Chapter 3

An emerging Technology: bovine somatotropin

Contents

Figures

Tables

Chapter 3

An Emerging Technology: bovine Somatotropin

The U.S. dairy industry has a rich history of technological advances underpinningg steady and significant increases in the efficiency and economic returns of milk production. Progress in biotechnology and information technology will carry this trend into the 1990s. Through the application of biotechnology, farmers will be able to manipulate to an unprecedented degree herd reproduction, genetics, and the physiological variables that affect their animals' productive efficiency.

Genetically superior (more productive) animals are distinguished by their regulation of nutrients; new concepts of how this occurs have recently been established (6,10,1 1). Potentially one of the most significant of the new biotechnologies is bovine somatotropin (bST). Recent work has demonstrated that somatotropin exerts a key control over nutrient use. When administered exogenously, it markedly improves the productive efficiency (milk per unit of feed) in lactating cows. It does so by coordinating the metabolism of body tissues such that more nutrients are used for milk synthesis.

However, a number of questions involving human safety, animal safety, economic concerns, and ethics surround bST. Lay articles focusing on human and animal safety issues of bST imply that little research has been done. In fact, the scientific literature on bST contains at least 1,000 studies involving some 10,000 dairy cows.[1] This chapter provides an overview of bST technology and the concerns surrounding it. It assesses the validity of these concerns based on current scientific knowledge and on dairy industry trends.

STATE OF THE ART

Somatotropin, a hormone, was discovered about 50 years ago. Initial investigations showed that when rats were injected with a crude pituitary extract, growth rate was increased (only later did scientists discover that milk yield of lactating animals increased as well). This extract factor was called somatotropin from the Greek derivation meaning "tissue growth. " Based on this derivation, somatotropin is sometimes referred to as growth hormone or GH.

Somatotropin is produced by the anterior pituitary gland, a small gland located at the base of the brain. Like any hormone, it is transported in the bloodstream to the various body organs where it exerts its biological effects. In effect, it acts as a chemical link between different cells and organs of the body. The term "hormone" has taken on negative connotations in recent times, primarily due to steroid abuse by athletes. However, the chemistry of hormones is as diverse as their biological functions. For example, vitamin D (with which pasteurized milk is fortified) is a steroid hormone.

Somatotropin is also a protein, unlike steroids, which are nonprotein hormones. Like all proteins, it is composed of amino acids. (There are 20 different amino acids, which combine in specific sequences to form some 10,000 different proteins in the body. Amino acids are analogous to letters in an alphabet, which combine to form a diverse vocabulary of words.) The amino acid sequence of somatotropin is known for many species, including cattle (41,79). Bovine somatotropin can be either 190 or 191 amino acids long and either of two different amino acids (leucine or valine) occupy position number 126 in the sequence (80). Thus, four different variants of bST are produced naturally. Typically, the pituitary produces equal amounts of the 190 and 191 amino-acid bST. About two-thirds of the total bST produced has leucine at position 126, while the remaining one-third has the amino acid valine at position 126.

Artificially introduced somatotropin must be injected to be biologically active. If somatotropin is given orally, it is broken down by digestive track enzymes to amino acids for absorption. This is true for all dietary proteins and large protein hormones in all species. Just as human diabetics must take insulin injections (insulin, another protein hormone, is also inactive if taken orally), humans deficient in somatotropin must take injections of *human* somatotropin (hST). Studies have demonstrated that when fed to rats, bST was inactive even at a daily dose (units/

[1]Because of the large quantity of research on bST, this chapter will mainly cite review articles of these studies.

body weight) equivalent to 2.3 million times what a human would be exposed to in five 8-ounce glasses of milk (38,67).

Somatotropin is referred to as “species limited” in the scientific literature. This means that there are differences in the ability of somatotropin from one species to elicit biological effects when injected in other species. To have a biological effect, a protein hormone must first bind to a specific receptor located on the cell surface. The amino acid sequence of somatotropin gives it a unique three-dimensional shape, which determines whether the protein will be able to bind to tissue somatotropin receptors and elicit a biological response.

Some 25 years ago it was discovered that certain types of human dwarfism were due to an inadequate pituitary production of somatotropin. Because hST was scarce, physicians conducted an extensive series of studies in which patients were treated with injections of bST. These clinical studies uniformly demonstrated that bST does not elicit any of its normal biological actions in humans even if injected (20,38,41,79). Somatotropin isolated from the pituitary glands of sheep, pigs, and whales was also ineffective in humans, Biological activity in humans is only observed if somatotropin from primates is used.

The reason for bST’s lack of effect in humans became clear when its amino acid sequence was identified; the sequence of bST, which gives it its three-dimensional shape, differs by about 35 percent from that of hST (79). Thus, bST is not able to bind to the somatotropin receptors of human tissues (36,38). In contrast, ovine somatotropin and bST differ in only one amino acid position so bST is biologically active if given to sheep.

Recombinantly derived bST products differ slightly from the bST produced by the pituitary gland in that a few extra amino acids may become attached to the end of the bST molecule in the manufacturing process. The number of extra amino acids varies from 1 to 8 depending on the particular manufacturing process (38). For some manufacturing processes, no additional amino acids are produced. Some claim that for processes that produce extra amino acids, and the fact that recombinantly derived bST is produced by bacterial ribosomes, it renders the product hyperpotent to cows and dangerous to humans (23,46,64). However, the additional few amino acids on the end of the protein do not alter the biological activity of bST in dairy cows or the lack of activity of bST in humans because the three-dimensional shape of the active part of the molecule is not changed (36,79). This shape, moreover, is determined by the *sequence* of amino acids, not by whether or not bacterial ribosomes were used for the synthesis.

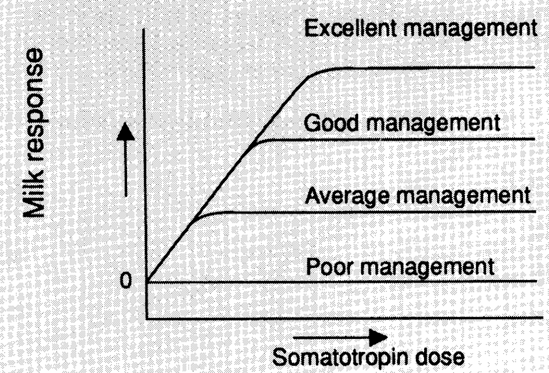
The first bST research with lactating cows was reported in 1937 by Russian scientists (l). With advances in protein chemistry, somatotropin preparations gradually improved in purity and several dozen studies have since been conducted with dairy cows. Particularly significant were a series of studies in the 1940s by scientists in the United Kingdom (81) and later studies by Brumby and Hancock (13) and Machlin (49).

Prior to the 1980s, bST research progress remained slow for two reasons. First, bST availability was limited to what could be extracted from the pituitary glands of slaughtered animals. Thus, only a small number of cows could be treated for short-term studies. Second, because bST was thought to act by acutely stimulating the use of body fat reserves, scientists believed it would work only in fat cows with a low milk yield. Thus, only low producing cows (generally less than 7 kilogram (kg) milk/day) were studied. It was assumed that bST would cause ketosis[2] and adverse health effects in high producing cows.

Scientists at the National Institute for Research in Dairying in England, and others at Cornell University, in the late 1970s began to work on bST. Both groups concluded that the physiological basis for genetically superior cows (i.e., those more efficient in milk production) was better use of absorbed nutrients (10,12). Based on new concepts of how animals regulate the use of nutrients (7), both groups hypothesized that somatotropin could play a key role in nutrient regulation and that the previously proposed mechanism of action (acutely stimulated use of body fat) was wrong. Over the last decade these concepts have been applied to research with somatotropin and the biology of nutrient use during growth, pregnancy, and lactation for many species.

[2]A metabolic disorder that occurs when production of ketones exceeds the ability of the body to use them. Occurs in dairy cows when the need for glucose exceeds the production of glucose.

Figure 3-1—Effect of Quality of Management on Milk Response of Dairy Cows Receiving bovine Somatotropin



SOURCE: D.E. Bauman, "Bovine Somatotropin: The Cornell Experience," Proceedings of the National Invitational Workshop on Bovine Somatotropin, pp. 46-56, USDA Extension Service, Washington, DC, 1987.

Initial investigations with cows used pituitary-derived bST. After landmark breakthroughs in biotechnology, in 1982, the Cornell scientists conducted the first study with dairy cows using recombinantly derived bST produced by Monsanto Co. and Genetech Co. (8). Since that time the quantity and scope of research with bST has increased exponentially.

