Lymphosarcoma (Leukemia) of Cattle*

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This disease is a neoplasia of lymphoid tissue and can properly be called lymphosarcoma. The designation *leukemia* may be misleading since an increased lymphocyte count (persistent lymphocytosis), while common, is not a constant feature. However, the word *leukemia* is useful in referring to the bovine leukemia virus (BLV) now associated with lymphosarcoma of cattle so that the virus may be considered along with the other known leukemia viruses of chickens, mice and cats.

The four forms of bovine lymphosarcoma are clinically distinct from each other. In the *adult* form, affecting cattle three or more years old, scattered lymph nodes are enlarged and often the heart, abomasum and uterus are affected. In addition to involvement of a few lymph nodes, a large tumor develops near the jugular vein and trachea in the neck of cattle about two years old in the relatively rare *thymic* form. Nearly all lymph nodes and many internal organs are affected in the *calf* form which may even be fully developed at birth. The rare *skin* form is usually seen in cattle 1½ to 3 years old and in some cases lesions of the adult form also occur.

Natural regression of the lesions has occurred in some cases of the calf and skin forms and has been suspected in some cows with the adult form.

In previous surveys of the prevalence of the disease, the investigator had to depend on actual lymphosarcoma as manifested by necropsy evidence of tumor development or data from inspection at slaughter establishments, and repeated counts of circulating lymphocytes to detect persistent lymphocytosis. Studies based on these criteria have provided much information on the extent of the disease in various countries and a concept of bovine leukemia as an infectious disease, as well as ideas to control the disease.

A brief review follows of what previous investigators had found. A study in West Germany indicated that after World War II, the incidence of lymphosarcoma, as shown by tumor found at slaughter, had increased in areas where animals had been transported from northeastern areas (East Germany) into the north (West Germany) (39,40). A spread of leukosis to northern areas from southern areas of Sweden was indicated by one investigator (19). Certain areas of Denmark had ten times more leukosis than other areas, and until systemic controls were introduced in 1960, the disease was gradually increasing (3,4). Only sporadic cases of leukosis were reported from Norway, Holland, Belgium, Switzerland and Austria (5,7,22,48,53). Workers in Czechoslovakia, Bulgaria, Yugoslavia, and Romania reported leukosis and believed it to be due to the importation of breeding stock from countries with leukosis (23,38,44,45). Reports of leukosis in other countries such as Israel and Turkey again implicated imported cattle (17,29). Studies in California in 1961, 1963, 1964 showed a higher frequency of lymphosarcoma in dairy cattle as compared to beef cattle at the time of slaughter (47). Factors studied as possible means of dissemination of the disease were inheritance, soil type, climate, feed type, seasonal influence, hormonal influence, breed susceptibility, and association with other viral infections. Vertical transmission of the infectious agent was suggested as transplacental or colostral transmission (42,46) and thus was prevalent in certain cow families (33,49). Familial occurrence in beef as well as dairy cattle has been noted (20). Evidence of horizontal transmission by contact was found (3), and body fluids and secretions were suspected. Transmission of leukosis by the inoculation of piroplasma vaccine made from infected calves' blood was reported (30). A study of ten leukosis herds in W. Germany suggested contact infection from an infected bull. One herd had 8 of 15 cows affected within eight months after introduction of the infected bull (41). Observations in numerous experiments noted that the calf was particularly susceptible to the disease (42).

Measures for the control of the disease were instituted in countries where leukosis had been a problem. In Denmark, for example, a control agency made repeated blood counts of cattle for persistent lymphocytosis, and proceeded to eradicate the herds where it was found (4). A program eliminating only animals with lymphocytosis has been used in Germany (16). Calves from lymphocytosis positive dams were not saved for breeding purposes and other calves were raised with milk from lymphocytosis free cows (16).

