REVIEW ARTICLE

A Brief History of Glandular Therapy: More Than Just Thyroid

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Abstract

In the late 1800s, treatment with thyroid extract caused dramatic improvement in patients with myxedema. Shortly thereafter, multiple other glandular extracts became available, both individually and in combinations. Their use gradually fell into disfavor, partly due to overpromotion by the manufacturers. The history of the use of thyroid, pancreatic, adrenal, thymus and liver extracts suggests that glandular extracts can be beneficial, especially when potential mechanisms of action and methods of preparation are considered.

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Animal glands have been valued as food and as medicine for millennia. Weston A. Price, in his book *Nutrition and Physical Degeneration*, described the dietary habits of indigenous peoples around the world that he had observed during his travels in the early twentieth century.[1]

He reported:

> For the Eskimos of Alaska the native diet consisted of a liberal use of organs and other special tissues of the large animal life of the sea, as well as of fish. … The bulk of their diet, however, was fish and large animal life of the sea from which they selected certain organs and tissues with great care and wisdom. …
>
> For the Indians living inside the Rocky Mountain Range in the far North of Canada … I found the Indians putting great emphasis upon the eating of the organs of the animals, including the wall of parts of the digestive tract. Much of the muscle meat of the animals was fed to the dogs.[2]

As scientists determined the functions of the various endocrine glands in the late 1800s and early 1900s, glandular extracts of various kinds were widely used in the medical community.[3] While medical practitioners have administered glandulars parenterally, this article focuses on oral use.

Thyroid. Thousands of years ago, practitioners in China used thyroid tissue medicinally, dried and formed into pills, or powdered and mixed into wine.[4] They also used seaweed for the treatment of goiter.

Myxedema was thought to be related to the thyroid because the thyroid glands of patients with that disease, on autopsy, were practically nonexistent. When surgeons began removing goitrous thyroids in the 1800s, patients developed myxedema, confirming that malfunction or atrophy of the thyroid caused it.[5] In 1891, Murray treated a patient with myxedema with injections of thyroid extract, with dramatic improvement.[6] Soon after, physicians successfully treated patients with oral thyroid, at first as food, later in pills.

Merck's 1905 Manual of the Materia Medica included: "Thyroidin Merck. Dried extract sheep's thyroid; 1 part represents 6 parts fresh gland … Dose: ½-1 grn. (0.03-0.06 Gm.), gradually increased to 2 grn. (0.12 Gm.), 3 t. daily, in tablets."[7]

When synthetic l-thyroxine sodium became available in the 1950s, bit by bit practitioners were steered away from prescribing thyroid extracts.[8] Opponents emphasized its variability in strength, partly caused by differences in potency between different animal species.[9,10] By the 1970s, many endocrinologists considered desiccated thyroid to be obsolete.[11] However, some patients insisted that they felt better on desiccated thyroid, and its use has continued to this day.

A 2013 publication of the results of a randomized, double-blind, crossover study of desiccated thyroid extract compared to levothyroxine, reported that nearly half the participants preferred the extract to levothyroxine.[12]

A 2021 follow-up study compared treatment with thyroxine (T4), T4 + triiodothyronine (T3), or desiccated thyroid extract.[13] Thyroid stimulating hormone (TSH) remained within reference range for all groups; a subgroup analysis of patients symptomatic on T4 alone found a strong preference for the combination therapy or for desiccated thyroid extract. A 2020 retrospective study

examined the stability of TSH values in patients on levothyroxine therapy compared with patients on desiccated thyroid and found no difference.[14]

With these recent studies, the medical world may be coming back to the position from a 1970 pharmacology textbook: "[Desiccated thyroid extract] is a highly satisfactory preparation for clinical use. Its continued popularity does not derive merely from a reactionary attitude, although at first sight the preparation might seem to be crude, old-fashioned, and poorly standardized. It is evidently uniformly well absorbed unless it has an enteric coating, and the potency is sufficiently standard that variation cannot be detected clinically if the official preparation is prescribed."[15]

Pharmaceutical companies typically process prescription forms of thyroid glandular material to concentrate the thyroid hormone, requiring the same caution as for levothyroxine. Too high a dose can precipitate iatrogenic thyrotoxicosis. Pharmaceutical products should be used in cases of overt hypothyroidism, because the amount of thyroid hormone in a nonprescription, lyophilized thyroid product is quite low.