PRODUCTION RESPONSE

Quality of management will be the major factor affecting the magnitude of lactation response to bST (4,16,17,57). This concept is illustrated qualitatively in figure 3-1. Across 45 field trial studies conducted in the United States, Europe, and Africa a correlation of 0.58 was observed between pretreatment group milk yield (an indication of management quality) and kg milk response to bST (57). A similar relationship between management quality and gains realized is observed for other technologies, such as artificial insemination (AI) with semen from superior sires.

Facets that contribute to the quality of the overall management program include the herd health program, milking practices, nutrition program, and environmental conditions. Inadequate management can result in a near zero response to bST supplement (51,52,57). McCutheon et al. (51) studied bST's effects as the quality of herd nutritional management varied over the course of the 26-week treatment period. Cows were fed only pasture, and milk responses to bST were greatest (+18 percent) in the spring when pasture supply was adequate, declined to zero during the summer drought, and were again significant during the fall. As this illustrates, bovine somatotropin is not magic. If cows are given an inadequate amount of feed or fed a diet that is not nutrient-balanced, the magnitude of the response to bST will decrease accordingly (see figure 3-l).

While the milk response to bST on an individual farm will vary according to quality of management, a reasonable expectation is that successful adopters would experience an average gain in productivity of 12 percent. This gain in productivity could lead to substantial savings in dairy cattle feed nationally. Assuming 100-percent adoption and milk production at 1988 levels (26), then decreased cow numbers (10.7 percent) and increased productive efficiency would translate into annual savings in dietary energy equivalent energetically to 2.5 x 10^9 kg of corn grain. Annual savings in dietary protein supplements would be equivalent to 5.6 x 10^7 kg of soybean meal (see table 3-l). These savings in feedstuffs represent

Table 3-1—impact of bST on Animal Numbers, Feed Requirements, and Waste Production of Dairy Cows To Achieve 1988 U.S. Milk Production[a]

Variable	Impact of bST[b]
Animals:	
Cow numbers	Decrease by 10.70/.
Milk yield per cow	Increase by 12.0?4.
Feed:[c]	
Energy equivalent as corn grain	Decrease by 2.5 x 10^9 kg
Protein supplement equivalent as 44% soybean oil meal	Decrease by 5.6 x 10^7 kg
Waste:	
Manure[d].	Decrease by 6 x 10^9 kg
Urine[e].	Decrease by 8 x 10^9 L
Urinary nitrogen[e].	Decrease by 8 x 10^7 kg
Methane[f].	Decrease by 8 x 10^{10} L

[a]U. S. 1988 milk production values were 10.24x 10^6 cows, 6,460 kg milk per cow, and 66 x 10^9 kg total milk production (26).

[b]Assumed 100-percent adoption and that use would increase average annual milk yield per cow by 12 percent. If commercially approved, expected impact would be less because technology rarely achieves 100-percent adoption.

[c]Based on nutrient requirements for dairy cows averaging 650 kg body weight and producing milk of 3.5-percent fat content (54).

[d]Based on an *average* diet composition of 1.62 Meal net energy/kg, a diet digestibility of 65 percent, and fecal dry matter of 16 percent (72).

[e]Based on a daily urine production of 20 L per cow with 1-percent nitrogen in urine (72).

[f]Assumed that methane production represents 5 percent of gross energy intake (72).

SOURCE: D.E. Bauman, "Bovine, Somatotropin: Review of an Emerging Animal Technology," commissioned background paper prepared for the Office of Technology Assessment, Washington, DC, 1990.

maximal estimates because commercial adoption of new technology is rarely 100 percent (see ch. 5).

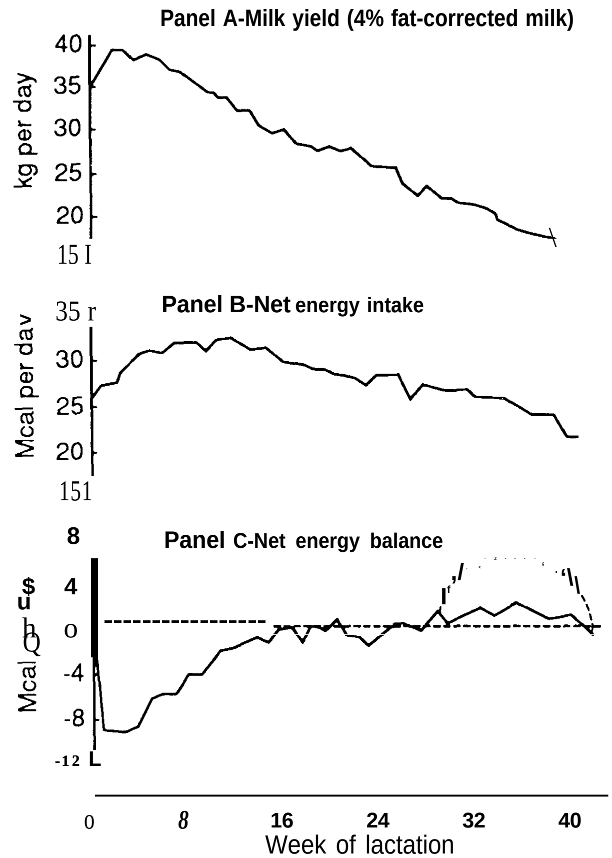
Milk yield gradually increases the first few days of bST treatment, peaking at about the sixth day (37,56). A maximum milk response is achieved at a bST dose (daily injection) of about 30 to 40 milligrams (mg) per day; no further increase occurs even at doses several-fold higher. Most production trials have used a bST dose between 10 to 50 mg per day. Exogenous bST must be introduced every day (by injection or via a prolonged-release formulation) in order to maintain an augmented milk response. This is because bST is cleared rapidly from the bloodstream and is not stored in the body. Removal is by protein breakdown to amino acids—a normal body function. Several prolonged-release formulations have been developed and are administered by subcutaneous injection at intervals ranging from 2 to 4 weeks (17).

Response to bST varies according to stage of lactation (see figure 3-2). In general, the milk response is small or negligible when bST is administered in early lactation (the interval immediately postpartum, prior to peak milk yield) (4). The biological basis for this low response relates to the nutrition/endocrine status of the animal during this interval. In contrast, substantial increases in milk yield occur when bST is administered after peak yield of milk is attained. Lactational responses to bST have been reported for all dairy breeds examined, including North American and European breeds as well as Murrah buffalo, and for animals of different parity (lactation number) and genetic potential (16,17,56).

Marked improvement in persistency of lactation occurs in cows receiving bST (16,17,56). The greater overall milk yield with bST supplementation occurs in part because of an immediate increase in milk yield, but mainly because of a reduction in the normal decline in milk yield that occurs as lactation progresses.

Cows treated with bST show a range of responses. In a few instances this has been cited as evidence of individual variation in response. However, this is misleading. All studies with bST have shown that the yield variations within bST-supplemented groups is similar to that of untreated groups (5,57). Thus, to a large extent, all cows in a herd respond to bST in a fairly similar manner. The bST-supple-

Figure 3-2—Temporal Pattern of Milk Yield, Net Energy Intake, and Net Energy Balance During a Lactation Cycle in Dairy Cows



Cows averaged 9,534 kg milk (21,000 lbs) over the first 305 days of lactation. Typically, daily milk yield peaks during the first month after parturition (birth of the calf) and then progressively decreases through the remainder of the lactation cycle (Panel A). The rate of this decline in daily milk yield is referred to as the persistency of lactation. Typically, voluntary feed intake increases gradually over the first few weeks of lactation and peaks about 6 to 10 weeks after parturition (Panel B). Dairy cows are generally in negative energy balance during the first portion of the lactation cycle (Panel C). During the first month of lactation for these cows, the body reserves being utilized (i.e., net energy deficit) were energetically equal to about one-third of the milk produced. Under normal management conditions the daily cow is overfed (positive energy balance) during the last third of lactation to allow for replenishment of body energy stores needed to support the next lactation cycle (dashed line, Panel C).

SOURCE: D.E. Bauman and W.B. Currie, "Partitioning of Nutrients During Pregnancy and Lactation: A Review of Mechanisms Involving Homeostasis and Homeorhesis," *J. Dairy Sci.* 63:1514-1529, 1900.

mented cow that ‘‘appears’ to be a low responder simply matches the low producing control cow.

