitamin E-Se seem rational. Additionally, vitamin E-Se injections given to fatty liver cows improve the killing ability of PMNs compared to those of non-injected or E-Se deficient cattle. **Nicotinic acid** has been used to prevent and treat ketosis by reducing the mobilization of free fatty acids. Daily doses

of 12 g/cow eliminated ketosis in affected cows within 9 days.[23] Large doses of 50-100 g/cow acted as appetite suppressants and reduced milk production significantly for 7 days following withdrawal of the treatment.

Because of the reduced resistance to disease demonstrated in cattle with hepatic lipidosis, it is reasonable to cover the animal with **antibiotics**. All identifiable problems should be aggressively treated. Attention should be paid to antibiotic withdrawals so that the animal may be salvaged if improvement is not seen.

In valuable cattle with hepatic lipidosis and showing signs of endotoxemia (high heart rate, diarrhea, weakness) the **non-steroidal anti-inflammatory drug** (NSAIDs) should be given.[24] Flunixin meglumine, phenylbutazone, and aspirin all have been shown to reduce the synthesis of the endotoxic mediators thromboxane A2, prostcyclin and PGE2.

Biblography

1. Stinson O. So-called post parturient dyspepsia of bovine and its treatment *Vet Rec* (1929) 9:1115-1119
2. Williams W. Diseases of the Stomach in T*he Principles and Practice of Veterinary Medicine* 5th ed. (1888) William R. Jenkins NY,NY.
3. Steel JH *Diseases of the Ox* (1890) John Wiley and Sons, NY,NY.
4. Sollman T. *A Manual of Pharmacology and its Application to Therapeutics and Toxicology* 6th ed. (1924) WB Saunders, Phila, PA
5. Alston JT Acetonemia or Ketosis *Veterinary Medicine* (1934) 29(9):379-383
6. Morrow DD Fat Cow Syndrome *J. Dairy Sci.* (1976) 59 (9): 1625-1629
7. Holtenius P., Hjort M. Studies on the pathogenesis of fatty livers in cows *15th World Buiatrics Congress* (1988) 214-220 Graficas GAMA, Leon Spain
8. Reid JT, Moe PW, Tyrrell HF Energy and Protein Requirements of Milk Production *J. Dairy Sci.* (1966) 49:215
9. Wagner DG, Loosli JK Studies on the energy requirement of high producing cow Memior 400 NY Agri Exp. Stn. (1967), Ithaca, NY.
10. Husveth F, Karsai F, Gaal T Changes in certain lipid components of the blood plasma and liver of dairy cows during the perinatal period *Magyar Allatorvosok Lipja* (1982) 37 (10): 689-696
11. Hidiroglou M, *Hartin KE Vitamin A,E and Selenium* Blood Levels in the Fat Cow Syndrome *Can Vet J.* (1982) 23(8):255-258
12. Hove K. Noctural plasma insulin levels in cows with varying levels of plasma ketone bodies: Relation to plasma sugar and acetoacetate *Acta Endocrinologica* (1974) 76:513-524
13. Herdt TH, Leisman JS, Gerloff BJ, Emery RS Reduction of serum triaclglycerolrich lipoprotein concentrations in cows with hepatic lipdosis *AJVR* (1983) 44(2):293-296
14. Aiello RJ, Kenna RM, Herbein JH Hepatic Gluconeogenic and Ketogenic Interrelationships in the Lactating Cow *J. Dairy Sci* (1984) 67(8): 1707-1715
15. Roberts CJ, Reid IM Fat Cow Syndrome and Subclinical Fatty Liver in *Current Veterinary Therapy: Food Animal Practice 2* (1986) JL Howard, ed WB Saunders, Phila, PA
16. Herdt TH, Goeders L, Leisman JS, Emery RS Test for estimation of bovine hepatic lipid content *JAVMA* (1983) 182:953
17. Garry FB Serum Bile Acids as a Test of Liver Function for Cattle with Hepatic Lipidosis *Proceeding of 7th Annual Veterinary Medicine Forum* ACVIM, San Diego CA (1989) Omnipress, Madison, WI
18. Baxter C, Kleiber M, Black *Biochima Biophys. Acta* (1955) 17: 354
19. Braum RK, Bergman EN, Albert TF Effects of Various Synthetic Glucocorticoids on Milk Production and Blood Glucose and Ketone Body Concentrations in Normal and Ketotic Cows *JAVMA* (1971) 157(7): 941-946
20. Reid IM, Rowlands GJ, Dew AM, Collins RA, et al The relationship between postpartrient fatty livers and blood composition in dairy cattle *J. Agri Sci. UK* (1983) 101(2):473-480
21. Cote JF Bovine Ketosis: Principles of Therapy *Can Vet. J.* (1971) 12(1):19-20
22. Brockman RP Effects of glucagon and insulin of lipolysis and ketogenesis in sheep *Can J Comp Med* (1976) 40(2):166-170
23. Fronk TJ, Schultz LH Oral Nicotinic Acid as a Treatment for Ketosis *J. Dairy Sci.* (1979) 62:1804-1807
24. Jarlov N., Anderson PH, Hesselholt M. Pathophysiology of experimental bovine endotoxicosis III: Prevention of endotoxin-induced synthesis of thromboxane A2, prostacyclin (PG12) and prostaglandin E2 by some non-steroidal antiinflammatory drugs *15th World Buiatrics Congress* (1988) p. 1422-1427 Graficas GAMA, Leon, Spain.

