A Public Health Mystery

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Gastroenteritis in swine. Also researchers are attempting to produce an effective vaccine against Bovine Infectious Keratoconjunctivitis. In all about 25 different diseases are studied at any one time. Included in the research program are 25 cooperative projects in 14 U.S. universities and 8 projects in 3 foreign countries.

ARS serves the practitioner in the field in 2 important ways. First, methods of disease control are perfected. This is usually accomplished through the production of new vaccines or improving existing ones. Once the vaccines have proven to be effective, drug companies buy the license to produce them and the improved products are passed on to the veterinarian. Secondly, new diagnostic tests are developed or old ones perfected for more efficient detection of disease. These advances are passed on to the diagnostic laboratories across the nation providing the most up-to-date services available.

The second agency associated with NADC is the Veterinary Services Laboratory (VSL) of the Animal and Plant Health Inspection Service. Under the direction of Dr. M. T. Goff, the VSL is an important national center for veterinary diagnostic work and veterinary biologics quality control. It represents the 1973 consolidation of the former Veterinary Services Biologics Laboratory and the Veterinary Services Diagnostic Laboratory.

All veterinary vaccines produced for interstate commerce are tested at VSL for safety, purity, efficacy, and potency. In addition, VSL gives diagnostic assistance to various state and national agencies. The services provided include diagnostic reagent production, diagnostic examination, field consultation away from the central facility, and research projects seeking new and improved diagnostic procedures. Finally, VSL serves as a training center for State and Federal regulatory and diagnostic personnel.

VSL will soon start construction of a new laboratory just south of the main complex of buildings at NADC. At present, VSL has buildings at various locations around Ames. The consolidation and expansion with the new buildings will provide promise to increase productivity, efficiency, and economy of the agency. Work on the new laboratory is expected to start this coming summer and should be completed by the summer of 1978. The new facility will provide 45,000 square feet of laboratory space and 35,000 square feet of animal holding space on 153 acres of land.

Thus, NADC and VSL make Ames, Iowa one of the world centers for veterinary research in the fields of disease control, monitoring of biologics, and diagnostic work.

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A Public Health Mystery

by

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The next time you hear a public health official describing in glowing terms the challenge of his work, dramatically

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similar. All public health work does not involve sixteen herds of pseudorabies-stricken swine or twenty-five Boy Scouts with spirochetal relapsing fever, either. It can involve a small animal practice as easily as a phone number can be dialed. It can involve one child, one animal, and you, the veterinarian. That's how the case of T.Z. began. As the greatest detective of fiction, Sherlock Holmes, put it, "It seemed to be one of those simple cases which is so extremely difficult."

T.Z. was born September 6, 1970. She weighed six pounds seven and one-half ounces at birth, normal enough infant statistics for a child of small parents—a father five foot eight and a mother five foot five. Indeed, she seemed at birth normal in all other respects as well. T.Z. was born into a family of two older brothers and a third child who had died young. Her mother's consequent oversensitivity about her new baby girl, however, could not explain T.Z.'s slow postnatal development. She was physically slow, cut her teeth late, gained little weight and height— at age five she weighs 28 pounds and stands under a yard tall at 35 inches. She was mentally slow—walked and talked later than the other children had and even now lacks motor coordination to the degree that she may have to repeat kindergarten. The only thing she excelled at seemed to be illness. She went through an infancy punctuated with medical problems. At four months of age she was hospitalized for bronchitis, at eight months for gastroenteritis, at two years for a tonsillectomy and for a urethral stricture and urinary infection at age four and a half. The possibility of immunodeficiency occurred to her doctor, who occasionally instituted regimes of gamma globulin injections at six week intervals for several months. However, with or without the injections, T.Z.'s gamma globulin always tested at normal levels, and T.Z. continued to get sick.

On July 27, 1975, T.Z. woke up ill with nausea, vomiting, fever, rhinitis, sore throat and cough. Her ever-conscientious mother took her to Lutheran Hospital emergency room, where a doctor gave her a penicillin injection for a "minor ear infection" and sent her home to recover.

In the next two days, however, her condition worsened. On July 29, she had 104°F temperature and was depressed and lethargic. Her mother took her to Northwest Hospital, where she was admitted with a hyperemic nose and throat, tender anterior cervical lymph nodes, and bilateral rales. Very loud hyperactive bowel sounds were noted by at least two of the clinicians who saw her. No rash, neck stiffness, abdominal distension or hepatomegaly was noted.