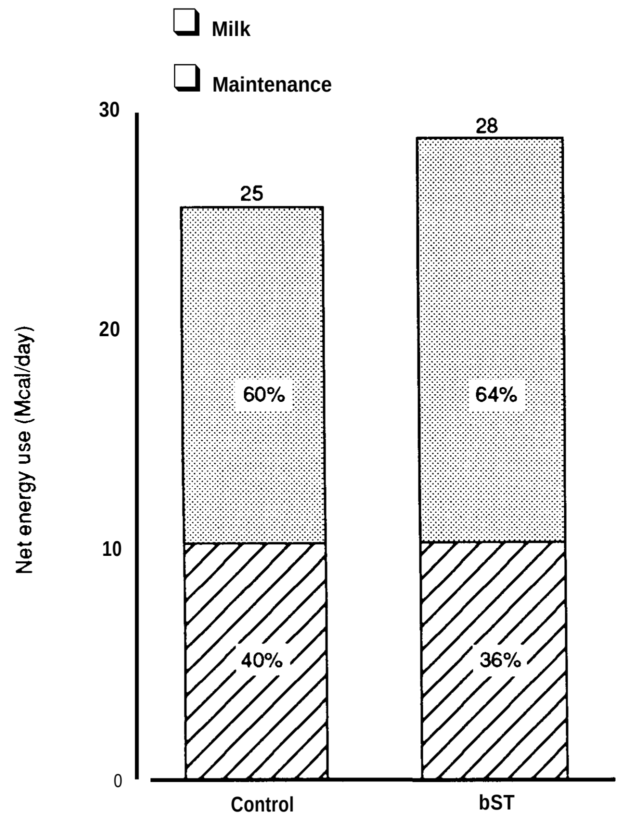
NUTRIENT REQUIREMENTS

Nutrient requirement tables are unchanged for bST-supplemented dairy cows(11, 16). The basis for this is two-fold. First, digestibilities of dry matter, carbon, nitrogen, and energy are not altered when lactating cows are receiving bST. Second, bioenergetic studies have demonstrated that bST does not alter energy expenditure for maintenance, or for the synthesis of a unit of milk. Nutritional needs for maintenance, milk production, pregnancy, and to replenish body reserves over a lactation cycle for a cow producing 10,000 kg milk per year are the same regardless of whether she received bST or not.

No special diets or unusual feed ingredients are needed to obtain a milk response to bST: substantial milk responses have been observed on diets ranging from pasture to forage concentrates.[3] Overall, however, the dairy cow receiving bST has a greater total nutrient requirement because she is producing more milk. She has a higher productive efficiency because a larger proportion of her total nutrient intake is used to make milk (see figure 3-3).

Voluntary intake of feed increases in bST-supplemented dairy cows, beginning after a few weeks of bST supplementation, and persisting throughout the interval of bST use. This has been consistently observed across a wide range of diets (16,17,56). Overall, cows supplemented with bST adjust their voluntary intake in a predictable manner related to the extra nutrients required for the increased production of milk. The magnitude of increase in feed intake is dependent on the response in milk yield and the energy density of the diet (17). It is expected with current feed costs that use of bST for dairy cows will, on average, lead to a predictable increase in the energy density of the diets used (increased ratio of concentrate to forage). This is because income over feed cost increases with level of milk production even though the cost for higher energy ingredients is greater. However, as noted, bST increases milk yield even when pasture is the only dietary ingredient.

Figure 3-3-Efficiency Gains by Reduction in the Proportion of Nutrients Used for Maintenance[a]



[a]For this example, the hypothetical control cow Produced 6,818 kg (15,000 lb) of milk in a lactation and use of bST increased milk yield by 20 percent

SOURCE: D.E. Bauman, "Biology of Bovine Somatotropin in Dairy Cattle," *Advanced Technologies Facing the Dairy Industry: bST*, Cornell Cooperative Extension Animal Science Mimeograph Series #133 (Ithaca, NY: Cornell University, 1989), pp. 1-8.

BOVINE REPRODUCTIVE PERFORMANCE

Of special interest are the effects of bST on reproductive variables such as conception rate (services per conception), pregnancy rate (proportion of cows becoming pregnant), and days open (days from parturition to conception). Normally, variation in reproduction variables is large. Effects of bST supplementation are small enough that large data sets are needed to allow definitive conclusions. Several reviews have summarized many of the studies on reproduction variables (28,55,59). In general, these summaries indicate that bST supple-

[3]Use of somatotropin for growing animals will require modification of the maintenance and growth components of the nutrient requirement tables because of the shift in the type of growth (increased protein, decreased lipid).

mentation results in a decrease in pregnancy rate but that conception rate is not altered. For example, Ferguson and Skidmore (28) found that pregnancy rate (n >3,000 cows) was 89.2 percent for controls and 81.2 percent for bST-supplemented cows (bST dose ranged from 5 to >200 mg per day). Days open increased a few days in bST-supplemented cows according to most studies.

The studies that identified changes in pregnancy rate and days open for bST-supplemented cows followed management practices geared to achieve a 12- to 13-month calving interval. Thus, period of breeding (commencing 50 to 60 days postpartum) would generally have coincided with the early period of bST supplementation when milk yield had increased but before voluntary feed intake had increased. It is well established that decreased pregnancy rate and increased days open are associated with increases in milk yield (15). This is because of the inverse relationship between level of milk production and energy balance that typifies the early stage of lactation. Ferguson and Skidmore (28), for example, found the decrease in pregnancy rate to be related to the increase in milk yield rather than the dose of bST when they analyzed their multistudy data by controlling for confounding factors. Hard et al. (35) summarized a series of studies that had a similar design and found that days open increased by 5 days in the bST-supplemented group; however, when data were stratified by level of milk production, days open did not differ between controls and bST-supplemented cows (35). Thus, effects of high milk yield on reproductive performance are the same whether or not the high yield was due to the use of bST

Calving interval for optimum economic return for U.S. dairy farms will probably increase with bST supplementation. Although conventional wisdom has been that a 12- to 13-month calving interval maximizes profit, many managers of high producing dairy herds indicate that their calving interval is longer (6). In the case of bST supplementation, not only does milk yield increase, but persistency of lactation is also improved. Thus, it is logical that the calving interval for optimum economic return may be substantially increased when bST is used. Ferry (29) modeled the effects of a 12- and 14-month calving interval on a herd basis and concluded that with bST use, income over feed cost was considerably increased with a 14-month calving interval. More extensive modeling, which included factors such as veterinary costs and replacement values, yielded a similar conclusion (70).

Extending the calving interval also has some benefits from the standpoint of the physiology of the cow. In the case of reproduction, increasing the calving interval improves conception rate (71), probably as a consequence of the nutritional status of the cows as discussed earlier. In addition, the majority of health problems and veterinary costs for dairy cows occur during the first 45 days postpartum (24). Thus, increasing the calving interval reduces health problems and costs on an annual basis for a herd and over an individual animal's lifetime.

Optimum calving interval with bST use probably will be different in the United States than in other countries, particularly countries that have a seasonal supply of feedstuffs and a beef industry largely based on the offspring of dairy cows. Thus, the actual calving interval that optimizes economic return will vary according to a number of management and economic factors; still, a major determinant will be the magnitude of milk response and the increased lactation persistency that occurs with bST use.

Genetic evaluation of sires might be affected by use of bST if an interaction between genotype and the milk response to bST occurs, or if bST is inappropriately used to manipulate sire proofs. Several studies have concluded that no evidence exists of a genotype-response interaction in bST-supplemented cows (32). Sire evaluations involve the comparison of the performance of a bull's daughters with the performance of their contemporary herdmates. A bias in sire evaluations can occur (and has) if a farmer gives preferential treatment to the daughters of a particular sire that he hopes to market commercially (25). Potential for bias from the use of bST is similar and can be handled by properly coded records and/or use of AI-proven sires (25,32), With proper coding of records, bST-treated daughters could be compared only with herdmates that had also received bST supplement. Similarly, when the sire is evaluated with AI records, many more daughters in a large number of herds will be involved; thus the chance for bias is negligible.

MILK AND MEAT COMPOSITION

Gross composition of milk (fat, protein, and lactose content) and meat has been examined inmost bST production trials, and is not substantially altered

by bST supplementation (3,16,50,56,75). There can be minor changes, primarily in fat content of milk, during the first few weeks of bST supplementation as the cow's metabolism and voluntary feed intake adjust. However, these changes are temporary and minor when compared with variations that normally occur over a lactation cycle. Whereas the lactose content of milk is relatively constant, the content of fat, and to a lesser extent protein, normally varies widely due to many factors including genetics, breed, stage of lactation, age, diet composition, nutritional status, environment, and season (48). These factors affect the fat and protein content of milk in the same manner in bST-supplemented and nontreated cows (3,16,56). The meat derived from treated cows has a lower fat content but is otherwise identical (53).

