PHARMACEUTICALS AND MEDICINALS OF ANIMAL ORIGIN*

JOSEPH P. DAILY
Armour Pharmaceutical Company
Kankakee, Illinois

Throughout history, the inter-dependency between man and animals has been profound. Man has relied on animals for companionship and for food. He has often utilized animals as a sacrifice in his religious ceremonies. Excavations of ancient tombs have revealed the skeletons of animals interred with the skeleton of the human. When the skeleton found has been a dog, it is presumed that this animal friend was to guide the owner safely into the next life. In addition to our dependence on animals for nutritional needs, our dependence on animals for maintenance of our health is greater today than ever before.

Animal tissue extracts have been used to meet various needs of medicine over the past century. Drugs of animal origin designed to meet the present unfilled needs of medicine are under development in both academic and industrial laboratories at this time. One new hormone derived from animal tissue, expected to be of considerable therapeutic importance has just recently been introduced into medical practice and will be discussed later.

Today, many of our major drugs are derived directly from animal tissue, primarily the tissue of cattle and hogs. In general, these tissues provide drugs that are agents in the regulation of functions of the body. They are the catalysts of the biochemical reactions of our cells and are such agents as enzymes, vitamins or hormones.

A discussion of the diseases requiring such drugs and the extent of use of these preparations may be of interest.

One common general metabolic deficiency occurs in which the patient is usually lethargic, loses incentive to exercise, gains weight, undergoes personality changes, experiences sensitivity to cold, develops a slow deep-toned speech and dry thickened edematous skin. Medical examination revals a lowered metabolic rate and a low serum bound iodine. More definitive assessment of blood chemistry indicates a lowered triiodothyronine binding capacity and a low serum thyroxine. The diagnosis is, of course, that the patient is hypothyroid or myxedematous and this is one of the medical conditions that is almost completely correctable by medication. Similar symptoms are sometimes observed in patients who have experienced surgical removal of the thyroid or have undergone extensive radioiodine therapy. The medication in

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this case is thyroid tablets which are usually prepared from pork thyroid tissue. Beef thyroid can also be used for this purpose. Two of the active ingredients of thyroid glands, triiodothyronine and thyroxine have been synthesized and can likewise be administered in tablet form.

The condition of hypothyroidism is not unusual. It is estimated that in the United States in 1975, more than 1 billion tablets were administered to the 3,300,000 persons on thyroid medication. About 59% of these were obtained from animal tissue, the balance contained the synthetic hormone.

Just as the thyroid secretes one or two substances and regulates a great number of body functions, the adrenal gland secretes at least twenty steroids and these likewise act directly to control biochemical reactions at the cellular level. These steroids were formerly obtained from adrenal tissue and administered as adrenal cortical extract. The advances of chemistry in the decades of the 40's and 50's made it possible to provide some of these steroids synthetically. The patient benefits from the use of these steroids has been especially impressive in the treatment of inflammatory conditions in the fields or dermatology and rheumatology.

Another gland of interest is the pituitary gland. This gland yields a number of regulatory hormones that are used in human medicine. One of these, adrenocorticotrophic hormone (ACTH), stimulates the adrenal to excrete the hormones produced in the cortex or outer layer of that gland. This hormone, which is peptide in structure, is used to treat inflammatory diseases in a manner similar to the synthetic steroids. The hormone has been found especially useful in rheumatic disorders such as arthritis, collagen diseases such as lupus erythematosus, dermatologic diseases and allergic states such as bronchial asthma.

It is estimated that in the United States, the pituitaries from 60,000,000 hogs are processed annually for this hormone and that 16,000,000 human doses of ACTH are administered per year. This hormone is administered by injection and, unlike the steroids, in the U.S., all of this hormone is still produced from animal tissue.

