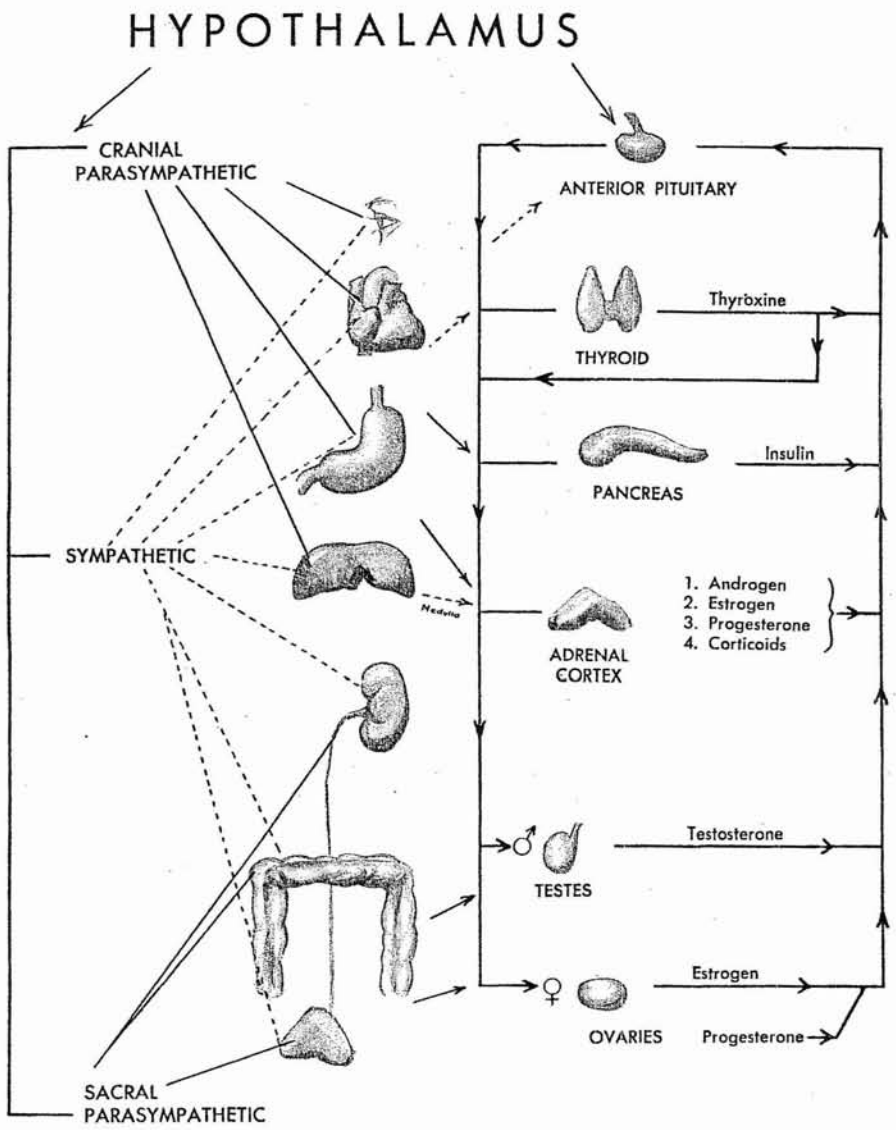

The GP and the Endocrine Glands

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Dedicated to my parents

The A. L. Rubels

Preface

So presumptuous a project as another book addressed to the physician seems to demand an explanation; first, in answer to the legitimate question, "Why write the book," and second, to provide a delineation of the make-up and divisions of the work.

The objective in these pages is to bring to the attention of the medical practitioner the relationship that exists between endocrine dysfunction and many conditions, frequently encountered in daily practice and often consider mental or emotional aberration. There is generally a firm physiological basis for these symptoms, many of which are discussed in the following chapters, together with a satisfactory rationale of therapy which has in my practice proved successful—the definition of success being in this case the return of the patient's physiology to a normal, symptom-free existence.

In many medical treatises there are discussions and reports of meticulous research work done on laboratory animals. These reports, interspersed in the general context of the article, although valuable to the experimenter, often cloud the issue and arrive at a point of little or no practical importance to the doctor in general practice. It will be my effort in this book to avoid all digressions of this type, the proof of my statements being contained within some or all of the references listed at the end of each chapter.

The text of the following pages is meant to convey a simple, logical, integrated presentation of symptomatology,

with an explanation of the physiology pertinent thereto, the philosophy of therapy becoming thus obvious. The more controversial points are eliminated; and since this is primarily a discussion of functional endocrinology, pathological problems, such as pheochromocytoma, basophilic tumors of the pituitary gland, of the thyroid, and of the uterus, pituitary dwarfism, acromegaly, and Simmonds' cachexia are not within the scope of this text.

The objective here will be those conditions that are considered functional rather than pathological. Aberrations of functions display patterns of symptomatology very definite in character, and capable of being diagnosed by their presence or absence. Were the tissue whose function is involved to be examined microscopically, there would be found no pathological change. This type of disorder deserves clarification because too often the diagnosis is relegated to a classification of mental or emotional. The person suffering dysfunction can be helped, and often the problem can be traced back to a definite physiological abnormality.

Dysfunction of the glandular system, nervous system and nutritional support are of concern in connection with "balance" or equilibrium. Balance does not mean that a specific part of the body is not functioning, but rather that it is not functioning in a synchronous, correlation to other parts of the body. There is no one facet that can be solely responsible for illness with no connection to other aspects of the physical body. Therefore, disorder of the endocrine gland system affects the nutritional system, nervous system, mentality, personality, physical appearance and the general health of the person. The clinician is expected to be fully conversant with these problems and their therapy, since this imbalance is the most common single problem of general

practice. The obvious pathological condition, while requiring considerable acuity of diagnostic ability, is a definite, tangible, structural, physical change in the part in question. Dysfunctions and derangements herein discussed are within the ability of all doctors to diagnose and there are certain laboratory aids which definitely point the way. The therapy should be directed toward reestablishing normal balance and normal synchronism with all other parts of the body, rather than being aimed at a specific function as would an anticoagulant.

The objective of the book is to indicate the overall integrated physiology of the human body, one part with another. While each chapter will treat a particular aspect, nevertheless, it is the author's hope that the chapters will be so connected that interrelationships become obvious. The liver in relation to the glandular physiology and the autonomic nervous system will be discussed in one area, while protein metabolism with its relationship to liver physiology, to each endocrine gland, and to the autonomic nervous system will be taken up in detail in another section. Each individual member of the endocrine gland system will be discussed separately and there will be chapters on disease conditions very commonly found in all physicians' practices.