The temporary shift in milk fat that can occur during the first few weeks of bST supplementation relates to nutritional status (11,16,56). Cows in negative energy balance produce milk with a higher fat content due to a greater reliance on lipids mobilized from body fat stores. Milk fat content is most likely to increase when bST supplementation is initiated in the first 100 days postpartum, when cows are typically in a lower energy balance. However, the negative energy balance typical of this period (and especially of the first 8 weeks of lactation) is far in excess of that associated with bST supplementation.

The lipid composition affects the milk's nutritive value, flavor characteristics, and manufacturing properties. Studies demonstrate that fatty acid composition and cholesterol content of milk are not altered by bST (3). Cows that are in negative energy balance (as occurs early in lactation) shift milk fat composition toward longer chain, unsaturated fatty acids whether or not they receive bST supplementation. In addition, the same fatty acid composition changes are observed in untreated and bST-supplemented cows as lactation progresses.

Composition of milk proteins has been examined in at least a dozen studies because of the impact on functional properties of milk used in the manufacturing of dairy products (3,75). These studies have demonstrated that the content and composition of casein (et-casein, ß-casein, k-casein) are not altered by bST supplementation; and that casein as a percent of true protein is either unchanged with use of bST or shows a small numerical decrease (often nonsignificant). One short-term study reports a small increase in ct-lactalbumin content of milk in bST-supplemented cows but this was not observed in long-term studies. The nonprotein nitrogen (NPN) content of milk from bST-supplemented cows should vary with nutritional status just as it does in untreated cows. Some countries routinely test NPN levels in bulk milk as a management tool for farmers to evaluate the protein adequacy of their nutritional program (61).

Mineral content of milk from bST-supplemented cows has been examined in short- and long-term studies involving large numbers of animals (3,75). Results have uniformly demonstrated that bST does not alter ash (total mineral content) or any nutritionally important mineral. Only one published report exists on the vitamin content of milk, but milk from bST-supplemented cows did not differ in content of any vitamin (vitamin A, thiamine, riboflavin, pyridoxine, vitamin B^{12}, pantothenic acid, and choline) except for biotin, which showed a slight increase (75). The increase in biotin content of milk is too small to be considered a benefit; biotin, a member of the b-vitamin family, is widely distributed in plant and animal food products and is also synthesized in the intestine of humans.

Manufacturing characteristics of milk have been investigated in a smaller number of studies but results have consistently demonstrated that milk from bST-supplemented cows does not differ from milk of untreated cows (3,75). Characteristics studied include freezing point, pH, alcohol stability, thermal properties, proteases, lipases, susceptibility to oxidation, and sensory characteristics, including flavor. Similarly, no differences were observed in cheese-making properties, including starter culture growth, coagulation, acidification, and syneresis, or in the yield, composition, or sensory properties of the various cheeses.

Minor constituents of milk include hormones such as estrogen, progesterone, glucocorticoids, thyroid hormones, prolactin, and growth factors. Trace concentrations of bST also normally occur in milk and meat but this concentration is not appreciably altered when cows receive exogenous bST (38,53,65,75). The level of bST in milk is only a small fraction of the blood concentration. Only when blood levels are increased about 30-fold by a substantial dose of bST is there a small, but significant, increase in milk concentrations of bST

(65). This lack of an appreciable change in milk concentration of bST when exogenous bST is administered is expected, given that mammary epithelial cells do not have receptors for somatotropin (19). Pasteurization of milk destroys 85 to 90 percent of immunoreactive bST (33).

Some part of the biological actions of somatotropin may be mediated by insulin-like growth factor I (IGF-I). IGF-I, a protein hormone and member of the somatomedin family, normally occurs in trace levels in milk. The concentration of IGF-I is higher in cows' milk (3 to 10 parts per billion) than in human milk (1 to 3 parts per billion). Administration of bST to dairy cows results in an increase in the amount of IGF-I in milk (by 2 to 5 parts per billion), but the levels are still within the range typically observed in early lactation of untreated cows (31,38,65,75). There is approximately twice as much IGF-I in meat of treated cows (2).

Studies with laboratory animal models have demonstrated that IGF-I, like bST, has no biological activity if administered orally (38). It is digested into its amino acid, di- and tripeptide constituents by gut enzymes. Similarly, no evidence exists that fragments of IGF-I are biologically active in humans, nor is there evidence of systemic biological effects in humans from any IGF-I absorbed intact. The amounts of IGF-I that might potentially be ingested in food products from treated cows are orders of magnitude less than those required to produce such effects (53).

The amount of IGF-I ingested in one liter of milk from bST treated cows approximates the amount of IGF-I in human saliva swallowed daily by adults (31). Young children and infants already ingest IGF-I in regular cows' milk. The importance of the additional amount of IGF-I in milk from bST-treated cows—whether it has a local effect on the esophagus, stomach, or intestine of infants-is unknown (53). However, most infants are either breast fed or fed commercially prepared infant formulas; the heat treatment used in the manufacture of these formulas inactivates approximately 90 percent of IGF-I.

MECHANISMS OF ACTION

Somatotropin regulates the use of absorbed nutrients. When milk production is increased, extra nutrients are needed by the mammary glands to provide the raw materials and energy to make milk. Somatotropin coordinates the metabolism of various body organs and tissues in a manner that supports the increased nutrient use by the mammary glands. These coordinated adjustments in tissue metabolism involve all nutrient classes--carbohydrates, lipids, proteins, and minerals (see table 3-2), and are due to the direct action of somatotropin on tissues (e.g., liver and adipose). The adjustments made are characteristic of metabolic changes needed to support lactation in all mammals (11,56,77).

Glucose metabolism illustrates the coordinated manner in which bST alters tissue processes. Glucose is a carbohydrate used as an energy source by many tissues and as a raw material for milk synthesis (primarily for production of milk sugar). Nearly all of a cow's daily glucose requirement is made by the liver and the mammary glands typically use about 85 percent of the total. With bST-supplementation, the uptake of glucose by the mammary glands increases in a manner parallel to the increases in milk production. This increased use of glucose for milk synthesis is accommodated by whole-body adjustments which include increase glucose production by the liver and reduced glucose use for energy by other body tissues. In part, these adjustments occur because bST alters the response of tissues to acute signals (e.g., insulin), thereby allowing a greater allocation of glucose for milk synthesis while still maintaining normal body functions. Without such adjustments in metabolism, initiation of bST supplementation would cause the glucose use to exceed that which is available, resulting in ketosis and death. Ketosis from bST supplementation has not been observed in the hundreds of studies performed, even in tests where bST resulted in increased milk production of 40 percent or more.

Lipid metabolism provides another example of the coordination which occurs with bST supplementation. The adjustments in tissue lipid metabolism depend on the nutritional status of the cow at the time bST-supplementation is initiated. Normally, if a cow's nutrient intake is greater than her requirements, the excess nutrients are used to make body fat. BST administration causes adipose tissue to reduce its use of nutrients to synthesize body fat and allows for reallocation of these nutrients to support increased milk production. A different metabolic adjustment occurs if the cow's nutrient intake is equal to or less than her requirements. In this instance, somatotropin directs adipose tissue to mobilize deposits of body fat so that these energy reserves can be used to support increased milk

Table 3-2—Effect of bST on Specific Tissues and Physiological Processes in Lactating Cows[a]

Tissue		Process affected during first few days and weeks of supplement
Mammary	T'	secretory activity and maintenance of mammary glands
	'r	blood flow and nutrient uptake
	T	synthesis of milk with normal composition
Liver	T	production of glucose
	o	response to acute signals (e.g., insulin) that allow for greater glucose production
Adipose	~	mobilization of fat stores to meet needs for increased milk production if nutrient intake is inadequate
	J'	use of nutrients for fat storage so that they can be used for increased milk production if nutrient intake is adequate
	o	response to acute signals (e.g., insulin and other hormones that affect lipid metabolism) that allows for synthesis and breakdown of body fat reserves to be coordinated with changes in use and availability y of nutrients
Muscle	~	uptake of glucose
Pancreas	o	insulin and glucagon secretion reponse to changing glucose levels
Kidney[b]	~	production of 1,25 vitamin D_3
Intestine[b]	T	absorption of Ca, P and other minerals required for milk
	'r	ability of 1,25 vitamin D_3 to stimulate calcium binding protein
	T	calcium binding protein
Whole body	·J	use of glucose by some organs so more can be used for milk synthesis
	T	use of fat stores for energy if nutrient supply is inadequate
	·J	use of nutrients to make body fat if nutrient supply is adequate
	o	insulin and glucagon clearance rates
	o	energy expenditure for maintenance
	'T	energy expenditure consistent with increase in milk yield (i.e., heat per unit of milk not changed)
	'r	cardiac output consistent with increases in milk yield
	T	productive efficiency (milk per unit of energy intake)

[a]Changes (↑=increased, ↓=decreased, ø=no change, o=change) that occur in initial period of bST supplement when metabolic adjustments occur to match the increased use of nutrients for milk. With longer term treatment, voluntary intake increases to match nutrient requirements.
[b]Demonstrated in nonlactating animals and consistent with observed performance in lactating cows.