Suggestive evidence of a bovine leukemia virus in lymphosarcoma materials had been previously reported (51) but a method for culture and demonstration of BLV was first reported in 1969 (24) and confirmed in U.S. and Germany (6,13,21,43,50). This virus will produce lymphosarcoma in cattle (1,-27) and sheep (34,52) and infect goats (18). Such animals develop precipitins which react with ether

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treated BLV as antigen in gel diffusion tests (27). This BLV antigen is different from the antigen in mouse or cat leukemia virus (8,14,36).

Neither virus antibody nor BLV can be demonstrated in the calf or thymic forms of bovine lymphosarcoma but experimental calves inoculated with such material have developed BLV infection and antibody (27). Thus there appears to be variation of interplay between virus and animal in the different forms of bovine lymphosarcoma.

There are now three serological methods of demonstrating antibody to the bovine leukemia virus antigen; immunofluorescence (IF) (10,15); immunodiffusion (ID) (9,25); complement fixation (CF) (26). Each method demonstrates certain antigen-antibody reactions and selection of a method depends on what is desired. Serums from 175 cattle had been sent to three different laboratories (New Bolton Center, School of Veterinary Medicine, University of Pennsylvania; Department of Veterinary Science, University of Wisconsin; and National Animal Disease Laboratory, Ames, Iowa) by a fourth agency for testing by the three methods (1). Each laboratory was proficient in one of the respective methods and received the serums as unknowns. No antibodies to bovine leukemia virus were found in 146 serums by the three methods. Of the 29 serums with antibodies, 16 were positive by all three tests, five positive by CF only, one by IF only, one by ID only, five by CF and IF, and one by CF and ID. Thus there was remarkably good agreement of results by the three methods. The variations are due to sensitivity of the methods and qualitative differences in antibodies to different antigens as recognized by the methods of testing. Recently, two BLV antigens, an ether senstitive (es) and an ether resistant (gs) have been demonstrated (35). The CF test can measure antibodies to both when using culture fluid as antigen; ID with specific antigens can demonstrate antibody to either es or gs, and IF appears to demonstrate antibody to gs antigen (37).

Application of Serologic Tests

The gel diffusion test for gs precipitins, as specifically designed for BLV antibodies has been used in preliminary surveys. In one, about 1000 cows in 11 selected herds were tested and 222 reacted (32). Five herds with no lymphosarcoma for 13 to 33 years had a lower percentage of reactors (2% to 16%) than six herds with 24 cases of lymphosarcoma in the last seven years (24% to 42% reactors). The BLV was demonstrated by cultures in 100 of 117 reactors including cattle in the five herds with no lymphosarcoma. The survey has been expanded to over 7000 cattle in the north central states. Reactors have been found in two thirds of 100 herds of 4400 dairy cattle and only one seventh of 50 herds of 2800 beef cattle (2). It may be significant that very few cattle less than two years old were found to react to the gel diffusion test. This suggests a slow development of the virus infection.

In 22 herds with BLV infection 13.5% of 1354 cows were reactors to BLV gs antibody test and 10.4% of 96 bulls (2), thus the prevalence of infection appeared to be about the same in bulls and cows.

No reactors to gs antigen were found in 100 dairy cows in ten herds on the Island of Jersey and 16 cattle on Bornholm Island of Denmark, or in 126 dairy cattle of an isolated herd in the United States (1). Lymphosarcoma or persistent lymphocytosis has not been on these islands or in the isolated U.S. herd for more than 25 years.

Serums from 97 cattle were received from Denmark, and tested as unknowns for precipitins to BLV gs antigen (1). The results were sent to Denmark for correlation with the history of the cattle. Antibodies were found in 19 serums of cattle from herds with multiple cases of lymphosarcoma or cases of persistent lymphocytosis. Serums from two cattle with lymphosarcoma and two cattle with persistent lymphocytosis were negative. Serums from 32 cattle in herds with no history of lymphosarcoma or persistent lymphocytosis were negative. Serums were also negative from 42 cattle in the clinic of the Royal Veterinary College, each affected with a variety of illness other than lymphosarcoma.