The diagnostic workup began and the next three days produced a battery of lab data. Chest radiographs showed clear lung fields. A blood analysis gave hemoglobin levels of 13.3 gm.%, a white cell count at 4,800 with 40% bands and immature granulocytes—a "leukamoid reaction." A marrow biopsy showed granulocytic hyperplasia with no leukemia cells. Alkaline phosphatase was elevated—180 S.U., compared to an adult normal range of 30-80 S.U. Lactic dehydrogenase was 387—elevated from the 100-225 normal. Serum glutamic oxaloacetic transaminase was elevated—159, compared to a normal range of 7.5-40. Total bilirubin was not elevated—0.9 mg., compared to 0.15-1.30 mg. normal. Clinical pathologists also began a process-of-elimination program. A lupus erythematos test and a monospot test (for infectious mononucleosis) were both negative. Febrile agglutinin assays for typhoid, paratyphoid A and B, O antigen, H antigen and Brucella were all negative. A marrow culture showed no growth. A hemoglobin electrophoresis was run to check for thallassemia, a blood dyscrasia carried by T. Z.'s father and brother, but her hemoglobin was normal. Acute antibody titers were taken for histoplasmosis, cytomegalovirus, ECHO virus 4, influenza A and B, adenovirus and toxoplasmosis. The titers were in all cases less than 1:8, except for toxoplasmosis, which was 1:32. A blood culture was made and it proved negative, as it would repeatedly through the course of her illness. A fecal exam for parasites was also to prove consistently negative. A fecal culture was negative. Urine was cultured positive, but the urologist considered it "okay", possibly due to T.Z.'s bout with infection a few months earlier.

On July 31, T.Z.'s condition changed. A maculopapular rash developed on her face
and spread to her body by afternoon. This rash persisted for the next five days, until August 4. She also developed an acute abdomen with tenderness especially marked in the right upper quadrant. A sudden acute abdomen often indicates acute appendicitis in the young, especially in the immunodeficient. T.Z. was prepared for an emergency laparotomy.

Through a right flank incision, the surgeon examined all the abdominal organs he could reach. The mesenteric lymph nodes, right kidney, pancreas, duodenum, stomach and all palpable intestines were normal. A small amount of serous fluid was withdrawn but it was culture and Gram stain negative. The appendix was normal with no inflammation, but the surgeon removed it. The only abnormal organ was the liver, which was enlarged, soft and smooth and of normal color. A needle biopsy was taken, and it showed intact lobular architecture, moderate edema, lymphocytes, plasma cells and some eosinophils—the signs of a chronic, active, nonspecific inflammation.

T.Z. spent the next three days under close observation. On August 3, another monospot test had negative results. On August 5, ECHO virus 4, was isolated from the fecal culture. By August 11, the blood liver enzymes had begun to return to normal—alkaline phosphatase was 163 S.U., lactic acid dehydrogenase was 329 BBU and serum glutamic oxaloacetic transaminase was 40 SFU. T.Z. was treated with Ampicillin, Lincocin and Noxacillin during her hospitalization, but the antibiotics did little visible good. From August 11, she made a gradual recovery and "pretty much got well on her own." In the first weeks of September, T.Z. returned home, showing no clinical signs of her yet undiagnosed disease.

Because T.Z.'s presenting signs and the progress of her disease were not any recognizable human syndrome, her doctors began to suspect a zoonotic disease. Zoonoses, like accidental parasites, often have protein, non-diagnostic symptoms. Among the zoonoses which cause lymphadenopathy, skin rash, nausea and fever in humans are:

1. Rat Bite Fever, which is the common name for two very similar diseases carried by rats, mice, and the carnivores which prey upon them. Spirillum minus produces a disease called "sodaku", characterized by cyclic bouts of lymphadenopathy, fever and chills, arthralgia and gastrointestinal upset. Haverhill disease is caused by Strep-tobacillus moniliformis; it consists of fever and chills, sore throat, vomiting, arthralgia and skin rashes. Both kinds of rat bite fever are effectively treated with penicillin.

2. Cat Scratch Fever, which is an enigmatic disease appearing increasingly in medical literature. Its etiology is unknown but assumed to be a multiple virus infection. The clinical syndrome is a local lymphadenopathy proceeding to suppuration of the lymph nodes; rarely it progresses to generalized lymphadenopathy and hepatosplenomegaly. Other signs are generalized aching, nausea and skin rashes. No disease has ever been isolated from accused carrier cats, but there is a statistical link to families with new cats, especially kittens. There is no treatment.

3. Brucellosis, which is a disease capable of infecting every domestic species except, apparently, the cat. The human syndrome varies with strain, virulence, route, dose and host resistance, and is so varied that it has been nicknamed "mimic disease." Most common signs include fever and chills, joint pains, weakness and gastrointestinal upset. Young children are quite resistant and the usual route of human infection is raw milk. The treatment is a combination of tetracycline, streptomycin and sulfonamide.