Additional readings

Smith J. Liver Function Parameters in High-Producing Postparturient Dairy Cows *Proceedings of the fifth annual Veterinary Medical Forum* (1987)405-408

Herdt TH and Emery RS Fatty Liver Disease in Dairy Cows *Proceedings of the fifth annual Veterinary Medical Forum* (1987) 421-429

Rings DM. Ketosis *Proceedings of the 10th Annual Food Animal Conference: The Use of Drugs in Food Animal* Medicine (1984) 175-182

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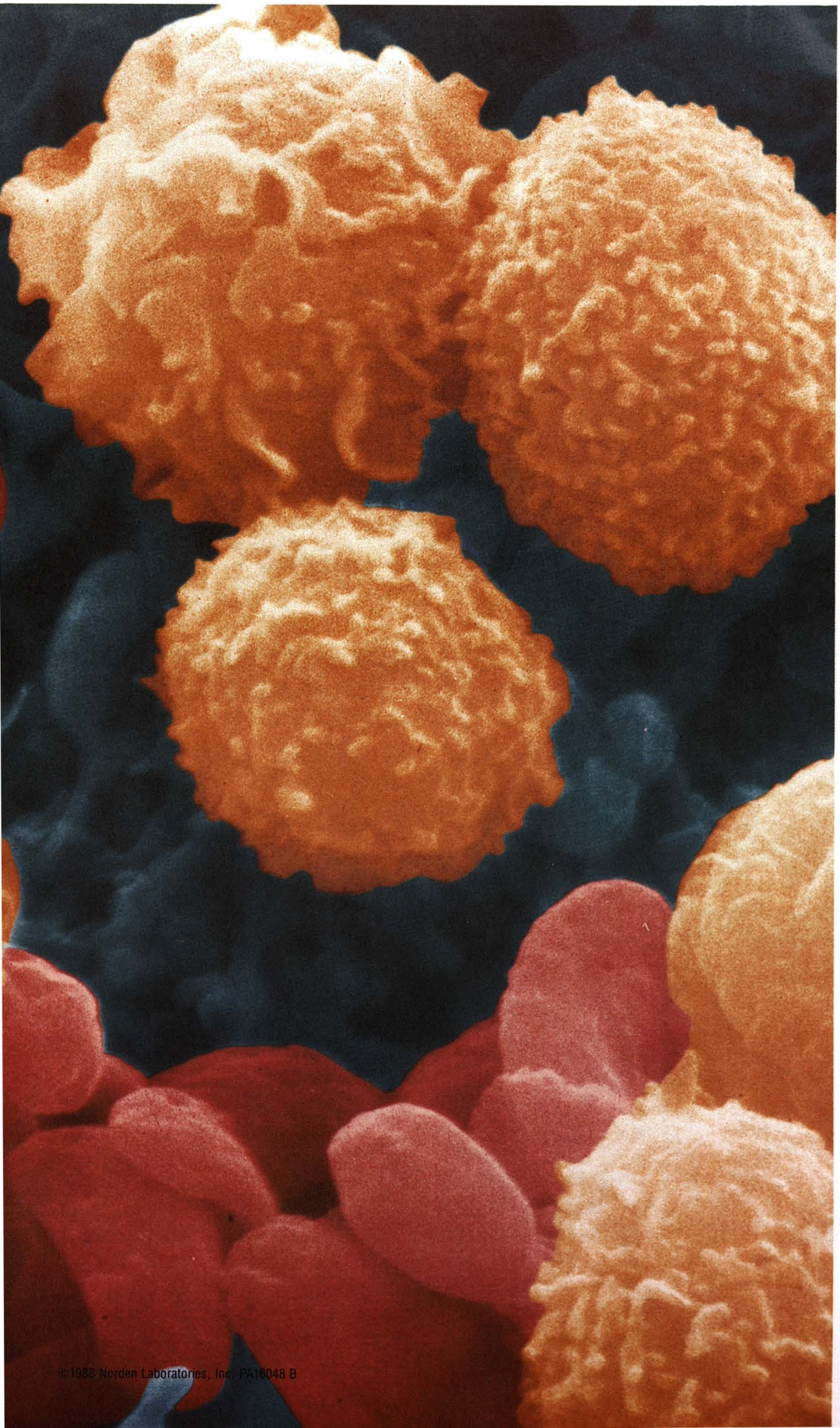

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