Another hormone from the pituitary gland, thyrotropic stimulating hormone (TSH), is used primarily in diagnosis. This hormone stimulates thyroid tissue to produce thyroid hormone. It has been found especially useful in combination with radioactive iodine to locate small bits of thyroid cancer that have spread to other parts of the body. In this use of the hormone, the patient is permitted to drink what has become known as the atomic cocktail, or radioactive sodium iodide. This radioactive iodide is incorporated by the thyroid and by thyroid cells that may have migrated to other sites in the body. Thyrotropic stimulating hormone is then injected for 3 to 7 days and the various body sites are scanned to determine radioactivity. If radioactivity is found at an unexpected location, it indicates that thyroid cells have migrated to that area and proper steps can be taken for their

removal or destruction. Thyrotropic stimulating hormone is also used for other diagnostic procedures relating to thyroid function. It is obtained from beef anterior pituitary glands.

Enzymes that digest protein have found numerous uses in medicine over the past two decades. Two proteolytic enzymes from the pancreas gland, trypsin and chymotrypsin, have been administered both by injection and orally to produce an anti-inflammatory effect. These same enzymes have been used topically as debriding agents to remove dead tissue at the sites of wounds, ulcers and burns.

One of the less widely known applications of proteolytic enzymes is in cataract surgery of the eye. In this application, the enzyme is used to digest the zonular fibers that are attached to the lens of the eye. In the employment of the enzyme in cataract surgery, an incision is made in the corneosclera or outer film of the eye, and the posterior chamber is then irrigated with one or two milliliters of enzyme solution. After about two or four minutes, enzymatic digestion has been completed and the excess enzyme solution is washed away. The lens is then removed mechanically and the incision sutured. The use of enzyme solution substantially reduces the number of scalpel strokes and the attendant risk of the surgical procedure. It is estimated that approximately 280,000 cataract operations in the U.S. per year are performed using this enzymatic method.

Diabetic ketoacidosis is a serious medical event and the glandular product insulin is life saving in this situation. Although most insulin dependent diabetics can be controlled by balancing their carbohydrate intake, energy output and insulin dosages, imbalances do occur. These are more frequent in the patient group who cannot be taught to regulate their insulin use to insulin requirement. Ketoacidosis does sometimes occur in careful and usually well-controlled diabetics, however, during severe infections or other illness.

Severe ketoacidosis results in the patient becoming comatose. In this condition, his skin is dry and flushed, his thirst is intense, he frequently vomits, he often has abdominal pain, he exhibits exaggerated breathing and his breath smells of acetone. He will fortunately respond to insulin treatment with gradual recovery over a 6 to 12 hour interval. Other aspects of his metabolic imbalance must also be corrected during this recovery period. For the insulin dependent diabetic, insulin will permit a nearly normal useful life. For the diabetic in ketoacidosis coma, this drug from animal tissue is life saving.

In the U.S., approximately 3,500,000 persons are diabetic and 1,150,000 are being treated with insulin. It is estimated that in 1975, 420,000,000 doses of insulin were administered in the U.S.

The therapeutic products I have mentioned were developed over the past several decades. I have mentioned only a few. The list of drugs from animal tissue includes such other important drugs as heparin,

from intestinal mucosa, bile salts from ox gall, liver extracts from beef liver, the spreading enzyme hyaluronidase from bull testes, posterior pituitary hormone from beef pituitaries and glucagon from beef pancreas. All have been introduced in this century and each has a special place in medicine.

In 1877, Sir James Paget of England described a bone disease involving abnormal calcium metabolism that he called "osteitis deformans." His accounts of the disease described wide-spread skeletal involvement and multiple bone deformity. The disease was found to be progressive and in the advanced stages, produced severe bone pain, lead to spontaneous fractures of weakened bone and occasionally to high output cardiac failure due to increased vascularity of the diseased bone. Remodeling of the involved bone frequently resulted in deformity of the vertebrae, limbs or skull. An interesting side observation made by Paget in his original article was that the hat size of one of his patients changed each year and from 1844 to 1876 increased from 22 1/2 inches to 27 1/2 inches. Photographs of the patient showed evidence of not only his deformed skull, but deformed spine and legs.

Over the years, various forms of drug therapy for Paget's disease were investigated. These were found to be non-specific and usually not satisfactory.