SOURCE: D.E. Bauman, "Bovine Somatotropin: Review of an Emerging Animal Technology," commissioned background paper for the Office of Technology Assessment, Washington, DC, 1990.

production. In both situations, these adjustments involve alterations in adipose tissue response to acute signals (e.g., insulin and other hormones that affect lipid metabolism) thereby allowing the use of body fat reserves to be coordinated with changes in the animal's need for, and availability of nutrients. Over time, bST teated cows gradually increase their feed intake so that stores of body fat are replenished during a lactation cycle. This replenishment occurs under a wide range of dietary conditions (11,16,17). If these adjustments in lipid metabolism did not occur, cows would become emaciated, decrease their milk production, and be less efficient in their use of feed for milk production. These effects have not been observed; cows administered bST have demonstrated increased milk production and improved feed efficiency.

In addition to the direct metabolic effects that bST coordinates, somatotropin indirectly affects the mammary gland via its impact on other controlling compounds (e.g., somatomedins such as IGF-1). Effects include increased cellular rates of milk synthesis and improved maintenance of secretory cells (i.e., slower rate of cell loss). The net result is that bST-supplemented cows have higher daily milk yields and produce higher levels of milk throughout the lactation cycle. Over the years, selection of higher producing dairy cows has resulted in the same improvements. Thus, it is not surprising that cows that produce high levels of milk have higher circulating levels of naturally produced somatotropin than do cows that produce low levels of milk (6).

BOVINE HEALTH AND STRESS

Catastrophic health effects have been postulated to occur with bST supplementation of dairy cows. Ketosis, fatty liver, and chronic wasting have all been proposed as possible side-effects of bST use (12,43). Crippling lameness, milk fever (a feverish disorder following parturition), mastitis (inflammation of the udder), infertility, heat intolerance, sickness, suffering and death are recent additions to the list of adverse health claims (23,30,45,62,63,64). These postulated catastrophic effects were not based on actual data but rather on the presumption that bST caused the mobilization of lipids from body fat reserves and/or overtly caused stress.

Metabolic disorders, if they occurred, would most likely manifest themselves during the first few days of bST use. None of the above catastrophic health effects have been observed in any of the short-term or long-term studies with dairy cows going back to the frost bST study in 1937. They were not observed in chronic toxicity studies (22,55), or in acute toxicity studies where dairy cows were given 30,000 mg of bST over a 2-week period, an amount approximately equal to what would be administered in four lactations (about 40 months) (78). Nor were adverse effects observed in studies where inadequacies in the overall quality of the management program resulted in negligible milk responses to bST supplementation. An increase in ketones (an indicator of subclinical ketosis) was reported in one earlier study involving two cows given bST for 9 or 10 days (42). However, that pituitary-derived preparation was contaminated with other hormones (42,44), and this work has not been verified in acute or chronic studies using larger numbers of cows treated for longer periods with a wider dose range of purified bST (1 1,16,59,78).

It also has been postulated that somatotropin will reduce resistance to infectious and contagious diseases and thereby increase sickness and suffering in dairy cows (23,30,63,64). Incidence of disease is generally very low in dairy cows and a thorough evaluation of these claims will require extensive summarization across studies to obtain a large data set. However, none of the hundreds of bST studies reported lower milk yield or decreased productive efficiency, both of which are associated with any increase in sickness and suffering. On the contrary, somatotropin plays a key role in several aspects of maintaining immune competence (39). Immunity and disease resistance are compromised in somatotropin-deficient laboratory animals and humans and somatotropin supplementation enhances immune competence in both groups. Such studies have not yet been extended to lactating cows, but it has been demonstrated that bST supplementation had a beneficial effect on cows' recovery from experimentally induced E. *coli* mastitis (14).

Stress is more difficult to evaluate, but several indices exist that demonstrate no stress effects due to bST. Dairy cows that are stressed produce less milk less efficiently and expend more energy as heat than expected. All of the several hundred studies of bST in the scientific literature report increased milk yield and productive efficiency. The duration of bST use in these studies has ranged from a few weeks to at least four successive lactations. While numerous physiological variables have been monitored to assess stress and have been shown not to change, nothing illustrates the normalcy of bST-supplemented cows as effectively as the persistent gains in milk yield and productive efficiency throughout the treatment period. Recent studies spanning positive-to-negative energy and nitrogen balances, moreover, have clearly demonstrated that bST has no effect on the energy expended for maintenance or for the synthesis of a unit of milk (40,68,73).

Subtle health effects require examination of ''large numbers of animals treated under a range of environmental and management conditions" (21). A complete summary of individual studies done throughout the world is beyond the scope of this review. Many have appeared as abstracts in the last 2 years and have not yet been published as full-length papers. However, these summarizations are required of companies seeking the Food and Drug Administration (FDA) approval and are used by regulatory agencies in their evaluation. Phipps (59) summarized a substantial portion of the studies conducted through 1988. This review showed that the indices of animal health for bST-supplemented animals were similar to these for controls and were consistent with values reported in the literature for untreated cows at a similar level of milk production. Variables examined included physical examinations, bone radiography, blood chemistry, metabolic disorders, subclinical ketosis, udder health, and welfare of the treated cows as well as the health, growth, and performance of their offspring.

Subtle effects on the incidence and duration of mastitis are of special interest. Major factors affecting the incidence of mastitis include milking management and herd health programs. However, the incidence of mastitis and milk somatic cell counts are also positively correlated with milk yield (58,60,69). Effects are quite small and amount to an annual increase of approximately 0.4 cases/cow for each 1,000 kg genetic gain in milk yield. Thus, it will take very large numbers of cows to detect and evaluate whether subtle effects, independent of milk-yield response, occur with the use of bST. Phipps (59) summarized the incidence of clinical mastitis across studies totaling over 1,300 cows and found that the relative incidence of mastitis was not affected by bST supplementation. Ferguson (27) likewise summarized eight studies reporting mastitis and found that there was no indication that bST was associated with increased mastitis infections.

Concern has been raised that even the small increased incidence of mastitis from higher producing animals will increase the use of antibiotics in cows. However, Burvenich et al. (14), reported that recovery time from experimentally induced mastitis is reduced in cows receiving bST supplement; it will be of interest to learn whether the same beneficial effects of bST supplement are observed for naturally occurring cases of mastitis under field conditions.

ONFARM ENVIRONMENTAL POLLUTION

Environmental pollution is reduced with bST use as a result of the gain it yields in productive efficiency. Substantially less feed is required to produce the same quantity of milk. This correspondingly reduces the use of fertilizer and other inputs associated with producing, harvesting, processing, and storing of dairy feedstuffs.

Total U.S. animal fecal waste could also be reduced by as much as 6×10^9 kg assuming 100 percent adoption and production of milk at 1988 levels (see table 3-l). Similarly, the productive efficiency gains with use of bST supplement could result in an annual reduction of 8×10^9 liters urine and 8×10^7 kg of urinary nitrogen for the total U.S. dairy herd (see table 3-l).

Ruminants also produce methane, a gas having a strong greenhouse effect. Ruminants and animal waste account for about one-fifth of total worldwide methane emissions (18), with cattle accounting for about three-fourths of the livestock methane emissions or about 15 percent of total global methane emissions (47). Because of the gain in productive efficiency when bST is used, methane production by dairy cows could be reduced by as much as 5.5 percent per unit of milk produced. For milk production at 1988 levels, this amounts to an annual reduction of 8×10^{10} liters of methane in the United States (see table 3-l).