It is intended that underlying and running through these discussions will be an impression of interdependence and physiological co-ordination, connecting each tissue with every other tissue. The disease processes alluded to in some chapters and based upon the observation and therapeutic management of numerous other physicians in general practice are not only illustrative of the specific condition mentioned, but they can be cemented into a philosophy applicable to all functional aberrations. The manifestations peculiar

to the individual patient are often related to the patient's heredity (genes and chromosomes), the weakest link in the chain allowing one tissue to fail before the process becomes apparent in a stronger tissue.

It is my intention also to point out the dependence of endocrine gland functional imbalances to nutrition. Many patients would not be suffering from ill health had their nutritional intake throughout their formative and adult years been adequate in each of its constituents. It has been my experience to find patients, obese by nature, who have attempted to correct the obesity by dieting, only to so deplete their nutrition, that in self-defense the thyroid gland decreased its activity, with a consequent lowering of metabolism in order to preserve life. The decrease of metabolism and of production of thyroxine in turn caused an increase in production of tropic hormones from the pituitary gland. The end result was that the patients presented symptoms of hyperpituitarism, although at the bottom of their problem was faulty dietary intake. The patients would not show microscopic evidence of pathology, but would in many metabolic functions indicate an imbalance of the endocrine gland system with particular reference to the anterior pituitary gland.

It was intended that this book be written in such a manner that each point follows in logical order. There are so many relationships, interdependencies, and simultaneous functions that many times it has been quite difficult to carry out this proposal. Accordingly, I did not subdivide and break into categories each function and each physiological action, but tried rather to integrate this discussion in order that the whole underlying philosophy would become apparent.

Contents

Protein

Protein is necessary for every cell, organ, tissue, and function of the human body. It is united with other foodstuffs to form cell walls. It becomes a part of the cell protoplasm and as such has enzymatic action. Recent experiments indicate that, while many of the protein constituents of the protoplasm were formerly considered inert, given a specific antigen these protein molecules become enzymes in their own right. Protein molecules in the blood stream, both as serum protein and as constituents of the blood cells, are carrying agents for other enzymes, minerals, fats, sugar, vitamins and hormones. The hormones themselves are protein in nature. The pituitary gland, the adrenal gland, and the gonads unite molecules of protein with molecules of another substance, in these instances cholesterol, to form their steroid hormones. The thyroid unites proteins with iodine. The pancreas joins protein with zinc. These combinations may also contain fats and sugars in which case they become lipoproteins or glyco-proteins. The protein supply as such is not stored in the body. Only the necessary requirement of a cell is present at any given time. There are instances of severe dehydration or accompanying hemorrhage, diarrhea, profuse vomiting, sweating, or high fever in which the protein concentration apparently is elevated but this is simply a relative increase accomplished through dehydration. The actual content of protein is not changed, but is concentrated.

The protein in one compartment of an organism may be drawn upon to supply deficiency in another compartment. The University of Illinois proved that for every gram of protein in the blood stream a healthy joint surface requires 30 times as much. The relationship of protein in the joints as compared to that in the blood stream is in the ratio of 30 to 1. Protein must be picked up daily from the diet.

When the protein intake equals the output we have a condition of protein balance, otherwise expressed as nitrogen balance. When it is metabolized more rapidly than it is replaced, there is a negative nitrogen balance. This occurs in conjunction with disease, hemorrhage or increased metabolic processes. If protein is used normally but the intake is less than normal, or assimilation or digestion is disturbed, this also results in a negative nitrogen balance. In order to have an adequacy in the blood stream, it is necessary to have sufficient protein intake. This is achieved by eating a variety of protein foods, such as meat, milk, fish, fowl, eggs, cereal, and the vegetables with a higher content of protein. A variety is absolutely necessary.

When ingested, this food is acted upon in the stomach by hydrochloric acid and pepsin. Here there is a breakdown or hydrolysis from a natural state to intermediate substances known as polypeptides and proteoses. The acid content of the stomach has been determined in the average normal person to be ideal at the age of 25; at the age of 40 there is 15 per cent less hydrochloric acid in the stomach; at the age of 65 there is but 15 per cent present of the amount produced when at 25 years of age. It is apparent that many people are predestined to have a failure or fault in the first stage of digestion. The acid content of the stomach is influenced by emotions, by tensions, by exercise and activity,

and by food intake. The person who has been unable to eat protein food has not provided a stimulus to the stomach for hydrochloric acid production; therefore there is a deficiency of hydrochloric acid due to starvation.

Among the signs and symptoms of low gastric acidity are anemia, the apparent lack of desire for protein foods, flatulence, and gaseous distention of the stomach shortly after eating, or even before the patient has finished eating. This is high in the abdomen pressing upward on the diaphragm. It is relieved in some instances by belching; in some it causes embarrassment of the diaphragm excursion with a resultant short-windedness or cardiac palpitation. Pruritus ani may be present due to the fact that the fecal material is too alkaline, never having been completely acidified in the stomach.

When the polypeptides and proteoses are emptied through the pyloric sphincter of the stomach into the intestines they are acted upon by secretions from both the intestinal wall and more particularly the pancreas. The pancreas functions on the basis of foodstuffs present in the duodenum as a precipitating stimulus to secretion. It is also influenced by the degree of acidity of the stomach. An adequate acid present in the stomach will increase the secretion, the consistency, and the quality of the enzymes manufactured and secreted by the pancreas. These are in the form of proteolic, amylolytic, and lipotropic enzymes. As you will remember, all enzymes are of a protein nature. With severe protein deficiency the body is attempting to conserve all proteins. There often is an insufficiency of the pancreatic production due to a lack of protein in the blood stream.

One of the essential amino acids derived and from which protein receives its reputation as a lipotropic agent

is methionine. Methionine is the precursor to choline and inositol. Choline is an essential lipotropic agent both in the intestine and in the liver. In the absence of choline, which reverts back to an absence of methionine, there is a deposition in the liver of products known as phospholipids. Phospholipids are the form that fat assumes in order to be transported from the intestinal tract to the liver. In the transport of fat and fatty digested material the cell wall of the intestinal tract unites the essential fatty acids, the fatty acids of all types, with phosphorus forming a phospholipid which is carried through the portal system to the liver. The phospholipid as such is deposited in the hepatic cell. In the presence of choline, the phospholipids unite with the choline to form lecithin. Lecithins are the movable forms of fat. Without choline, the liver retains the phospholipids which show up grossly and anatomically as fatty degeneration or fatty metamorphosis. This is the first stage of cirrhosis. Choline is instrumental not only in uniting phospholipids to form lecithin, but as a lipotropic agent in that it will combine fatty deposition of the blood vessel walls with itself, again to form lecithin, to move the fatty deposition and fatty plaques or atherosclerosis from the blood vessel wall. Acetyl choline is a metabolic product of choline and is an essential element relating to the integrity of the parasympathetic nervous system.