In 1962, Dr. Harold Copp and co-workers at the University of British Columbia discovered the presence of a calcium regulating hormone as a result of experiments wherein calcium solution was infused intravenously into a dog. Dr. Paul Munson and co-workers at Harvard Dental School then found that this hormone, later named calcitonin, could be extracted from mammalian thyroid tissue.

Armour Pharmaceutical Company initiated work directed toward the extraction and purification of the hormone from pork thyroid tissue and Dr. John Potts and his associates at Massachusetts General Hospital initiated work directed toward elucidation of the chemical structure of the Armour material. The hormone was found to be a peptide containing thirty-two amino acids. Further work on the pharmacology, toxicology, dosage form development, manufacture, and clinical efficacy was conducted by Armour in association with numerous clinical investigators in the U.S. and Europe. It was found that this hormone, injected on a regular basis either subcutaneously or intramuscularly, to patients with Paget's disease of the bone is effective in reducing the chemical and many of the clinical manifestations of Paget's disease.

The primary chemical changes associated with Paget's disease are an increased excretion of alkaline phosphatase and increased excretion of hydroxyproline. Treatment of the patient with calcitonin causes a reduction of both of these chemical indices.

The clinical symptoms of bone pain, deteriorating bone structure and abnormal bone remodeling are also corrected by administration of the drug. In some cases, with prolonged treatment it has been found that the irregular distorted Pagetic bone has been reformed into more normal bone.

The early work on calcitonin was conducted on material obtained from porcine glands. In the course of work on the species-to-species variation in the structure and properties of the hormone, Dr. Copp, the original discoverer, found that calcitonin obtained from the ultimobronchial glands of salmon was at least twenty times as active as porcine hormone. Studies of this material showed that the clinical effects of salmon calcitonin were nearly identical to those of porcine calcitonin. Because of the increased potency of the salmon sequence, it was considered feasible to synthesize this molecule on an economic basis.

Calcitonin obtained from pork thyroid tissue was first introduced as a licensed pharmaceutical product into Europe. It is currently being marketed in the U.K., Spain, France and Italy. Calcitonin of salmon sequence is prepared synthetically and is now being marketed in Europe, South Africa and the United States.

Compared to hypothyroidism and diabetes, the incidence of advanced Paget's disease is low. To those patients suffering from the advanced stages of the disease, however, the availability of this new drug is of major importance.

The professionals in the pharmaceutical industry are dedicated to providing needed diagnostic and therapeutic agents for the maintenance and improvement of human health. Many of these agents are derived from animal tissue. We are dependent upon those of you whose professional careers are related to the animal industry for providing healthy and uniform animal tissue in ever increasing quantities. The successful development of pharmaceuticals and medicinals of animal origin depends upon work you have done in the field of animal science in the past and the splendid job you are now doing. We express our appreciation.

Alpha Chymotrypsin

Ophthalmic Procedures Utilizing Enzyme	280,000

Adrenocorticotrophic Hormone (ACTH)

Number of Human Doses Per Year (U.S.)	16,000,000
Number of Pituitaries Processed Annually	60,000,000

Thyroid Medication

Number of Patients in the U.S.	3,300,000
Number of Thyroid Tablets Per Year	1,000,000,000
Percent Derived From Animal Tissue	59%

Insulin Medication

Number of Diabetics in the United States	3,500,000
Diabetics on Insulin Therapy	1,150,000
Doses of Insulin Administered Annually	420,000,000

Harold Herring: Are there any questions?

John Romans, Illinois: What percentage of insulin comes from animals?

Joseph Dailey: Oh, all of it. Insulin has been synthesized. It has about 130 amino acid residues. Two European companies are doing work on it. It does not appear to be economically possible to make it synthetically. At the moment, the raw materials to make it synthetically cost about ten times the price of the insulin from the animal tissue. So, all of it comes from animal tissue. There is a world shortage, most of it comes from beef in the United States, although some of it's from pork. The insulin from pork is almost identical to human insulin. In other words, there is only one amino acid difference. Insulin from beef has maybe four or five differences in amino acids.