Serums from 416 cattle were received from Sweden to be tested as unknowns for BLV gs antigens (1). The results were sent to Sweden for correlation with history of the cattle. There were 197 serums from four multiple case herds and 24% to 39% of the cattle in each herd were reactors. Cattle in the vicinity of Kalmar, Sweden, have had a high incidence of lymphosarcoma. Fifteen of 130 serums obtained at the Kalmar abbatoir had precipitins. Thirty-six serums were submitted from cattle with "leukosis" (lymphosarcoma and/or lymphocytosis) and 20 had antibody to BLV. Serums from 53 cattle on the island of Aland, now apparently free of bovine "leukosis", were all negative.

To investigate the possibility that BLV might have a reservoir in other animals, 2321 serums were tested and found negative for precipitins to BLV gs antigen (1). These included 792 pigs, 479 goats, 382 sheep, 7 ponies, 689 wild animals (17 species), and 72 wild birds (5 species). In addition, 175 animals (mice, rats, hamsters, guinea pigs, rabbits, kittens, pigs, chipmunks, grey and ground squirrels, and fawns) and 23 birds (chickens, pigeons, coturnix quail, and doves) have been inoculated with BLV and after more than one year none have developed tumor or antibody to BLV.

A herd of 350 cattle in which annual observations are made is providing much information on BLV infection (1). Tests for BLV antibody and cultures for virus indicate infection can be apparent, though rarely, at less than one year of age. An infected cow had a calf which was infected at less than one year of age but her next calf has remained negative for two years.

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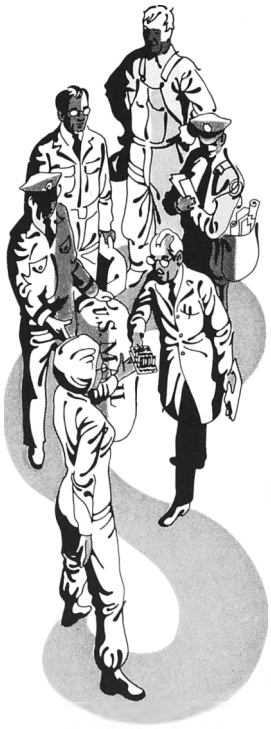

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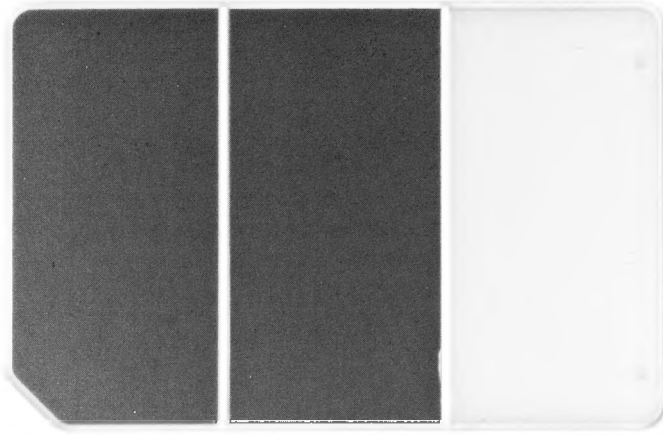

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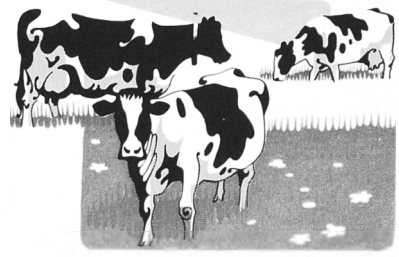

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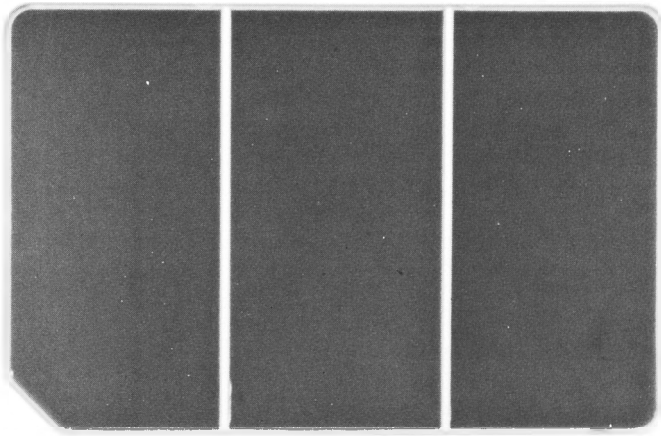