For subclinical hypothyroidism with mild fatigue, the current author finds that lyophilized products can be quite helpful, using caution with older adults or those who are prone to palpitations. In many cases, the patient can stop taking the product when fatigue improves.

Pancreas. The function and clinical uses of the thyroid were established first among the endocrine organs because the thyroid stores the hormones it makes. Another gland that stores its products is the exocrine pancreas, and scientists also determined the digestive function of those enzymes in the late 1800s.

Pancreatic proteolytic enzymes were initially called *ferments* because their action was similar to the well-known processes of fermentation of food. Despite primitive technology, nineteenth-century scientists figured out that pepsin, trypsin, and enterokinase had different functions and that a precursor form of trypsin existed, well before the nature of protein was understood.[16,17] *Fairchild's Hand-Book of the Digestive Ferments,* published in 1898, offered oral pepsin, trypsin, and amylase for digestive issues as well as forms for injection into abscesses or necrotic tissue.[18]

Medical practitioners primarily use pancreatic extracts to treat digestive problems. Trypsin is inactive in an acid environment and pepsin destroys it, so many products have enteric coatings to protect the enzymes during transit through the stomach.[19] These coatings may dissolve at the wrong times and can cause their own side effects.[20]

Most pancreatic-enzyme preparations are made by removing fat from macerated pancreas with various solvents, as illustrated by Levin's patented process.[21] In tests of the stability of the proteases when exposed to acid and pepsin, researchers used purified enzymes and processed, defatted pancreatin. Alternate ways of preparing the product, such as lyophilization, would leave the fat intact in the product and could protect the enzymes because fat suppresses pepsin and acid production.[22]

In a study in dogs with pancreatic insufficiency Westermarck gave the dogs various pancreas preparations, including raw pancreas, and took samples from the jejunum to evaluate enzyme activity.[23] In the study's abstract, Westermarck reports: "The highest lipase activities in the jejunal samples were achieved using raw pig pancreas. Commercial enzyme preparations yielded activities that were only one tenth of those attained with raw pancreas." Westermarck also measured proteases, which were elevated with raw pancreas to about the same degree as with the commercial enzyme preparations. Westermarck concluded that raw pancreas was the most cost-effective way to treat pancreatic insufficiency in dogs. Dogs reportedly are quite enthusiastic about raw pancreas, but most humans would prefer a lyophilized product.

In addition to their role in aiding digestion, pancreatic enzymes may be helpful for other conditions, such as arthritis and cancer.[24-27] Critics would say that this is impossible, because the molecules are too large to be absorbed and proteolytic enzymes function only to destroy proteins. However, a recent review article detailed a much wider role in physiology for proteases than previously believed, because they can modulate many cellular reactions through protease-activated receptors in cell membranes.[28]

Protease-activated receptors help regulate intestinal permeability, and proteases may interact with those receptors to facilitate their own absorption.[29] Finally, since ingested pancreas can improve the digestion of food, changes in the microbiome could have a systemic effect.[30,31]

Finally, while the role of the pancreas in blood sugar control was recognized as early as 1893, and a few reports of successful treatment of diabetics with oral pancreas appeared in the 1920s, academics of the time dismissed those reports.[32,33] However, Reddy et al found that oral administration of syngeneic pancreatic extract to young diabetes-prone mice significantly decreased the development of diabetes.[34]

Adverse effects from pharmaceutical pancreatic enzyme preparations include gastrointestinal complaints, such as abdominal pain, gas, bloating, frequent or abnormal bowel movements, and sore throat.

In the experience of the current author, problems such as these are rare with the use of lyophilized pancreas. High-dose prescription pancreatic enzyme therapy in children with cystic fibrosis has been associated with fibrosing colonopathy with strictures. However, prescription pancreatic enzymes have an enteric coating. Patients have developed a similar fibrosing colonopathy with other drugs using the same enteric coating, suggesting that the issue is the coating, not the enzymes.[20]

Adrenal gland. After scientists discovered the clinical usefulness of dried thyroid gland in the 1890s, a wide

variety of glandular products came into use. Decades earlier, Addison had described patients with hypotension, nausea and abdominal pain, skin pigmentation, and eventual death, with abnormal adrenal glands on autopsy. Experimentation with adrenal removal in animals confirmed that the adrenal glands are essential to health.