Don Kinsman, Connecticut: On that, is orinase a synthetic?

Joseph Dailey: Yes, it's not insulin like. It is synthetic and is a small molecular weight drug. Its job is to conserve the insulin that is present rather than to substitute for insulin. I am not totally qualified to answer this question, but in general, the individual must be producing some of his own insulin for the orinase to be effective. In the case of insulin, it can be given to a person who is secreting no hormone at all.

Don Kinsman: What would be the relative proportion of insulin users to oral anti-diabetic agents?

Joseph Dailey: I think about a third of the diabetics are on insulin. Those are generally the more advanced diabetics.

A. W. Kotula, Meat Science Research Lab.: For years, the medical profession has been seeking to find a cure for improper bone growth in children when one leg stops growing and the other one continues. Would calcitonin work in this instance and is anybody doing anything in that area?

Joseph Dailey: Calcitonin probably would not be appropriate for that. The mechanism of calcitonin is to block the calcium coming from the bone. As you probably know, all the calcium is absorbed orally, and there is a very rapid turnover of calcium into the bone, calcium out of the bone. For example, in a rat, if we block the calcium coming out of the bone, and that's what calcitonin does, we can get a 10 percent drop in serum calcium in one hour. In children, this is likewise very rapid. In adults, it's very slow. The calcitonin was tried in Paget's Disease first, because that is a very high turnover calcium disease. Another interesting disease which is much more wide spread is Osteoperosis, where there is a general demineralization of calcium from the bone. It would be nice to stop the calcium coming out in osteoperosis, and thus maintain a normal balance rather than a continuous negative balance. That's under study, but it's not an approved indication at the moment. The condition you speak of, I think, would not be appropriate for calcitonin.

Melvin Hunt, Kansas State: Do you have any dollar value of these types of products that are used in the United States?

Joseph Dailey: No, I don't. The ethical pharmaceutical business in the United States (by ethical I mean essentially those items that are sold by prescription) is about 3 billion dollars at the manufacturers level. I don't know, but I would have to guess, that under 10 percent of that is from natural products through animal tissue. I don't have those figures exactly.

Paul Lewis, Arkansas: Can the pancreas from cattle be frozen for storage for insulin? How long can it be stored?

Joseph Dailey: Yes, pancreas glands are stored frozen and they can be stored for a considerable period of time. Both enzymes and the insulin can be obtained from pancreas glands, but the economics are such in this country that that's seldom done. It's done in some of the European countries. But it definitely can be stored for years.

Harold Herring, Armour: What is the incidence or frequency of Paget's Disease, and is there any particular ethnic group that is affected by Paget's Disease?

Joseph Dailey: I guess that there are ethnic groups that are affected by Paget's Disease. It appears to have high incidence in the United States and in North and Central Europe. It does not appear to be of any importance in Japan. The incidence of it is about 2 percent of the population over the age of 40. However, severe Paget's Disease is much more rare than that. Paget's Disease is usually picked up by the x-ray people. They will often be taking x-rays for some other purpose, and they will see a deformed bone. In most cases it can be caught before it reaches the advanced stage. Until calcitonin, there was nothing that could be done for it. So many, many more Paget's patients are showing up now that there's a cure available

Harold Herring: To continue with this morning's program on By-products Utilization, we've got for our next topic, "Batch, Continuous and Low Temperature Rendering." Since Mr. Peterson is out of the country, we're very fortunate to have Mr. L. G. Hansen give the presentation. Mr. Hansen is the Vice President and Manager of the Northern Division of Peterson Manufacturing Company of Emeryville, California. He was born and raised near Missoula, Montana, on a farm. He graduated from Montana College in Bozeman with a B.S. Degree in Industrial Engineering. He previously worked for a seed processing firm that was called Northrup, King and Company. He also worked for an aircraft fabrication group with Boeing Aircraft. He is presently General Manager of Edible and Inedible Rendering for Peterson Manufacturing Plants in northeran California.