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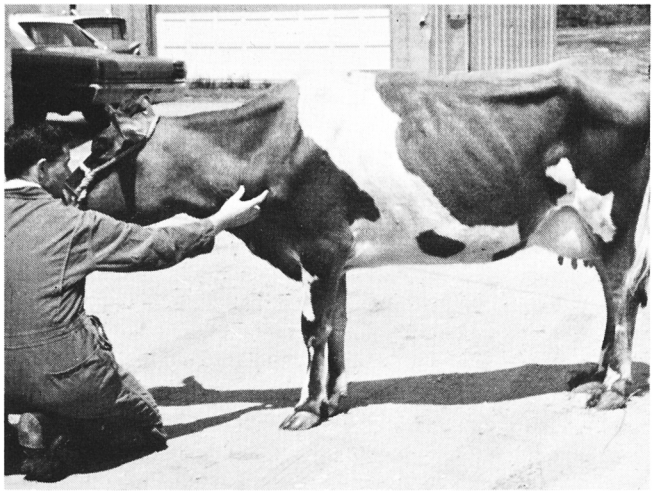

Figure 1. Adult form of lymphosarcoma in a 2½-year-old cow. Note enlargement of prescapular and prefemoral lymph nodes and emaciation.

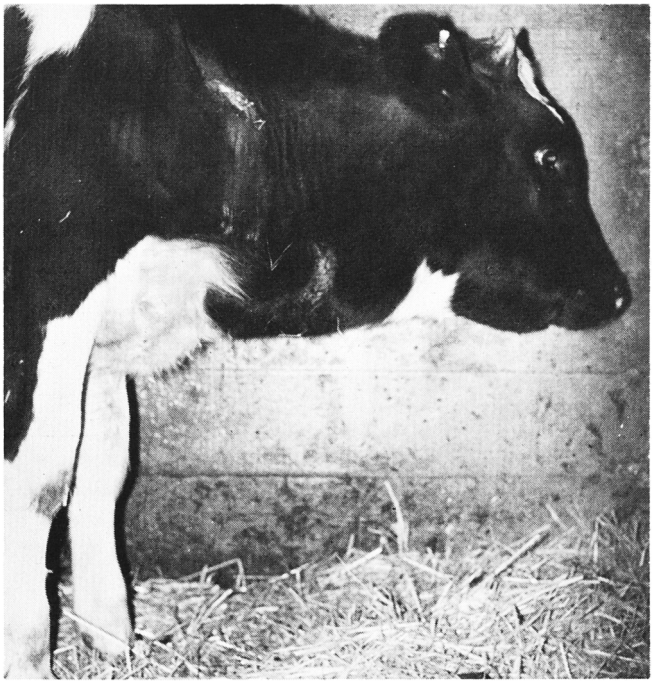

Figure 2. Thymic form of lymphosarcoma in a 1-year-old calf, with firm swelling from tumor in neck.

Cows up to eight years old have been negative on one or two annual tests, then have both BLV antibody and BLV on culture. A pair of twins were both negative at five years of age then one became infected and has remained so for three successive years while the other has been negative. Evidence for recovery from BLV infection has, thus far, not been clearly evident. Usually cows once infected remain so, although there can be variations in antibody titer. These observations support the earlier concept of transmission from dam to progeny as well as by contact between cattle.