Merck's 1905 Manual of the Materia Medica included: "Suprarenal Capsule, Dried, Merck. 1 part represents 5 parts fresh capsule," recommended for the treatment of Addison's disease, hay fever, and neurasthenia.[7] Clinicians used adrenal glandular material, raw or dried and formed into a tablet, to treat conditions such as asthma, with some success.[35]

Adrenaline was purified from the adrenal medulla well before the hormones from the cortex were isolated.[36] In 1920, Muirhead, a pharmacology professor with Addison's disease, devised a treatment that required 1200 mg of dried whole gland per day, orally, together with adrenaline injections. Muirhead was bedridden before beginning this treatment, improved substantially on it with clearing of his pigmentation, but after several months, deteriorated and died.[37] In a series of patients treated at the Mayo Clinic in the 1920s, Rowntree et al described the Muirhead method as being beneficial for half of the patients treated.[38]

As it became clear that the adrenal cortex made the crucial component, whatever it might be, various solvents were used to make extracts of the adrenal cortex. However, they were expensive and difficult to produce. One extract used in the early 1930s brought about remarkable improvement in moribund patients, but to make one day's dose took 600 grams of bovine adrenal cortex, from roughly 20 cows.[38] Another group gave patients 3 grams per day orally of dried, whole adrenal gland, together with a high-salt diet, using the expensive adrenal extract when a patient was in crisis.[39]

The concentration of cortisol in bovine adrenal gland is quite low, between 2 and 4 micrograms/gram.[40] The product used in the Muirhead regimen, which generated clinical improvements and resolution of hyperpigmentation, could have had no more than 0.024 milligrams of cortisol.[41] The extract made with 20 cows worth of adrenal cortex could have had at most 3 milligrams of cortisol, probably less given inevitable losses in processing. While some clinicians worry about adrenal suppression when they hear a patient has been taking adrenal glandular, the supplement can't contain enough corticosteroid to cause it. A 200 mg capsule would require roughly one gram of raw material to produce, containing only 4-5 micrograms of cortisol.

Oral adrenal glandular materials fell out of use by the medical establishment when manufacturers devised methods of large-scale corticosteroid production in the 1940s. The side effects of corticosteroids were recognized fairly quickly; as early as the 1960s, caution was advised in their use.[42]

Given that astute clinicians in the 1930s saw improvement in seriously ill patients with products that couldn't have contained a significant amount of cortisol, something may be in the whole gland, whether raw, dried, or crudely extracted, that can help support a weak adrenal gland. Further research on this subject might prove valuable.

The concentration of catecholamines in bovine adrenal medulla is roughly 75 micromoles per gram.[43] Using the molecular weight of epinephrine and considering that the medulla is roughly 30% of a bovine adrenal, the whole adrenal would have about 4 mg of catecholamines per gram. A 200 mg capsule of adrenal would then contain about 0.8 mg of catecholamines.

It's difficult to assess the potential toxicity of this dose of catecholamines because physicians typically administer epinephrine, one of the adrenal catecholamines, parenterally or via inhalation, not orally; so no data on oral pharmacokinetics is readily available.

A review article about epinephrine in anaphylaxis states that it' is rapidly degraded in the intestinal tract by catechol-O-methyltransferase.[44] In Warren et al's study of the pharmacokinetics of inhaled epinephrine, healthy volunteers inhaled 2.4 mg of epinephrine, followed by an additional 4.8 mg.[45] The doses were well tolerated, causing a short-lived increase in physiological tremor.

In the current author's experience, it's important to take adrenal glandular with food. Adrenal glandular can cause nausea, abdominal pain, headache, and heart palpitations, especially if taken on an empty stomach. Taken late in the day, it can cause insomnia. The product is generally well tolerated and helpful when started with a fatigued patient, but with clinical improvement, it may begin to cause symptoms. requiring discontinuation. Practitioners should use caution with older adults and those prone to heart arrhythmias as well as with those on stimulants and monoamine oxidase inhibitors.