It has been suggested that even though total environmental pollution may be reduced, the more relevant concern is whether animal wastes (manure and urine) are dispersed widely or concentrated (34). On large feed-lot farms, located primarily in the West and South, most feed is not grown on site and animal wastes are collected and stored. Such operations may represent point-sources of surface and groundwater contamination. On diversified farms located in the Upper Midwest and Northeast most feed is grown on site; animals have access to pasture, and wastes are left in pasture fields and/or recycled onto the fields. Some argue that diversified farms are less polluting than confined operations because wastes are spread over a more extensive area. A concern exists that bST will provide the economic incentive to create more confined operations and thereby increase pollution of ground and surface water.

These concerns are questionable. Diversified pasture operations are potential nonpoint sources of pollution in ground and surface water. If not properly managed, they could be significant sources of pollution. By the same token, handling practices and environmental regulations can minimize the threat of pollution from confined operations. Effective in-use handling practices include: 1) flush, lagoon irrigation systems; and 2) mechanical scrapers, storage pit, and tank wagon transport systems. In some areas, there is also a market for wastes for use as fertilizer, feed stuff, or fuel. In addition, the U.S. Environmental Protection Agency has provided regulations for confined livestock and poultry operations for surface-water protection and several States and local entities have stringent groundwater protection requirements for these operations (74). It is expected that these requirements will become quite common throughout the United States and eventually be applicable to most farming operations. Many small, diversified dairy operations will be at an economic disadvantage compared to larger operations in meeting these environmental requirements (66).

INSTITUTIONAL INVOLVEMENT IN bST RESEARCH

Research in the technology of bovine somatotropin has involved scientists and financial support from Federal agencies (NSF, NIH, USDA), State agricultural experiment stations, and private industry worldwide. This extensive collaboration has been of tremendous value in developing an understanding of the biology of somatotropin and of lactation. The number of publications on somatotropin to date is probably unprecedented for an animal technology not yet approved for commercial use. The bST literature is substantially larger than that for many dairy technologies in current use.

Some claim that extensive cooperation has totally compromised the quality and value of the research with bST. Kronfeld (44,45,46) has claimed that academic and government scientists are ‘ ‘indentured’ and ‘‘biased’ because of this association. Rifkin (63,64) and Epstein (23) have quoted Kronfeld and echoed these claims, repeatedly suggesting that the reporting of data has involved exclusion of sick cows and the suppression and deletion of adverse or negative results observed with bST supplementation of lactating cows. While these individuals offer no specific documentation of scientific fraud, such claims are not to be taken lightly. Current events demonstrate that research fraud is possible. However, a distinguishing feature of science is that research results are examined and repeated by others. This mechanism helps to identify inaccurate research. Published studies on bST have involved at least 10,000 dairy cows and results have been verified not only by numerous groups of U.S. scientists but by many other scientists throughout the world. The claims of Kronfeld, Rifkin, and Epstein imply a worldwide conspiracy involving at least 1,000 animal scientists in academia, government, and industry and hundreds of dairy farmers involved in the bST experiments. The possibility of such a conspiracy seems remote.

TIMING OF' COMMERCIAL INTRODUCTION

Commercial use of bST requires approval by FDA and until this occurs, bST cannot be sold legally. Currently, bST is under review by the FDA and Federal law prohibits the agency from disclosing proprietary information on a drug under review. However, companies interested in bST have been relatively open about the fact that they are seeking approval and have published a considerable quantity of their own proprietary research. In addition, FDA has published an article using the companies' data to demonstrate the safety of bST for human consumption (38). This extensive disclosure of information on a drug under review is rare.

Each company wishing to market bST must prove that its product is effective (does what the company claims) and safe in order to secure FDA approval (67). The safety evaluation involves three areas: safety of the animal food products for humans; safety of the bST supplement to the target animals; and safety of using bST to the environment. In addition, each company must prove to the FDA that their manufacturing process can produce bST to consistent and acceptable quality standards.

In 1984, the FDA had sufficient scientific information from extensive published literature and then-unpublished studies (38,67) to make the determination that the milk and meat from bST-supplemented cows were safe for human consumption. Specific conclusions were:

1. bST is a protein that is digested enzymatically like any food protein when consumed orally.
2. bST has no biological activity in humans even if injected.
3. A trace level of bST naturally occurs in milk and meat but this level is not appreciably altered in cows receiving bST supplement.
4. The overall composition of milk is not altered due to bST treatment. The minor changes that can occur in the first few weeks of treatment due to shifts in nutrient balance are temporary and well within the normal variation encountered over the course of a lactation.

Thus, animal products were allowed to be marketed for the remainder of the investigational period.

In all other countries where bST is under review, the appropriate regulatory agencies have also completed the human safety evaluations and without exception, allow the milk to be used for human consumption. By 1990, a few countries completed all facets of their review and registered bST for commercial use by one or more companies (Soviet Union, Czechoslovakia, Bulgaria, Mexico, Brazil, and South Africa). In March 1991, the Committee for Veterinary Medicinal Products of the Commission of the European Communities released a favorable opinion on the application by one company for the marketing of bST.

PRODUCT LABELING

Some States are seriously considering mandatory labeling of all food products derived from milk of cows supplemented with bST. The basis for labeling seems to be a concern about the safety of the products for human consumption. At least two considerations need to be addressed.

First is the scientific merit or basis for labeling. If there is a valid safety concern then the food should not be marketed for human consumption. Labeling is not the appropriate method for handling a valid concern for consumer safety. If the regulatory system to evaluate food safety is inadequate, then the system should be changed. Labeling does not excuse the inadequacy. As just discussed, food safety concerns have been addressed and the conclusion reached is that food produced from bST-treated cows is safe for human consumption (38).

The second consideration is verification. An effective labeling program requires development and adoption of appropriate regulations and the establishment and funding of a system for implementation and verification. In the case of bST, there is no known test or technology that could be used to distinguish milk from bST-supplemented cows (38, 67). Indeed, no change in milk composition as a result of bST supplementation was found in human safety evaluations by FDA or analogous agencies in other countries.

CONCLUSIONS

OTA concludes that recombinant bovine somatotropin has no known adverse health effects on the cows receiving bST supplements or on humans drinking milk or consuming milk products from these cows. Recombinant bovine somatotropin is the first major biotechnology developed for agriculture. It will have potentially significant impacts on the dairy industry, based mainly on the fact that it can produce an average gain in milk per cow of 12 percent per year. However, this technology is not magic. It is distinguished only by the unprecedented magnitude of the productivity gains it yields. For example, the gain in productive efficiency obtained with bST supplementation would take 10 to 20 years to achieve using a combination of artificial insemination (using superior sires) and embryo transfer techniques (see table 3-3). Only the eradication of mastitis could increase milk yield per cow and productive efficiency as much as or more than the use of bST (6).

Table 3-3—Comparison of Theoretical Gains in Milk Yield Per Cow for Different Dairy Technologies

Technology	Theoretical annual gain in milk per Cow[a]
Artificial insemination (AI)	100 kg[b]
AI plus sexed semen	115 kg[b]
AI plus embryo transfer	135 kg[b]
Bovine somatotropin	>1,000 ka[c]

[a]Actual observed gain would average less because of variation in quality of management and other factors. For example, observed gain from using artificial insemination and superior sires is approximately 50 percent of the theoretical gain.

[b]From Van Vleck (76). Gain would be cumulative for successive generations so long as variation exists in the population.

[c]From Bauman et al. (9)

SOURCES: L.D. Van Vleck, "Potential Genetic Impact of Artificial Insemination, Sex Selection, Embryo Transfer, Cloning and Selfing in Dairy Cattle," *in: New Technologies in Animal Breeding,* B.G. Brackett, G.E. Seidel, Jr., and S.M. Seidel (eds.) (New York, NY: Academic Press, Inc., 1981), pp. 221-241; D.E. Bauman, P.J. Eppard, M.J. DeGeeter, and G.M. Lanza, "Response of High Producing Cows to Long-Term Treatment With Pituitary-and Recombinant—Somatotropin," *J. Dairy Science,* 68:1352-1362, *1985.*

For bST to be effective, dairy farmers must be expert managers. Poorly managed farms, where animals are stressed, underfed, and/or sick, will have negligible milk response to bST. In this respect, the bST-supplemented cow presents the same challenges as any high producing cow—the ultimate gains to be captured depend not on the technology per se, but on the management skills of its adopters.