The question of infection coming from semen of infected bulls has been examined in a preliminary way (1). Two bull studs have cooperated in this study involving 33 herds where there were 190 progeny from 11 bulls with BLV infection. Serums were obtained from about 1000 cattle over one year old including the progeny, their dams when available. Haphazardly selected other cows were tested also to provide an index of BLV infection in the herds. In three herds there were no reactors to CF test and in 30 herds reactors varied from 2 to 60%. There were only 29 (15%) reactors among the 190 progeny from 11 infected bulls. In the same herds there were 386 progeny from 21 negative bulls and 73 (19%) of these progeny were reactors. There were 52 progeny from infected dams, 48% of which were reactors compared to 7.6% reactors in 224 progeny from negative dams. Thus the infection status of dams was far more important than that of the sire. In addition, there were many reactor progeny when both sires and dams were negative indicating infection from another source, probably contact.

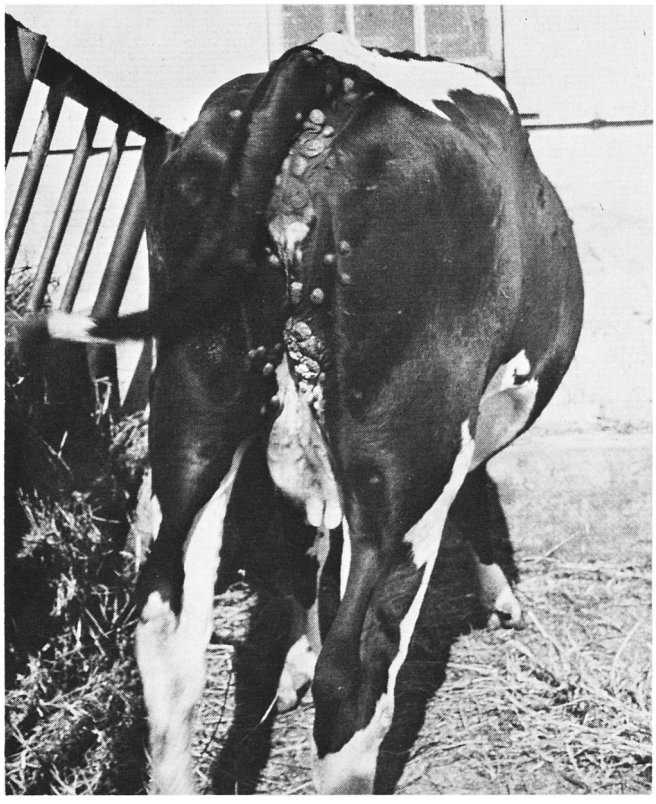

Figure 3. This cow has the rare skin form with tumors scattered over the body. All tumors regressed in this case. Cutaneous lymphosarcoma can be mistaken for warts which are not common in the escutcheon region.

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The practical application of antibody tests in bovine lymphosarcoma is still being explored. A positive test for antibodies involving precipitins, complement fixation, or immunofluorence merely indicates the animal has or has had infection with the virus. A few cows from which the virus can be isolated and a few cows with lymphosarcoma do not have antibodies.

All circumstances must be considered in interpretation of test results on a herd of cattle. Herds with previous cases of lymphosarcoma and several reactor cows should be watched for signs of the disease since some reactors will develop lymphosarcoma. Many cows with antibodies and BLV infection live to old age and die with no macroscopic evidence of lymphosarcoma. Since there is likelihood of infection passing from dam to daughter, calves from reactors should not be kept for herd replacements unless they can be foster nursed and raised in isolation from reactors. Reactors should not be condemned on the basis of the test for antibodies alone. Infection with the virus may have been overcome and the animal theoretically immune. Where only one or two reactors exist in a herd it would be advisable to remove them. With negative herds a test at yearly intervals and testing of new adult animals prior to their introduction in the herd should assure freedom from leukemia virus infection. Since cattle less than two years old are infrequently reactors, the dams of newly purchased calves could be tested for freedom from infection.

A serologic survey (2) indicates that BLV infection is more widespread in dairy cattle (10% reactors) than in beef cattle (1% reactors), although three beef herds did have an 11, 12, and 20% incidence of infection. Reactors were found in 66% of the dairy herds, and 14% of the beef herds. These results are similar to those found in the study of animals at slaughter in California (47) in which 79 histopathologically confirmed cases were dairy cattle, and eight were beef cattle.