Thymus. While writers have described the structure, location, and tastiness of the thymus gland for centuries, together with its prominence in infancy and its involution with age, it was the last of the glands to have its function determined.[46] Surgical removal of the thymus from adult animals had no ill effects.

In 1961, Miller reported that thymectomy of mice in the first few days of life resulted in lymphocyte depletion, immunological defects, and susceptibility to infection.[47] His findings were met with considerable skepticism, because at that time, immunologists generally believed that the thymus was a "useless organ," at best a "graveyard for dying lymphocytes."[48] His later experiments led to the discovery of the origins and functions of B-cells and T-cells; one critic likened "B and T cells to the first and last letters of the word 'bullshit.'"

By this time, the medical community had almost entirely abandoned the use of glandular products. Excessive promotion of them had occurred in the early

1900s, with advocates encouraging the simultaneous use of extracts of multiple glands, making it hard to determine which, if any, were beneficial.[3] But in the case of thymus, researchers found that calf thymus extracts restore immune function in thymectomized neonatal animals.[49] Manufacturers then began making extracts of thymus tissue to treat disorders of the immune system.

Several studies in the 1980s used the thymus extract thymomodulin, an acid-processed and partially-purified product. A 1989 review article reported that it was helpful for infections and allergies and that it improved immunologic functions in older adults.[50] In a retrospective study of 130 patients with different illnesses who received thymomodulin, those with an initial CD4+/CD8+ ratio outside the normal range (whether high or low), had a normalization of the ratio.[51]

In a double-blinded study of children with atopic dermatitis and food allergies, 10 children received oral thymomodulin during an initial elimination of food triggers, while nine children received a placebo.[52] Both groups had improvement of their skin during the elimination phase, but on food challenge, the placebo group had a marked worsening, while the children receiving thymomodulin had fewer cutaneous symptoms.

In another study with adults with mild asthma, eight received thymomodulin orally, and eight received a placebo.[53] At 90 days, the group receiving thymomodulin showed significant improvements in their bronchial responsiveness to methacholine.

A 1998 publication about a different product, Complete Thymic Extract, reported that it was ineffective for patients with chronic hepatitis C who had infections that hadn't responded to interferon.[54] That study was motivated by advertising for the product as a treatment for hepatitis C and didn't provide exact amounts of the ingredients, mentioning only "bovine glandular extracts of thymosin, thymopoietin, and thymic humoral factor," together with vitamins, minerals, and herbs. The outcome makes it clear that the advertising for the product was irresponsible. However, it is still possible that thymus extracts are valuable in other, less severe conditions, as the other studies mentioned above would suggest.

Liver. In the 1920s, Minot and Murphy reported success in treating pernicious anemia with a diet of a half-pound of liver daily; since most patients didn't want to eat that much liver, physicians used liver extract instead.[55] Investigations into the active component led to the discovery of vitamin B12. Liver has been widely recommended as part of a nutritious diet.

A 2012 article described an increase in exercise tolerance in mice given an oral suspension of a liver hydrolysate, Conclevan.[56] Yeh et al recently reported that liver hydrolysates, orally administered, can improve insulin resistance in a mouse model of diabetes.[57] Yamada et al found that liver can attenuate hepatic damage from ethanol in rats.[58]

Other glands. A wide variety of glandular materials have been used medicinally, such as brain, hypothalamus, spleen, aorta, intestine, and parathyroid. However, as pharmaceutical usage exploded in the mid-1900s, glandulars went out of fashion, and researchers were no longer interested in investigating their usefulness. Theoretical discussions of possible mechanisms of action may give some support to the clinical observations of practitioners who recommend them.

Possible Mechanisms of Action

Oral tolerance. When an antigenic substance is taken by mouth, the body's reaction to that antigen may downregulate.[59] Because autoimmunity causes many of the problems related to glandular malfunction, taking glandular extracts orally might decrease autoimmunity and thereby improve glandular function. Trials of oral tolerance to autoantigens have met with mixed success in the past, but subsequent researchers speculated that this may be due to issues with the gut microbiome.[60] Trials of oral tolerance in food allergies have been more successful.