4. Leptospirosis, which is called Weil’s disease in human medicine. It is another disease whose virulence varies with strain and resistance. The major signs are fever, gastrointestinal upset, rash, and splenic, hepatic and renal pathology. Direct transmission by bites of dogs and rodents is possible but rare; usually it is spread by urine contact. Cats are very rarely implicated in a human case. Treatment is of marginal value, and consists of penicillin, streptomycin and tetracycline in combination.

5. Toxoplasmosis, which is a sporozoan
parasite upholding an accidental parasitism in a human host, either as a congenital syndrome or as an acquired disease. The acquired form varies in virulence with strain and host resistance. In healthy hosts, the disease is mild and requires no treatment. In immunosuppressive and immunodeficient people, serious liver, spleen and heart pathologies can result. Sometimes a rash is seen. The only accepted diagnosis is a two-fold rise in titer. Treatment of the trophozoite is sulfonamide and pyrimethamine (Daraprim) and is more suppressive than curative; the cysts are not treatable.

The next step was to learn of the sick child's animal contacts. Inquiry revealed that the T.Z.'s family have a 12 year old pet house cat, and three stray cats—a female and two of her year-old kittens—had a random occupation of the greenhouse and backyard. Mrs. T.Z. reported that T.Z. often played with one of the stray kittens, a calico; the public health officials ordered the capture of the cat for testing.

On August 11, the cat was taken to a local veterinarian. The veterinarian observed that the cat was emaciated and ravenous, infested with hookworms and fleas, and had a protruding nictitating membrane and CNS signs. Its condition remained unchanged for its week of isolation. Meanwhile, T.Z.'s Brucella agglutinin test was reported negative and her toxoplasmosis titer was 1:32, so on August 15, the thin little calico cat arrived at Iowa State University Veterinary Clinic in a stout cage between two formidable public health men, bearing an equally ominous introduction—"Rat Bite Fever suspect."

The admitting senior student described the cat as "malnourished—left nictitating membrane partially covers eye—subtle mental confusion vague but present, tactile in nature—anisocoria, left eye smallest."

On August 19, the cat was anesthetized with surital for a CSF tap, and it took abnormally long to recover, remaining unconscious for five hours and ataxic until the following afternoon. The CSF culture was negative for bacteria. The CSF exam showed a glucose of 71 (a negative level) and 3,850 red blood cells per millimeter, 95% crenated, and five white cells per millimeter, all lymphocytes. Thoracic and cervical radiographs were taken and no skeletal lesions were found to explain the vague CNS disorders. On August 20, a fecal examination showed a heavy hookworm infestation, which was treated with Task the next day. A blood sample analysis showed anemia and an infectious response, with a hemoglobin level of 5.1 gm%, a packed cell volume of 16%, a white cell count of 16,500 with 5% bands, 72% segmented neutrophils, 19% lymphocytes, 3% eosinophils and 1% monocytes. The red cell morphology included polychromasia, anisocytosis, leptocytosis, poikilocytosis, rouleaux, and occasional atypical lymphocytes. The plasma protein was 6.4 gm%, the fibrinogen was 200 mg%, and the blood urea nitrogen was 33%. All blood parameters could be explained by the animal's emaciation.

Several neurological examinations were performed on the cat during its stay in the clinic. The consensus of opinions was that the cat had partial sight in the right eye, Horner's syndrome associated with the left eye, variable degrees of ataxia with a consistent compulsion to turn to the left.

On August 28, an immunofluorescent antibody toxoplasmosis titer was run and reported as 1:128. On September 9, a fecal examination was negative.

On September 18, another blood sample was sent for toxoplasmosis titer and the results were a one-dilution increase—1:256. That afternoon at 2:20, the cat was euthanized with pentobarbital. The post mortem demonstrated a very low grade, nonsuppurative leptomeningitis with an area of malacia in the pons, hepatocytes with extreme vacuolization and microgranulomas in the liver, a few tapeworms in the small intestine and no lesions in any other system or tissue. No Toxoplasma gondii cysts were found. Sporocysts in tissue are only variably
present in a toxoplasma infection, however; and fecal oocysts are demonstrable for only a few days, if at all (though there is some doubt cast on the validity of a negative fecal examination by the undiagnosed tapeworm infestation.) Serology is the only accepted diagnostic tool, though interpretation of serological data is still an area of subjective opinion. About 14% of stray cats carry a significant toxoplasma titer without disease,2 and the titer rise this calico cat displayed during its month at the ISU Clinic could be taken as a variance in reading by different lab technicians. The cat did show the required two-fold rise in titer, however; and Dr. J. H. Greve, the post mortem veterinarian, added the notation to his report that though *Toxoplasma Gondii* were not demonstrable “serology suggests their presence.”