There seemed to be a tendency for smaller dairy herds (less than 50 cattle) to have a higher percentage of reactors (more than 14%) compared to larger herds (2). The significance of this observation is not evident.

Arrangements have been made with the Agricultural Experiment Station of the College of Agricultural and Life Sciences so that tests for antibody to BLV can be done on bovine serums originating in other states as well as Wisconsin. A fee of $2.00 per test will be charged and protocol forms with directions for submission will be mailed to veterinarians upon request.

It is believed that the New Bolton Center of the School of Veterinary Medicine, University of Pennsylvania, will arrange to make fluorescent antibody tests for BLV.

Is Bovine Leukemia Virus Hazardous to Man?

Since BLV is probably shed in the milk and BLV can infect both goats and sheep with about 20% of the latter developing lymphosarcoma in two to four years (34), the potential hazard to man has been raised. In one study (11) it was claimed that two to six chimpanzees developed a type of leukemia after being fed milk suspected of containing BLV. Attempts to infect young chimpanzees with cultures known to contain BLV are underway at two laboratories (1,28). In another recent (12) report, a cluster of seven people associated with a powdered milk plant were found to have lymphosarcoma. Even though two of the patients and several other people of the area had no antibody to BLV (by one type of test) the possible association with bovine leukemia was stressed.

Serological evidence of its transmission to man thus far is negative since precipitins to BLV have not been found by tests on (a) ten laboratory personnel working with bovine lymphosarcoma or BLV (1), (b) dairymen with infected cattle (1), (c) 80 veterinarians in Wisconsin most of whom had extensive dairy cattle practice (1), 73 veterinarians in Iowa (28), and (d) about 100 human subjects with various forms of leukemia (1). Another laboratory has tested 400 human serums from cancer patients and matched controls using CF with purified disrupted BLV, infected tissue cultures, and gs antigens and no positive reactions were obtained (14). These cancer patients were adenocarcinoma 93, squamous cell carcinoma 51, undifferentiated carcinoma 9, malignant melanoma 11, small cell carcinoma 7, Hodgkins disease 14, lymphosarcoma 3 and sarcoma 15. The same report (14) also indicates serums from 43 patients with various forms of leukemia were found negative by National Animal Disease Center (Miller and Van Der Maaten).

The BLV added to cow's milk was destroyed by commercial pasteurization conditions of 74°C for 16 seconds (1). This loss of infectivity was tested by injection into lambs. Duplicate tests involved cultures of virus from two infected cows mixed with milk from two cows with no leukemia viral antibody. The four control lambs given non-pasteurized virus-milk mixtures had antibody at ten weeks; virus demonstrated in all by culture at six months, and one died with lymphosarcoma at 14 months and another at 21 months. Repeated tests for antibody and virus have been negative for 26 months in the four lambs given the pasteurized milk-virus mixture.