In the current author's clinical experience, hypothalamus glandular can be helpful for depression and chronic fatigue. In a 2021 study, De Bellis et al tested patients with chronic fatigue syndrome for antihypothalamus antibodies[61]; 33% of the patients had the antibodies, and those with higher titers had more severe symptoms than those without such autoantibodies. Those with higher titers of antibodies also had depressed levels of adrenocorticotropic hormone (ACTH) and cortisol.

Hormonal factors. Oral ingestion of thyrotrophin-releasing hormone (TRH), a hypothalamic hormone, can stimulate release of thyroid hormones.[62] While the amount of TRH in a hypothalamus glandular product is quite low and provoking hyperthyroidism with a hypothalamus glandular is unlikely, nonetheless ingestion of a glandular product could subtly alter the function of other body organs via substances in the administered gland.

MicroRNA. These short segments of RNA regulate posttranscription gene expression by their effects on messenger RNA. A 2015 article reported that several microRNA segments in bovine tissues are homologous to human microRNA and are stable to various cooking and processing methods.[63] In a review article about dietary microRNAs, Mar-Aguilar et al reported that they had confirmed that bovine microRNA is stable to cooking methods, but that there was no change in blood levels of these microRNA after consumption of a beef meal.[64]

Exosomes. Exosomes, also called extracellular vesicles, are small membrane-bound packets of material that contain messenger RNA, proteins, or microRNA. While an organism uses them for cell-to-cell communication, scientists have also found them in foods, and they can be absorbed from the intestinal tract.[65]

Methods of Preparation

The most cost-effective way to ingest glandular products is simply to eat them. However, most people choose not to eat animal glands, and because they are unpopular, they can be difficult to obtain. Glandular tissue must be collected and processed in a way that creates a stable product suitable for tablets or capsules. Commonly used methods include azeotropic processing, salt precipitation, and lyophilization.[66]

Azeotropic processing. The glandular material is frozen, then washed with a solvent to remove the fat. The solvent is distilled off and the remaining material is dried and ground into a powder. By removing the fat, fat-soluble products are also removed—good in case of toxins and bad in the case of essential fatty acids and fat-soluble hormones. Also, traces of the solvent remain.

Salt precipitation. The glandular material is ground in salt and water then centrifuged to separate the heavier proteins from the lighter fat. The process does not de-fat the material with potentially toxic solvents but beneficial materials in fat are removed, and the product becomes high in salt.

Lyophilization. Also known as freeze-drying, this method simply involves freezing the material, then removing the water at low pressure and low temperature. Unlike the other two methods, the fat remains in the finished product, together with fat-soluble materials and many other components that might be degraded or removed by the harsher processing of the azeotropic or salt-precipitation methods. For materials obtained through this method, it' is important that they be from animals that are raised in an environment that is as clean as possible.

Adverse Drug Reactions, Contraindications and Drug Interactions

Many of the articles discussing the use of glandular products involve small numbers of patients and don't discuss adverse reactions or interactions. For the thyroid, pancreas, and adrenal glands, which respectively store thyroxine, pancreatic enzymes, and adrenaline, this article discussed adverse reactions and contraindications in their respective sections. For the rest, no specific published information is available, and the current author's experience is that patients tolerate them well.

Because glandular products are animal products, meat allergies would be expected to cause reactions. Patients with alpha-gal syndrome should certainly avoid glandular products, although one study reported that two such patients with pancreatic insufficiency were able to tolerate porcine pancreatic enzymes, despite positive skin-prick testing.[67]

Most glandular products are from a bovine source, since it is easier to collect tissue from larger animals. It is critically important to use good-quality materials to avoid the prions that cause bovine spongiform encephalopathy (BSE). Even before the advent of BSE, Australia and New Zealand had strict restrictions on the importation of animals and animal products for many years.[68] No cases of BSE have occurred in Australia or New Zealand, and their governments are vigilant in the defense of their meat industries.[69]

Conclusions

This overview provides historical data to support the continued medicinal use of glandular extracts, especially for patients with autoimmune disorders. These products were widely used at one time, but the medical community eventually dismissed them because of excessive marketing, and because of the advent of pharmaceutical products that were felt to be more "scientific." With current, improved abilities to measure markers of autoimmunity and inflammation, it is now feasible to conduct investigations to see whether the clinical value that some practitioners place on these products is warranted.

Author's disclosure statement
The author declares that she has no conflicts of interest related to the study.

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