Protein through the action of proteolytic agents and vitamin and mineral catalysts is broken down into amino acids. The amino acids are absorbed and assimilated through the intestinal wall, and carried through the portal circulation to the liver. There are 10 essential amino acids; two of them, arginine and histadine, are considered essential only to growing youngsters, but for the purposes of discussion

will be included here to make a total of 10 essential amino acids. The body actually uses, our knowledge at the present time indicates, 26 amino acids. Of these 26, 16 can be synthesized in the body primarily in the liver from the 10 essential amino acids. The body is unable to manufacture the 10 essential amino acids; therefore, these must be supplied in the diet. The essential amino acids are: methionine, valine, threonine, tryptophane, arginine, histadine, phenylalanine, isoleucine, leucine, and lysine. Essential amino acids have a further peculiarity in that they must all be present at the same time. If nine of the essential amino acids are present, none of them will be used in adequate quantity. It is somewhat similar to the coopers of old who used to make barrels, and in the process found it necessary to use staves. If in imagination we consider each stave to be a separate amino acid and are going to make a barrel using 10 staves, the barrel will hold fluid only to the height of the shortest stave. Thus it is with the essential amino acids. If nine of them are present in adequate quantity but the tenth one is present in a very small amount, the body will use the ten essential amino acids until it has used the tenth one completely which was the one in short supply; after which time the other nine are wasted, discarded and excreted.

This stage of protein physiology can be considered the phase relative to digestion and assimilation. A person complaining of lack of desire for protein foods, or of flatulence, colon irritability, or anemia, may be suffering from a fault at this point. However, should the patient indicate that he has a good appetite for proteins and does not complain of flatulence either immediately after eating (which would be due to the lack of hydrochloric acid in the stomach), or several hours after eating with the gas low in the abdomen

(which might be due to absence of proteolytic enzymes in the intestinal tract) it is possible that there is very little or no perversion of physiology to this point.

It is essential in the digestion, assimilation, and absorption of protein foodstuff that there be acceptable vitamin and mineral content to act as catalytic agents in the breakdown of the more complex protein molecule, as well as in the assimilation of the amino acids. There must be an intact cell wall of the intestinal mucosa, as well as good permeability which is enhanced by the presence of the flavonoid factors and vitamin C. Vitamin B complex is essential to the breakdown of foodstuffs, so it is beneficial in the digestive process that adequate vitamin and mineral constituents be available. Vitamin C is also an essential factor in the adrenal cortex. Prior to the use of ACTH it can be demonstrated that there is a supply of vitamin C and cholesterol in the adrenal cortex. Subsequent to an injection of ACTH the vitamin C content and that of cholesterol are depleted, indicating that vitamin C is an essential constituent to the normal action of the adrenal cortex.

In the liver the amino acids are deaminated or transmethylated or transaminated for the synthesis of other amino acids; or, in the process of gluconeogenesis, they provide carbohydrate for Krebs cycle, with the by-products of ammonium, urea, carbon dioxide and water. After the amino acids have been duly processed in the liver (this is taken up in more detail in the chapter on liver physiology) they are available in the general circulation.

Even with an abundant supply of raw material in the form of protein food, and despite good gastric digestion, followed by intestinal hydrolysis, and normal liver function, the amino acids will not be used unless there is present a

normal physiological supply of the gonad hormones. The cell protoplasm will not unite with the blood amino acids except in the presence of normal quantities of sex hormones. This points up the fact that protein physiology involves a major portion of our body functions, as well as being necessary in each individual one. When the amino acids unite with the cell protoplasm we have a normal, healthy, living cell. The cell may flourish or sicken depending upon fluctuation in its supply of carbohydrate and lipid material. However, in the absence of protein the cell will inevitably sicken and die.

Endocrine hormones become protein anabolic or catabolic depending on the periods in life in which they are being considered, and depending upon their quantity.

During youth the pituitary growth hormone is a normal anabolic product, when supplied in normal physiological quantity; however, at times of pituitary overactivity, a pituitary drive is set up leading to disturbances of body configuration, increasing gluconeogenesis (transformation of available protein to sugar) leading to overweight. In this case the patient does not grow properly, becomes overly tired, has skin difficulties such as acne. A female may develop lack of progesterone with consequent dysmenorrhea. Since the youth is usually trying to keep up with classmates, resulting in a lack of sleep, he becomes tired, irritable, and eats improperly to keep weight down. In many of these instances there is an excess protein catabolism with a negative nitrogen balance.

Also in youth thyroid hormone is protein anabolic in normal physiological amounts, but in excess amounts is catabolic. The control is usually mediated by the available protein in the blood stream, since it takes an adequacy of

proper protein, especially that of tyrosine, to produce sufficient thyroxine.

As youth grows into adulthood, the pressure of business, lack of rest, a fast or higher standard of living, pregnancy and lactation, all result in a predominance of protein catabolism. With an increase of catabolism the body may draw from the total supply of protein, which could well be taken from any or every cell of the body.

At the climacteric stage of life there is no production of estrogen or progesterone, or testosterone, and the pituitary becames overactive in setting up a drive to find these hormones. Since there is no ovulation, the adrenal gland will be expected to supply these hormones with its products of estrogen and androgen. The pituitary drive to make this function occur causes some added stimulation of corticoids of the adrenal, forcing gluconeogenesis or a breaking down of protein in the liver. It is here very necessary that protein support and substitution with gonad hormones be supplied until the adrenal gland can produce its own, in order to prevent a severe depletion.

At the stage of senility, lack of steroids from the adrenal cortex may be the cause of protein deficiency, because these steroids are generally considered to be anabolic. From the foregoing statements it can be easily seen that a deficiency of protein is a very common and probable condition.

There is no disease, illness, or abnormality in the body that is not in some way related to protein metabolism.

This book is more particularly concerned with the endocrinological aspects of protein metabolism. It is however not possible to separate depletions of purely endocrine origin from those due to infection, injury, toxemias or other causes. With a hypoproteinemia any tissue can show symptoms,

since protein in one compartment of the body is capable of being transferred to another compartment of the body. The symptomatology will relate to that tissue which has surrendered its protein.

Arthritis is one of the very common conditions that is definitely related to this protein metabolism. In many arthritics there is an anemia, secondary in nature, and with all evidences of inflammation. Any inflammatory process metabolizes protein at a highly elevated rate. A patient running a high fever will be burning protein much more rapidly and present a much greater degree of hypoproteinemia than a person who is simply not eating enough protein. It has been found that the joint surfaces and the synovial membranes contain 30 grams of albumin for every gram present in the blood serum. In arthritis the body, in making an effort to maintain a blood serum level of albumin, will draw from these joint surfaces some of their protoplasmic albumin. When this activity has progressed to any degree, normal motion of that joint becomes trauma, with the consequent inflammatory reactions of trauma. The use of cortisone products and ACTH is helpful because they cause the release of albumin from muscle tissue and hence make it available to the blood stream and to the joint surfaces decreasing the irritability, inflammation and arthritic manifestations in the joint. This is accomplished at the expense of muscle tissue, and if long continued leads to protein depletions in other tissues even though the arthritic process has been relieved.