Acknowledgement

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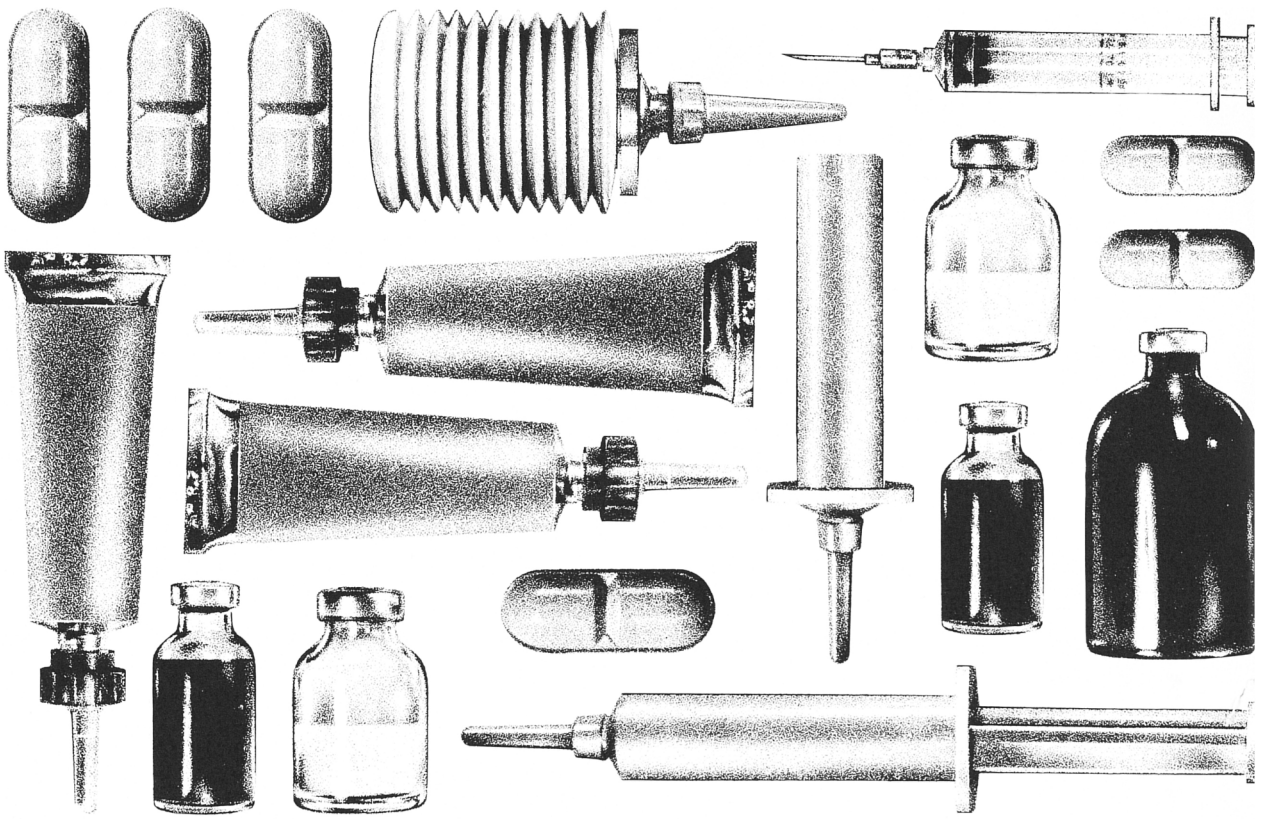

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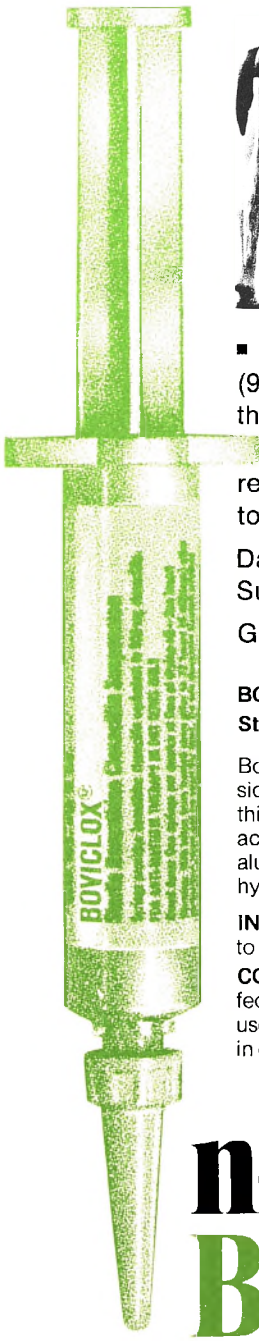

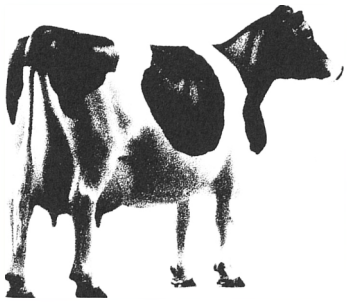

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