CHAPTER 3 REFERENCES

1. Asimov, G.J. and Krouze, N. K., "The Lactogenic Preparations From the Anterior Pituitary and the Increase of Milk Yield in Cows," *J. Dairy Sci.* 20:289-306, *1937.*
2. Baile, C., "Quality of Meat from bST-Treated cows,' ' NIH Technology Assessment Conference Abstracts (Bethesda, MD: National Institutes of Health, 1990), pp. 51-63.
3. Barbano, D.M. and Lynch, J. M., "Milk From bST-Treated Cows: Composition and Manufacturing Properties, ' *Advanced Technologies Facing the Dairy Industry: bST*, Cornell Cooperative Extension Animal Science Mimeograph Series #133 (Ithaca, NY: Cornell University, 1989), pp. 9-18.
4. Bauman, D. E., "Bovine Somatotropin: The Cornell Experience,' Proceedings of the National Invitational Workshop on Bovine Somatotropin, USDA Extension Service, Washington, DC, 1987, pp. 46-56.
5. Bauman, D. E., "Biology of Bovine Somatotropin in Dairy Cattle," *Advanced Technologies Facing the Dairy Industry: bST*, Cornell Cooperative Extension Animal Science Mimeograph Series #133 (Ithaca, NY: Cornell University, 1989), pp. 1-8.
6. Bauman, D. E., ''Bovine Somatotropin: Review of an Emerging Animal Technology," OTA commissioned background paper, Washington, DC, 1990.
7. Bauman, D.E. and Currie, W. B., "Partitioning of Nutrients During Pregnancy and Lactation: A Review of Mechanisms Involving Homeostasis and Homeorhesis," *J. Dairy Sci.* 63:1514-1529, *1980.*
8. Bauman, D.E. et al., "Effect of Recombinantly Derived Bovine Growth Hormone (bGH) on Lactational Performance of High Yielding Dairy Cows, " *J. Dairy Sci.* 65(Suppl. 1):121, *1982.*
9. Bauman, D.E. et al., "Response of High Producing Dairy Cows to Long Term Treatment with Pituitary- and Recombinant-Somatotropin,' *J. Dairy Sci. 68: 1352-1362, 1985.*
10. Bauman, D.E. et al., "Sources of Variation and Prospects for Improvement of Productive Efficiency

in the Dairy Cow: A Review, ' *J. Anim. Sci.* 60:583-592, *1985.*

11. Bauman, D.E. et al., "Regulation of Nutrient Partitioning: Homeostasis, Homeorhesis and Exogenous Somatotropin,'' keynote lecture in: *Seventh International Conference on Production Disease in Farm Animals,* F.A. Kallfelz (cd.) (Ithaca, NY: Cornell University, 1989), pp. 306-323.
12. Bines, J.A. and Hart, I. C., "MetabolicLimits to Milk Production, Especially Roles of Growth Hormone and Insulin,' *J. Dairy Sci.* 65:1375-1389, *1982.*
13. Brumby, P.J. and Hancock, J., "The Galactopoetic Role of Growth Hormone in Dairy Cattle," New *Zealand J. Sci. Tech.* 36A:417-436, *1955.*
14. Burvenich, C. et al., ''Effect of Bovine Somatotropin on Milk Yield and Milk Composition in Periparturient Cows Experimentally Injected with escherichia Coli, ' *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard, and A. Neimann-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 277-280.
15. Butler, W.R. and Smith, R.D., "Interrelationships Between Energy Balance and Postpartum Reproductive Function in Dairy Cattle, " *J. Dairy Sci. 72:767-783, 1989.*
16. Chalupa, W. and Galligan, D.T., "Nutritional Implications of Somatotropin for Lactating Cows, ' *J. Dairy Sci.* 72:2510-2524, *1989.*
17. Chilliard, Y., ''Long-Term Effects of recombinant Bovine Somatotropin (rbST) on Dairy Cow Performances: A Review,' *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard, and A. Neimann-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 61-87.
18. Cicerone, R.J. and Oremland, R. S., ''Biogeochemical Aspects of Atmospheric Methane, " *Global Biogeochemical Cycles* 2(4):299-327, *1988.*
19. Collier et al., ''Changes in Insulin and Somatomedin Receptors and Uptake of Insulin, IGF-I and IGF-II During Mammary Growth, Lactogenesis and Lactation, ' *Biotechnology in Growth Regulation,* R.B. Heap, C.G. Presser, and G.E. Lamming (eds.) (Butterworths, London: 1989), pp. 153-163.
20. Daughaday, W.H. and Barbano, D. M., "Bovine Somatotropin Supplementation of Dairy Cows: Is the Milk Safe?" *J. Am. Med. Assoc.* 264:1003-1005, *1990.*
21. Eppard, P.J. et al., "Effect of 188-Day Treatment With Somatotropin on Health and Reproductive Performance of Lactating Cows," *J. Dairy Sci.* 70:582-591, *1987.*
22. Eppard, P.J. et al., "Effect of Bovine Somatotropin on Animal Health," *Proc. Maryland Nutr. Conf., 1989,* pp. *74-79.*
23. Epstein, S. S., Report sent to the Food and Drug Administration entitled "Potential Public Health Hazards of Biosynthetic Milk Hormones," Jul. 19, 1989.
24. Erb, H.N. et al., ''Rates of Diagnosis of Six Diseases of Holstein Cows During 15-Day and 21-Day Intervals," *Am. J. Vet. Res.* 45:333-335, *1984.*
25. Everett, R.W. et al., "Dairy Genetics in a bST Environment," *Advanced Technologies Facing the Dairy Industry: bST,* Cornell Cooperative Extension Animal Science Mimeograph Series #133 (Ithaca, NY: Cornell University, 1989), pp. 81-83.
26. Fallert, R.F. and Liebrand, C. B., "Economic Implications of bST for the U.S. Dairy Industry,' *J. Dairy Sci. (in* press), 1991.
27. Ferguson, James D., "Bovine Somatotropin—Reproduction and Health," NIH Technology Assessment Conference Abstracts (Bethesda, MD: National Institutes of Health, 1990), pp. 65-81.
28. Ferguson, J.D. and Skidmore, A., "Bovine Somatotropin-Reproduction and Health," *Advanced Technologies Facing the Dairy Industry: bST,* Cornell Cooperative Extension Animal Science Mimeograph Series #133 (Ithaca, NY: Cornell University, 1989), pp. 57-69.
29. Ferry, J. W., "Managing the bST Treated Herd—A Veterinarian Perspective, " *Meeting the Challenges of New Technology,* Monsanto Technical Symposium Preceding the Cornell Nutrition Conference, Animal Sciences Division, Monsanto Agricultural Co., St. Louis, MO, 1989, pp. 45-54.
30. Fox, M.W., "Why bST Must Be Opposed," paper presented at the Athene Trust International Conference entitled ''Action Alert: The Bio-Revolution—Cornucopia or Pandora's Box?" (London, England: October 1988).
31. Gluckman, Peter D. et al., "TheEffects of Growth on Lactation and Performance in Ruminants and Humans: Mechanisms of Action and Effects on Milk Hormone Composition, " NIH Technology Assessment Conference Abstracts (Bethesda, MD: National Institutes of Health, 1990), pp. 41-45.
32. Gravert, H. O., "Influences of Somatotropin on Evaluation of Genetic Merit for Milk Production, " *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard, and A. Neimann-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 120-131.
33. Groenewegen, P.P. et al., "Bioactivity of Milk From bST-Treated Cows," *J. Nutr.*120:514-520, 1990.
34. Hanson, Michael K., Biotechnology and Milk—Benefit or Threat? An Analysis of Issues Related to bGH/bST Use in the Dairy Industry, Consumer Policy Institute, Consumers Union, Mount Vernon, NY, 1990.
35. Hard, D.L. et al., "Effect of Long Term Sometribove, USAN (Recombinant Methionyl Bovine Somatotropin), Treatment in a Prolonged Release System on Milk

Yield, Animal Health and Reproductive Performance-Pooled Across Four Sites," *J, Dairy Sci. 71(* Suppl. 1):210, *1988.*

36. Hocquette, J.F. et al., "The Human Liver Growth Hormone Receptor,'' Endo. 125:2167-2174, 1989.

37. Johnsson, I.D. and Hart, I. C., "Manipulation of Milk Yield with Growth Hormone, ''Recent *Advances in Animal Nutrition,* W. Haresign and D.J.A. Cole (eds.), Butterworths, London, 1986, pp. 105-123.

38. Juskevich, J.C. and Guyer, C. G., "Bovine Growth Hormone: Human Food Safety Evaluation,' *Science* 249:875-884, *1990.*

39. Kelley, K.W. et al., "Hormonal Regulation of the Age-Associated Decline in Immune Function,' *Neuroimmunornodulation,* B.D. Jankovic, B.M. Markovic and N.H. Spector (eds.) (New York, NY: The New York Academy of Sciences, 1987), pp. 91-97.