The same mechanism can be applied to bursitis, wherein the blood stream in its effort to maintain a normal level of serum albumin causes withdrawal from the joint surface and the synovial capsule of its albumin. Calcium in the

body is carried united with albumin. When the albumin has been withdrawn, the calcium is left as a precipitate and thus calcium deposits are discernible by x-ray examination in the condition of bursitis. The replenishment of protein to that joint causes the reuniting of calcium with albumin and hence absorption of the calcium nodule with consequent relief of the bursitis symptoms.

Whenever the body is undergoing an excessive gluconeogenesis and protein is being pulled from the peripheral tissue to the liver, the peripheral tissue is depleted of protein and the sugar metabolism of the tissue is also involved. When the body is successful in the breakdown of protein to sugar, the sugar enters peripheral cells carrying with it water. These patients have a tendency to become solid, firm and obese. When gluconeogenesis is not successful in supplying adequate sugar to the tissue the patient will present hypoglycemia as well as hypoproteinemia. The hypoglycemia can be evident in the nervous system—when the nerve tissue does not have a supply of sugar, inflammatory reactions start. There is an abnormal transmission of impulses, and neuritis and neuralgia are the consequence. Whenever the body withdraws protein from the periphery to supply the liver functions the symptoms will be evident in the tissue that released protein. When mucous membrane lining the stomach or the intestinal tract gives up its protein, the result is gastric or duodenal ulcer, spastic colon or colitis. Should the mucous membrane lining the sinuses relinquish its protein, bacterial infection finds a fertile soil in which to propagate, and sinusitis ensues.

Albumin is formed in the liver and is the supply of available protein to the body cells. Whenever the albumin falls below a normal level, the peripheral interstitial tissues

hold water due to disturbances in the oncotic pressure in the blood stream. This is explained in the chapter on liver physiology. Edema, ascites, thoracic cage fluid, semi-circular canal fluid, or any peripheral tissue fluid present is an evidence of a low albumin concentration in the blood stream. As a further follow-up on this statement the liver undoubtedly can not be producing sufficient albumin; therefore, a liver involvement or a failure to provide adequate protein intake is evident. The state of the skin, hair, and fingernails is an excellent criterion of the level of protein availability. Coarse brittle hair falling out easily, dry hard skin cracking and splitting, or fingernails that flake, are brittle, break easily, or do not grow properly are all the result of deficient protein supply.

The great majority of symptoms that are presented to the physician in his office today are the result of inadequate supply of available protein in the blood stream of his patients. In most instances protein deficiency can be detected by clinical signs and symptoms. When this is not the case, it is possible to resort to the laboratory for help.

For evaluating protein metabolism from the standpoint of laboratory tests and results, it is advisable to have a total protein, serum albumin, serum globulin, and albumin-globulin ratio examination made. The report of a total protein above 6.5 gm per cent is acceptable. A report of a total protein below 6.5 gm per cent indicates protein deficiency. However, the total protein is perhaps the least important information that can be achieved from this laboratory survey. Far more important is the serum albumin, which should give a reading of 4.5 gm per cent or above. The serum globulin is the most important single item that can be gleaned from these laboratory tests. Serum globulin

3 gm per cent or above is abnormal. A serum globulin from 1.5 to 2.9 gm per cent is within normal range but a serum globulin of 3 gm per cent or above indicates that the body is causing withdrawal of proteins (albumin) from some compartment of the body in order to maintain an adequate serum albumin level in the blood stream.

As serum albumin is withdrawn from these cells, globulin, which is a much larger molecule, is also pulled from the protoplasm of the peripheral cell and hence there is a rise in the globulin level. The reticulo-endothelial system manufactures globulin and under normal circumstances provides a level of serum globulin between 1.5 gm per cent and 2.9 gm per cent. In the event of a decrease of available albumin in the tissues the body, in order to maintain a level compatible with good health, draws into the blood stream from the protoplasm of other cells the albumin that already had been united therein. Along with this withdrawal of albumin, globulin is pulled into the blood stream, then a blood laboratory report shows a globulin of 3 gm per cent or above. The patient definitely is suffering from hypoproteinemia.

If a cholesterol check on this same blood is found to be abnormal (the cholesterol normally is acceptable with readings of 150 to 250 mgm per cent) it will be definite evidence that the liver is not producing albumin adequately and that the liver function is not normal. Our attention will have to be directed to correcting the liver physiology as discussed in the chapter on liver. Should this blood be further tested to determine the level of PBI and that level found to be raised obviously the body is not able to support an increased metabolism and is running out of protein. If the level of PBI is low as it is in most cases, it possibly is low

because this albumin is the same protein that is used to unite with iodine to form PBI. An inadequacy of protein could lead to a low PBI reading. Nevertheless, it must be borne in mind that a low PBI reading could just as well be a compensatory response on the part of the body metabolism in order not to overtax the available supply of protein. The albumin-globulin ratio normally should be 1.5:1 and limits are considered to be 1.5:1 to 2.0:1. However, the albumin-globulin ratio can be normal, the total protein can be acceptable, the albumin can be within reasonable range, but if the globulin is 3 gm per cent or above the body is maintaining all of these other factors at the expense of robbing body tissue to provide protein to the blood stream.

A simple blood count, i.e., the red blood cells, will indicate hypoproteinemia in any instance where the count falls below 4,500,000 r.b.c. per cubic centimeter. Without protein the bone marrow can not manufacture red blood cells and as a consequence secondary anemia is produced.

A new test has been devised to determine the component parts of the protein examination. This test is known as electrophoresis. It is concerned with the motion of protein molecules when placed in an electrical field and allowed to move at will on specially prepared paper. After a given length of time the paper is removed from the bath and a photoelectric cell measures the intensity of the dye accepted by this paper, the dye intensity depending upon the concentration of the specific protein particle present. The photoelectric cell graphs the color intensity and these graphs are then available to be studied by the examining clinician. The field is as yet very new and not completely developed.

From the present research work it is obvious that protein molecule movement forms specific patterns in specific disease

entities. The specimen obtained in this manner is compared to a library of previous electrophoretic patterns. The library is made up from known cases followed through to their expiration and checked by autopsy. The particular pattern followed by that blood during life forms the basis of comparison upon which diagnosis of a given specimen is made. Certain specific diseases are capable of being identified by this means.