The clue to the etiology of T.Z. 's mysterious illness came in a battery of convalescent antibody titers run at the end of August. As previously, titers for histoplasmosis, cytomegalovirus, ECHOvirus 4, influenza A and B and adenovirus were all less than 1:8. However, her toxoplasmosis titer had skyrocketed to 1:2048.

Once again, however, one must not jump to hasty conclusions about antibody titers. About 20% of cat-owning humans carry toxoplasma titers. As freshmen, the 1976 graduating class of the ISU Veterinary College had titers ranging from 1:2 to 1:128, and titers on the orders of 1:512 and 1:2048 (there was even a dairy worker found with an astronomical 1:4096 titer), all of whom “were unaware that they had been exposed to toxoplasma.” Those cases involved normal healthy humans, however, and not a possibly immunodeficient child. T.Z. ’s 64-fold rise in titer may represent a phenomenal immunological response—for her. Considering the sum of information, then—the child’s pathology, the cat’s titer, the other cats who could also have been involved—if one must arrive at a pat diagnosis, toxoplasma is the most likely candidate to be named.

Being involved in a public health case can be as simple and as complicated as that. To offset the time a veterinarian may put in, there are definite tangible and intangible assets to becoming involved.

The veterinarian stands to learn, if he will but meet the case as an opportunity to learn. The effort can involve as simple a process as checking up on a journal footnote, to a good deal of midnight oil and page-flipping in a book of differential diagnoses. A veterinarian should be well acquainted with common public health problems, but an off-the-cuff telephoned answer to a physician’s questions about pinworms—or rabies—does little for the physician and nothing for the veterinarian.

The public stands to learn, if the veterinarian and physician will but teach. In 1932, the governor of Iowa had to order out the National Guard to protect veterinarians from irate farmers as they tuberculin tested cattle. A rabies prophylaxis campaign such as exists in the United States would be impossible in a climate of public ennui, mistrust or misunderstanding. In late November, T.Z. ’s mother was still worried that a high titer to toxoplasmosis might be hurting her daughter. In all the weeks of medical concern and sophisticated labwork, no one had even roughly explained to her what an antibody titer is.

Finally, a small animal veterinarian must realize that the public health problems which come to him will very often be a mystery from beginning to end. Case histories must be pieced together, lab data come back weeks later than they are submitted, and sometimes the patient will recover before the disease is even named. You may never know if that raccoon that bit the Jones boy was rabid, or just who brought foot and mouth disease to Canada, or if T.Z. really had toxoplasmosis, or cat scratch fever, or an expression of her abnormal hematopoietic system. To shy away from a case because you may not be able to come up with a pat diagnosis is to adopt a “professional appearance” over a professional actuality. The challenge is to want to know; the trick is to have, like Sherlock Holmes, a voracious appetite for facts, for all the facets of your cases; to want to know them for their own sakes, without falling into the facetious habit of believing that medical detective work, whether on a public health case or on any medical case that comes to you, must be simply “Elementary.”
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Rumensin: R A New Feed Additive for Feedlot Cattle

by

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Because feed comprises over 80% of the cost of producing fat cattle, considerable research has been directed towards improving utilization of the energy in feeds by ruminants. Attempts to get more energy from cattle feeds have included grinding, pelleting, steam flaking, feeding ensiled high moisture grains and feeding high concentrate rations. Several years ago studies were conducted in the Lilly Research Laboratories of Eli Lilly and Company to improve efficiency of energy utilization by ruminants by searching for a compound which would change the proportion of volatile fatty acids produced during microbial digestion in the rumen. One compound which was found to consistently increase propionic acid production and decrease the production of acetic and butyric acids was monensin, a polyether produced by Streptomyces cinnamonensis, has weak gram positive antimicrobial activity and also is an effective coccidiostat. The compound is currently marketed as a coccidiostat for poultry under the tradename CobanR. Monensin was tested in cattle and found to improve the utilization of feed energy for growth. The product has recently been cleared by the Food and Drug Administration for use in feed lot cattle feeds at the rate of 5 to 30 grams per ton of complete feed and will be marketed by Elanco Products Company, the agricultural division of Lilly, under the tradename RumensinR (Monensin Sodium).

RumensinR is thought to act directly on the rumen flora to increase the production of propionic acid. The specific effects of the compound on the bacterial cells are not known. The microbes in the rumen break down starches and cellulososes in feeds to sugars and then to volatile fatty acids which supply energy to the ruminant animal. Acetic, propionic and butyric are the principal fatty acids produced, but the efficiency with which sugars are converted to these acids varies considerably. When acetic and butyric acids are formed some of the carbon and hydrogen (energy) are lost as CO2 and methane. No energy is lost, however, when sugars are converted to propionic acid. In a typical beef feeding

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