40. Kirchgessner, M., Schwab, W., and Muller, H. L., "Effect of Bovine Growth Hormone on Energy Metabolism of Lactating Cows in Long-Term Administration,' *Energy Metabolism of Farm Animals,* Y. van der Honing and W.H. Close (eds.), Pudoc Wageningen, Netherlands, 1989, pp. 143-146.

41. Kostyo, J.L. and Reagan, R. C., "The Biology of Somatotropin,' *Pharmac. Ther. B.* 2:591, *1976.*

42. Kronfeld, D. S., ''Growth Hormone-Induced Ketosis in the Cow," *J. Dairy Sci.* 48:342-346, *1965.*

43. Kronfeld, D. S., "Major Metabolic Determinants of Milk Volume, Mammary Efficiency and Spontaneous Ketosis in Dairy Cows, ' *J. Dairy Sci. 65:2204-2212, 1982.*

44. Kronfeld, D., "Concerns About Use of Growth Hormone in Dairy Cows,' Food and Drug Administration Seminar Notes of 9/10/86, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD, 1986.

45. Kronfeld, D., "Health Risks in Dairy Cows Given Biosynthetic Somatotropin," Proc. Nutrition Institute, NFIA, West Des Moines, IA, 1987.

46. Kronfeld, D., Letter to editor entitled: BST Milk Safety, *J. Am. Vet. Med. Assoc.* 195:288-289, *1989.*

47. Lerner, J., Matthews, E., and Fung, I., "Methane Emissions from Animals: A Global Resolution Data Base," *Global Biogeochemical Cycles 2(2):139-156,* June 1988.

48. Linn, J. G., "Factors Affecting the Composition of Milk from Dairy CowS," *Designing Foods-Animal Product Options in the Marketplace* (Washington, DC: National Academy Press, 1988), pp. 224-241.

49. Machlin, L. J., ''Effect of Growth Hormone on Milk Production and Feed Utilization in Dairy Cows," *J. Dairy Sci.* 56:575-580, *1973.*

50. McBride, B. W., Burton, J. L., and Burton, J. H., "The Influence of Bovine Growth Hormone (somatotropin) on Animals and Their Products, ' *Res. Dev. Agric.* 5:1-21, *1988.*

51. McCutcheon, S.N. et al., "Application of Bovine Somatotropin (bST) Technology to Pastoral Dairy Farming Systems," *Seventh International Conference on Production Disease in Farm Animals,* F.A. Kallfelz (cd.) (Ithaca, NY: Cornell University, 1989), pp. 332-335.

52. Mollett, T.A. et al., "Biosynthetic or Pituitary Extracted Bovine Growth Hormone Induced Galactopoiesis in Dairy Cows," *J. Dairy Sci.* 69(Suppl. 1):118, *1986.*

53. National Institutes of Health, "Technology Assessment Conference Statement on Bovine Somatotropin,' Bethesda, MD, December 1990.

54. National Research Council, "Nutrient Requirements of Dairy Cattle, ' 6th revised edition (Washington, DC: National Academy of Science, 1988).

55. Noakes, D. E., "Use of Somatotropin in the Dairy Cow with Regard to Cow Safety," *J. Dairy Sci. (in* press), 1991.

56. Peel, C.J. and Bauman, D. E., "Somatotropin and Lactation," *J. Dairy Sci.* 70:474-486, *1987.*

57. Peel, C.J. et al., "Bovine Somatotropin: Mechanism of Action and Experimental Results from Different World Areas," *Meeting the Challenges of New Technology,* Monsanto Technical Symposium Preceding the Cornell Nutrition Conference, Animal Sciences Division, Monsanto Agricultural Co., St. Louis, MO, 1989, pp. 9-18.

58. Philipsson, J. et al., Genetic Aspects on Breeding for Mastitis Resistance, Symposium on Bovine Mastitis, Munich, West Germany, 1978, pp. 1-14.

59. Phipps, R. H., "A Review of the Influence of Somatotropin on Health, Reproduction and Welfare in Lactating Dairy Cows,' *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard and A. Neimam-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 88-119.

60. Poutrel, B., "Susceptibility to Mastitis: A Review of Factors Related to the Cow," *Ann. Rech. Vet.* 13:85-99, *1982.*

61. Refsdal, A. O., Baevre, L., and Bruflot, R., "Urea Concentration in Bulk Milk As An Indicator of the Protein Supply at the Herd Level," *Acta Vet. Scand.* 26:153-163, *1985.*

62. Rifkin, J., Petition to Secretary of Health and Human Services and the Food and Drug Administration and Its Division of Veterinary Medicine, Apr. 1, 1986.

63, Rifkin, J., petition to the Food and Drug Administration, Sept. 16, 1987.

64. Rifkin, J., petition to the Food and Drug Administration, Aug. 23, 1989.

65. Schams, D., ''Somatotropin and Related Peptides in Milk," *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard, and A. Neimann-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 192-200.

66. Schwart, B. et al., "Size and Waste Management Costs," *Balanced Dairying Economics*, vol. 11, *No.* 1, Texas A&M University, College Station, Texas, 1991.

6'7. Sechen, S., ''Review of Bovine Somatotropin by the Food and Drug Administration, *Advanced Technologies Facing the Dairy Industry: bST*, Cornell Cooperative Extension Animal Science Mimeograph Series #133, Cornell University, Ithaca, NY, 1989, pp. 101-110.

68. Sechen, S.J. et al., "Effect of Somatotropin on Kinetics of Nonesterified Fatty Acids and Partition of Energy, Carbon and Nitrogen in Lactating Cows,' *J. Dairy Sci.* 72:59-67, 1989.

69. Shook, G.E., Genetic Aspects of Mastitis, Proc. 25th Annual Meeting National Mastitis Council, Inc., 1986, pp. 68-77.

70. Skidmore, A. L., Development of a Simulation Model to Evaluate Effectiveness of Dairy Herd Management, Ph.D. thesis, Cornell University, Ithaca, NY, 1990.

71. Trimberger, G. W., "Conception Rates in Dairy Cattle From Services at Various Intervals After Parturition," *J. Dairy Sci.* 37:1042-1049, 1954.

72. Tyrrell, H. F., Ruminant Nutrition Laboratory, U.S. Department of Agriculture, Beltsville, MD, personal communication, 1990.

73. Tyrrell, H.F. et al., "Effect of Bovine Somatotropin on Metabolism of Lactating Dairy Cows: Energy and Nitrogen Utilization as Determined by Respiration Calorimetry, "J. *Nutr.* 118:1024-1030, *1988.*

74. U.S. Congress, Office of Technology Assessment, *Beneath the Bottom Line: Agricultural Approaches to Reduce Agrichemical Contamination of Groundwater,* OTA-F-4 18 (Washington, DC: U.S. Government Printing Office, November 1990).

75. van den Berg, G., ''Milk from bST-Treated Cows: Its Quality and Suitability for Processing," *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard, and A. Neimann-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 178-191.

76. Van Vleck, L. D., "Potential Genetic Impact of Artificial Insemination, Sex Selection, Embryo Transfer, Cloning and Selfing in Dairy Cattle," New *Technologies in Animal Breeding,* B.G. Brackett, G.E. Seidel, Jr., and S.M. Seidel (eds.) (New York, NY: Academic Press, Inc., 1981), pp. 221-241.

77. Vernon, R. G., ''Influence of Somatotropin on Metabolism, " *Use of Somatotropin in Livestock Production,* K. Sejrsen, M. Vestergaard, and A. Neimann-Sorensen (eds.) (New York, NY: Elsevier Applied Science, 1989), pp. 31-50.

78. Vicini, J.L. et al., "Effect of Acute Challenge With an Extreme Dose of Somatotropin in a Prolonged-Release Formulation on Milk Production and Health of Dairy Cattle, " *J. Dairy Sci.* 73:2093-2102, *1990.*

79. Wallis, M., "The Molecular Evolution of Pituitary Hormones," *Biol. Rev.* 50:35-98, *1975.*

80. Wood, D.C. et al., ''Purification and Characterization of Pituitary Bovine Somatotropin, ' *J. Biol. Chem.* 264:14741-14747, 1989.

81. Young, F. G., "Experimental Stimulation (galactopoiesis) of Lactation, " *Brit. Med. Bull.* 5:155-160, *1947.*