The graph shows the component parts of the protein in the plasma and serum. These particles are divided into albumin and globulin, the latter particles being further subdivided into $alpha_1$, $alpha_2$, beta, and gamma globulin. The gamma globulin divisions are an indication of the resistance of that person but in certain abnormalities the gamma globulin shows an enormous rise in concentration. The alpha, beta, and gamma globulins can all be graphed and have specific peculiarities that are taken as a standard. A deviation from this normal indicates disturbances in these fields of protein metabolism. The overall picture should indicate that the albumin presents at least 60 per cent of the picture, and the globulin section should then make up the remaining 40 per cent. The total of the albumin-globulin components will always equal 100 per cent. The other components of the protein in the serum, namely, the fibrinogen, have been removed in the clotting process as this blood test is run specifically on the plasma. With the albumin a normal 60 per cent, the 40 per cent globulin is normally found to be represented in approximately this proportion: $alpha_1$ 5.+ per cent, $alpha_2$ 8.+ per cent, beta 14.+ per cent, and gamma 13.+ per cent. There are small fractions of each section but the accuracy to date is not perfected to the point where these are important. The specific

conditions known at the present time to be capable of diagnosis by electrophoretic pattern contain:

HYPOPROTEINEMIA. Nutritional protein deficiency usually results in a decrease of albumin and gamma globulin and an increase in $alpha_1$, $alpha_2$, and beta globulin.

MULTIPLE MYELOMA. The electrophoretic analyses reveals $alpha_1$, $alpha_2$, and beta globulin as normal, but with an increase of gamma globulin. In the urine a greater per cent of the protein is globulin.

RHEUMATOID DISEASES. Increases are observed in the alpha, beta, and gamma globulin.

INFECTIOUS MONONUCLEOSIS. Increases are observed in the gamma globulin with an occasional increase in $alpha_2$ and beta globulin.

MULTIPLE SCLEROSIS. Decreases are observed in albumin and in albumin-globulin ratio with increases in the $alpha_2$ and beta globulin separation.

HEMOCHROMATOSIS AND DIABETES RESISTENT TO INSULIN. The abnormally high insulin requirement accompanied by a high gamma globulin content of the serum is evidence of insulin inhibiting antibody formation. The gamma globulin content and the insulin requirement are decreased with the administration of ACTH.

MYELOID LEUKEMIA. A consistent globulin increase was observed.

NEPHROSIS. Decrease observed in the concentration of albumin, $alpha_1$, globulin and gamma globulin with an increase in the concentration of $alpha_2$ globulin and beta globulin.

The speed, accuracy, and adaptability of this laboratory routine as a diagnostic aid, together with the expanding list of diseases or conditions that may be analyzed electro-

phoretically, point directly to the position of importance that paper electrophoresis is assuming and maintaining in clinical laboratory methods. There are other tests which will prove deficiencies of available protein in the blood stream. The above enumerated tests are suitable for general office procedure.

Any tissue of the body deprived of sufficient protein will give rise to symptoms; therefore, we find our patients presenting blood tests evident of anemia. They complain of fatigue, sensitivity to cold, evident pallor, and a negative attitude. If the muscle tissue of the body is called upon to give protein in order to maintain an adequate concentration of albumin in the blood stream the patient experiences myalgias such as psoitis, wryneck, muscle spasms, muscle weakness, tremor, tenderness to very light external pressures. Atrophy can be due to protein lack. The nervous system may be called upon to release its protein. When that is the case symptoms are present of neuritis in whichever nerve is involved. It might be sciatica or brachial neuritis, or trifacial neuritis, when the trigeminal nerve is involved. Research evidence indicates that approximately 50 per cent of cases of multiple sclerosis can be helped by controlling protein metabolism. Muscular dystrophy may be due to trophic nerve trouble.

The synovial membranes are often the point from which protein is robbed giving rise first to rheumatoid arthritis and as the condition progresses it becomes hypertrophic arthritis. Eventually the progression leads to atrophic arthritis. Recurrent gall bladder pathology, inflammations and infections, duodenal and gastric ulcer or duodenitis, colitis, and constipation are all evidences of low protein availability. Leukopenia, a low white blood count, lowered resistance to

infection such as colds and boils are further and concurrent evidences of low protein or protein deficiency. Allergies are associated with deviation of protein metabolism; alopecia, and other skin diseases such as eczema, neuroedermatitis and even varicose ulcers, thickening of the epithelium with brittleness, and flaking of the fingernails, are all signposts pointing toward faulty protein metabolism. In this same vein it might be well to mention again edema and hypertension as being very related to protein availability in the blood stream.

In questioning the patient while taking the history, it is always advisable to bring out questions pertinent to protein metabolism, such as: aches? painful joints? ulcers? colds? tendency to bruise easily? constipation? ankle swelling; sinusitis? Check for brittle fingernails and dryness of the hands while observing the patient's hair, scalp, eyes, and skin texture.

Since the evidences of protein lack are so obvious it will be necessary to consider the therapy pertinent to the problem. To return to the beginning part of this chapter, it was pointed out that only by a variety of protein intake could all 10 essential amino acids be obtained, thus, point number one in our therapy is to ascertain and insure that this patient eats a variety of protein, which should include meat, fish, fowl, eggs, cheese, gelatin salads, and high protein cereals. A special emphasis is put upon cottage cheese and sea foods.

If the laboratory reports indicate a low total protein it is our policy to supplement the intake of natural food by some of the commercial products which are amino acid concentrates and therefore help to insure an adequacy and an availability of proteins to the stomach. Liver, iron, and vitamin B complex composite tablets are an excellent source of protein supplementation.

In order that the first stage of protein hydrolysis be accomplished successfully, it is necessary to insure a supply of hydrochloric acid and pepsin in the stomach since with age the normal production of this material regresses. Many people who suffer no gastric symptoms such as flatulence, belching, bloating, indigestion even to the extent of having a problem of palpitation and short-windedness due to the gaseous distention of the stomach just beneath the diaphragm may even so, be classified as having hypochlorhydria if the laboratory report indicates hypothyroidism, i.e., low PBI.

It is recommended that consideration be given to prescribing five drops of dilute hydrochloric acid, or tablets containing five grains of glutamic acid and one grain of pepsin before each meal. If the patient expresses a normal desire for food containing a high percentage of protein, generally this phase of protein digestion is normal. In every instance of pruritus ani this therapy is instituted.

Upon leaving the stomach the peptides and proteoses will be acted upon in the intestinal tract by pancreatic enzymes. It is here to be noted that one of the stimuli to the production of secretion from the pancreas, and the amount, depends upon the gastric acidity. Therefore, the administration of glutamic acid is effective in triggering secretion from the pancreas. With a laboratory report indicating an already present severe depletion it must be remembered that when the body conserves protein it will be conserving these digestive enzymes for they are protein in nature. It is advisable to assume that the pancreas is not producing adequate proteolytic enzymes for use in the intestine.

In supplementation of this field a product containing the lipotropic factors, methionine, choline, inositol, enteric coated, is advisable. In addition the bile and liver products

of dehydrocholic and desoxycholic acid function effectively as a supplement plus generally a small amount of bile salts to aid in the emulsification and saponification of fats. Pancreatin, i.e. desiccated pancreas substance, is frequently of value in stimulating the production of choline from natural sources and in the breakdown of methionine into choline so it should be included in this therapy also. Many pharmaceutical houses produce tablets enteric coated containing desoxycholic acid, dehydrocholic acid, pancreatin, methionine, choline, and inositol. Among the other functions present in this would be the ability of the choline to unite with fat deposited thus mobilizing and defatting the liver. These tablets should be given with each meal. If the reader prefers a tablet containing ox bile in addition, then the dose should be one tablet each meal unless there is too much laxative effect, in which case it will be necessary to decrease the dosage to the point of normal bowel activity. Many patients experience gaseous distention and general intestinal discomfort low in abdomen several hours after eating. This is an evidence of lack of digestive enzymes and an indication for the tablet just mentioned. Frequently it is necessary to use both glutamic acid and an enzyme type tablet to insure both stomach and intestinal protein hydrolysis.

In the breakdown of food and the processes of assimilation it is necessary that vitamin and mineral products be present. The body does not manufacture vitamins, and it is imperative to inquire into the person's eating habits to ascertain whether or not he ingests an adequacy of fresh fruits and leafy green vegetables. If he does not, benefit may be derived from the administration, with each meal, of a tablet of bioflavonoid factors combined with vitamin C. The vitamin C and bioflavonoid factors increase cell

permeability, strengthen the cell wall and thus promote better assimilation. Furthermore, since vitamin C has been found to be one of the raw materials necessary to the adrenal cortex in its production of the various steroid hormones, it serves a twofold capacity. When all of the above has been protected by supplementation and natural ingestion it is still necessary for the amino acids to be processed through the liver. In that capacity the chapter on liver physiology takes up the therapy relative to the amino acids. Suffice to say at this point that a high content of vitamin B complex is necessary in the processing of the raw materials, amino acids.

Despite all the foregoing points of therapy, and provided an adequacy of amino acids in the blood stream, the patient may be still suffering a protein depletion at the cell level. It is imperative that the gonad hormones be present in order that the amino acids be utilized by the cell protoplasm. This is the level at which the protein anabolic hormones serve their function. The chapter dealing with the gonad hormones will take this into consideration in far greater detail than space here permits.

It is often necessary to prescribe a sizable amount of medication for patients with hypoproteinemia. The reader may rest assured that while treatment may run into considerable money, it can not be compared with the time that would otherwise be spent in the hospital at far greater expense. With diligent application of therapy to the patients showing depletion of protein, successful management can be achieved.

The situation can be likened to that of a man working at a stated salary which is below his cost of living, who finds it necessary to borrow money at odd intervals from his friends, a small amount of it at a time. Then he is promoted in his work and given a raise in salary. However,

this person will not be able to reach into his pocket and find more money there until he has paid back to his friends what he previously borrowed from them. It is just so in the management of protein depletion.

The patient will in all probability not evidence a great deal of improvement until such a time as he has been able to repay to the tissues protein robbed from them, in the processes of maintaining his life. But once the protein is returned to the tissues whose function has been handicapped by its lack, the patient will express to his physician satisfaction with the way he feels and with the progress that he is making. Since protein as such is not stored in the body in excess of the body's needs it is impossible to overdo the administration of protein. What will not be assimilated from the intestinal tract will be passed on, excreted and will not be stored as fat deposition. When protein metabolism has been stimulated, especially by the anabolic sex hormones, water is frequently carried with the protein particles. In this case the patient will evidence a gain in weight, which is not deleterious but merely evidence that protein metabolism is improving.

The mechanism of constipation is here closely associated. As the cells of the intestine draw the amino acids into the portal circulation, water is carried with the amino acids and this leaves a dry, dehydrated stool. The patient then complains of constipation. Good elimination is a prime requisite of normal health, and if it is necessary to do so, a mild laxative can be used for the maintenance of regularity.

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Liver

The liver physiology encompasses so many functions that this chapter will discuss only those pertinent to the endocrinology involved. Many tests are available for determining liver function, and are easily found in any standard laboratory reference text. This discussion being specifically for use in general practice will remark on those easily performed in an office and yet valuable in the overall evaluation of the office patient. Due to the tremendous reserve of the liver and enormous regenerative capacity accurate evaluation of liver function is quite difficult and will tax the entire field of diagnostic acumen both clinical and laboratory.

Please keep in mind that the patients herein discussed are ambulatory and may show no definite signs of severe illness. Therefore the reference is to the average general daily patient.

The biliary tract, cholecystitis, cholelithiasis, obstruction to bile ducts, etc., are left to those with special interest in the subject.

The discussion of therapy will undoubtedly encounter opposition but suffice it to say the specific choice and dosage of therapeutic agents is left to the clinician's discretion and preference. The object here is to point the way based upon the physiology.

The first part of this chapter is devoted to the relationship of some commonly presented symptoms to the liver; follow-

ing this is a discussion of physiology, and it concludes with the rationale of therapy.

Muscle tissue is a combination of two proteins, myosin and actin, forming actomysin. In the research laboratories myosin injected into a water bath forms a fiber, the same type from which synthetic wools in clothing are made. Since it did not answer all the qualifications of muscle fiber, actin was injected into this fluid bath where it combined with myosin to form a fiber very similar to human muscle. A weight was tied on the end of the fibers and suspended in the water, the weight not touching the bottom of the container. All kinds of chemicals were put into the fluid: calcium, adrenalin, vitamins, hormones, with no response of the muscle fiber. Eventually adenosine triphosphate was injected into the fluid in which instance the weight descended to the bottom of the container.

Muscle tone is the state of semi-contraction of the muscle tissue. It is necessary for any muscle to have adenosine triphosphate in order to completely relax. In the absence of adequate adenosine triphosphate the muscle is capable of going into even greater degrees of spasm. Adenosine triphosphate is a product of purine and carbohydrate metabolism and is to a large extent manufactured in the liver. It is necessary to keep in mind, in connection with muscle spasm conditions, that your patient might be dieting. Adenosine triphosphate is peculiarly concerned with carbohydrate metabolism and in most reducing diets carbohydrates are decreased so it is advisable to ask patients who complain of muscle spasm, such as low back pain, if they have been dieting. The liver physiology must absolutely be intact in order to have normal carbohydrate metabolism and hence sufficient adenosine triphosphate.

In taking histories we ordinarily ask patients when they are hungry or if they are abnormally hungry. Some of them answer that they are always hungry, others will report that they are hungry around 10 a.m. and around 4 p.m., sometimes late in the evening while watching television. Being hungry seems quite an innocuous proposition, but not when you consider that this hunger and the appetite are related definitely to low blood sugar and that, as sugar concentration in the blood stream drops, there is set up a demand for food. Some of the patients will tell you that they particularly desire sweet and starchy foods of one type or another. The low blood sugar basically is related to carbohydrate metabolism. Secondly it is associated with endocrinology in that the target glands are not working properly: ovaries, a thyroid, or any target gland not performing competently arouses a drive from the pituitary gland causing stimulation of the pancreas with increased production of insulin. If the glandular system is unable to accomplish the purpose of correcting the target gland, the hypothalamus takes the effort into the autonomic nervous system. The vagus nerve stimulated activates the production of insulin. Since the sugar metabolism is closely connected with glandular physiology, it is also very much related to liver function. The liver is the storehouse of sugar and hence must be given consideration when a patient has an abnormal appetite or an appetite specifically for carbohydrates.

Many patients on initial examination will display hypertension, a high diastolic and a high systolic. In considering the physiology behind this phenomenon we have to consider the same mechanism in the endocrine gland system, perhaps stimulating a production from the adrenal medulla with a consequent increase of epinephrine. The action of adrenalin

being that of vasoconstriction, causes a contraction of the blood vessel musculature, which in turn raises the blood pressure. In addition to this, if there is a lack of adenosine triphosphate the contraction of the blood vessel muscles continues and it is impossible to relax the tissue because it does not have the phosphorus energy bond necessary for that relaxation. Add to this the overproduction from the adrenal cortex in the form of salt retention hormones, water retention hormones mediated through the liver, and we have an accumulation or an increase in fluid in the blood vessel system leading to hypertension. The adenosine triphosphate, epinephrine electrolyte balance are all partially managed through the liver.

The increase in adrenal cortical activity sets up a constant gluconeogenesis in the liver burning out that patient's protein, using it in excess. Many times the liver being in a state of debility, due to a low blood sugar resulting from excessive gluconeogenesis, is unable to remove or to inactivate or to form less potent salts of the gonad hormones. In that instance there is an excess of estrogen or androgen which is in some cases obvious when you first look at the patient. The female will show masculinizing symptoms, hirsuitism, edema, hoarseness and deepening of the voice, and menstrual irregularities. Frequently the male will show feminizing symptoms in hair distribution, in breast development, and voice changes, all due to the fact that there is a profusion of circulating gonad hormone, due to faulty filtration on the part of the liver.

Many patients have an edema which is fluid retention due to, in some instances, a failure of the liver to produce adequate albumin. In some instances fluid retention is due to retention of aldosterone, again connected with the liver's

failure to inactivate all the aldosterone which is produced by the adrenal cortex and intimately related to fluid retention. Edema need not be confined to the ankles. Many of these people will present an intractable bronchial cough. Frequently this edema fluid is deposited in the lung tissue. In some patients there is a certain amount of dizziness, vertigo, in which case the fluid can be contained in the semicircular canals leading to a loss of equilibrium.

The production of albumin is specifically a liver function. Edema can be brought on by the fact that the oncotic pressure, which is the water-binding pressure of protein—specifically albumin—is less than the blood pressure on the arteriole side of the capillary. As the pressure continues fluid is filtered through the semi-permeable walls of the capillary into the peripheral and interstitial tissues. As the blood enters into the venous side of the capillary, the pressure is reduced. The protein is concentrated by dehydration (a relative increase in oncotic pressure), and the fluid from the interstitial tissues is reabsorbed back into the blood stream. Now that is normal physiology. When there is a low albumin, the oncotic pressure on the venous side of the capillary is below normal, the fluid stays in the interstitial tissues and does not re-enter the blood stream.

Many of our patients enter complaining of headaches and frequently we consider these to be due to one of two things. One is the increased activity of the endocrine gland system with specific reference to the pituitary gland. The pituitary gland lies in the sella turcica which is a bone cavity or pocket. The only way that this pituitary gland itself can expand is upwardly. The pituitary gland does just as any other tissue in the body when it is overworked, i.e. it expands, engorges, congests, and enlarges. There are two

little pairs of processes on the sella turcica called anterior and posterior clinoid processes. From the posterior clinoid processes fibers of the dura run forward and entirely encompass the brain, but as they reach the posterior edge they are then posterior fibers and these pass to the anterior clinoid process. As the pituitary gland expands and enlarges it bows or tents these membranous covers which in turn tighten up the entire dura. This dura is attached to the cranial wall at various areas with thickened bands of fiber and the headache can be anywhere since the pull occurs on these attached fibers. There is of course concerned with this a disturbance in the flow of cerebrospinal fluid.

Many migraine headaches were at one time considered to be a peculiar specific headache, but if you realize that the optic chiasma lies anterior and superior to this pituitary gland, pressure of the swelling of the pituitary gland on the optic chiasma will give bitemporal blindness. It will cause visual aura preceding a migraine headache. The enlargement of the pituitary gland, due to an endocrine gland imbalance, is very capable of setting off what we formerly thought were migraine headaches. Today we feel that it is not a migraine headache. It is an endocrine gland disorder. Another reason for having these intractable headaches can be a low blood sugar level which in itself is a peculiarity of endocrine gland dysfunction. In both instances, whether the pituitary gland enlarges or hypoglycemia occurs, the factors that set this off are mediated through the liver.

Some patients enter with perhaps subclinical jaundice. It takes a good deal of physical examination to determine and to find this jaundice condition. There are tests that will be discussed showing the presence of this if it is below the level seen with the naked eye. Jaundice is due to failure

of the liver to empty bilirubin and biliverdin into the bile, with the result of increased concentration in the blood stream.

Many diabetics enter the office complaining of polyuria and polydipsia. Sugar carries water with it and since the concentration of sugar in the blood stream of these diabetics is high and the kidney is attempting to filter out the excess sugar it is filtering water out with the sugar leading to dehydration, polyuria and thirst. Take with that the fact that all metabolism of sugar is slowed in the absence of insulin and the muscle tissue of the body is failing to get sugar for its metabolism leading to muscle weakness. The concentration of sugar in the blood stream has a tendency toward a sclerosing action of the blood vessel intima. Most diabetics run a high cholesterol and they have the makings of atheromatous plaques, arteriosclerosis, thromboses and gangrene. Since the sugar is carrying water with it, the protein and the liver metabolism are involved, and there is a basis for the condition of "polyneuritis."

We have discussed symptoms, perhaps not in as great detail as they might warrant, but in an effort to indicate to you the all-important position of the liver in body metabolism.

The liver is one of the largest organs in the body. Research has revealed over 500 different separate functions of the liver. We will not be able to get into this as deeply perhaps as would be very interesting but some of the major functions deserve our consideration especially when one authority maintains that every obese person has a fatty liver.

The functions of the liver that we shall discuss concern the metabolism of foodstuff: the proteins, fats and carbohydrates. There are ten essential amino acids. They are essential because they cannot be synthesized in the body. The body uses 26 amino acids, the other 16 amino acids must

be formed or are capable of being formed in the liver from the ten essential amino acids. The liver has the ability to transaminate and deaminate amino acids. The amino acids are characterized by containing the amino group which is NH_2; in fact the amino acid is a carboxyl (COOH) group attached to one of these nitrogen-containing NH_2 groups. The liver is capable of breaking off or separating the NH_2 group in order to free the amino radical to be used on some other carboxyl radical to form another amino acid. The specific amino acid created in this way is characterized by the placement of that amino group in its molecular structure making it that specific amino acid. When the amino acid is broken down in this fashion the carboxyl radical is carried over into the metabolic pool known as Krebs cycle. Krebs cycle is the common final destination for all foodstuffs before they become oxidized and utilized by the body.

The amino groups that are not used in the formation of any other amino acid can be used in the formation of ammonia and urea. The ammonia radical is NH_4 and by splitting off NH_2 an accumulation of NH_2 radicals could be transformed into a lesser number of ammonia radicals. Ammonia and urea are definitely used by peripheral cell tissues in their life processes. The ammonia and urea speed up the transaction of the cellular functions. When they are not in use or when they are excessive, the material is passed out and excreted through the kidneys. The increase in ammonia can be considered perhaps as one of the causative factors of hepatic coma. There has been proved an increase in ammonia of the blood stream with patients having hepatic coma. The use of this NH_2 group, the amino group to be attached to another carboxyl radical is called transamination. The removal of an NH_2 group from an amino acid is deamination.

Let us mention one of the other functions that is accomplished here, just to bring out a possible relationship between ammonium chloride administered by mouth and deamination-transamination reaction in the liver. The ammonium chloride contains NH_4—the formula is NH_4CL. The ammonium radical being separated from the chlorine radical could conceivably be transformed into the amino group NH_2 for use in synthesis of amino acids. The chlorine radical might unite with sodium or be instrumental in the production of hydrochloric acid in the stomach, or it can be used generally in metabolism of chlorine and a potential source of some amino acids is present in ammonium chloride.

One of the other functions that the liver performs in the protein metabolism, is that of decarboxylation. Carbon dioxide is removed from amino acid structures forming different compounds and also when the amino group has been removed, the carbohydrate structure that is left can be decarboxylated or carbon dioxide can be removed from it to again form vital substances for use in Krebs cycle. Decarboxylation can be either anaerobic or aerobic. When sufficient carboxyl groups, which are combinations of carbon dioxide and water are formed they are used in the tricarboxylic acid cycle, which is a source of the carboxyl group and helps to activate Krebs cycle. In all of these functions of the liver it is necessary to have enzymes, co-enzymes and co-factors.

The enzymes are a protein molecule and as more and more research is being accomplished in the enzyme field, they are finding less inert protein material in a body cell, and more enzyme material. It seems that the protein has a specific enzyme activity, as the antigen protein is brought to the cell wherein this residual protein can work upon it. The co-enzymes and co-factors are not as a rule considered

protein in that they contain no nitrogen molecules. Co-factors and co-enzymes are in the field of vitamin and minerals. It is necessary in the breakdown of pyruvic acid, which is one of the very common end products of carbohydrate metabolism, to have diphosphothiamine nucleotide which is a component of vitamin B complex, and magnesium, which is a mineral.

Among the other functions of the liver in the management of proteins, are those of filtration and inactivation. These are accomplished by chemical activity known as oxidation, reduction, and conjugation. By means of adding oxygen, hormones of the various glands can be inactivated or relatively so. Many of the hormones can be inactivated or made to form salts and esters by the removal of oxygen which is reduction. Bacteria, toxin, hormones are all inactivated by conjugation, which is the joining of various substances in order to restrict their activity, or in the case of bacteria, to inactivate them. With overproduction of the gonad hormones, there is circulating in the blood stream an excess of estrogen or androgen, and the effect of detoxifying and filtering is specifically the duty of the liver.

The performance of the liver to inactivate the hormone, aldosterone which has been isolated from adrenal cortex and is responsible for sodium and hence fluid retention, is one of the means by which the liver is functionally active in the maintenance of electrolyte balance. There are other functions performed by the liver in the management of protein. For the purposes here we will leave the protein metabolism on the basis of transamination, deamination, decarboxylation, oxidation, reduction and conjugation.

The liver is expected to help in the management of fat metabolism. Fat itself is the storage mechanism of fuel,

and is simply the grouping together of carbohydrate molecules and depending on the peripheral needs of the body, either break fat down into carbohydrates or form fat as a storage mechanism. This is accomplished through the liver and the state of the fat in the liver depends on the peripheral need and supply of the body. In the breakdown of fat, fatty acids and glycerol are formed. The glycerol is broken down further into carbohydrates which then become a part of Krebs cycle. All foods eventually enter into Krebs cycle. The fatty acids can be combined with protein elements forming lipoprotein. Very frequently the fatty acids are combined with phosphorus in which instance they become phospholipids.

Phospholipids and lipoproteins are the carrying mechanisms of the blood stream. Other materials, hormones, antibodies, bacteria, and minerals are carried by means of being united with lipoprotein. Phospholipids must be united with choline, in order to form a lecithin. Lecithin is the material that causes the fat to remain in motion and not to be deposited in the liver. Fatty degeneration of the liver is, of course, just what it sounds like: the accumulation of too much fat therein. The ability to remove this fat is peculiar to lecithin. Lecithins are the combination of phospholipids and choline, therefore, it is necessary to secure an adequacy of choline or one of its precursors such as methionine.

The fat metabolism produces for Krebs cycle a substance known as co-enzyme A which is acetyl acetate. Co-enzyme A is very important in Krebs cycle activating most of the functions therein, and is one reason fat can enter into Krebs cycle. The presence of co-enzyme A facilitates the entry of fatty acids and fat breakdown into Krebs cycle, and when the fatty acids are broken into ketone bodies they enter the

Krebs cycle. The ketone bodies have the ability to be used by all of the tissues. They are essential in the body metabolism and to us they are not too important until they become excessive and show up as an excretory product; but the body in metabolism finds it necessary to use the ketone bodies. Ketone bodies compete with carbohydrates for oxygen and if the carbohydrates are able to get the oxygen then the ketone bodies are not used and spill over into the urine, and vice versa; if the ketone bodies get the oxygen, then the carbohydrates spill over into the urine.

Keeping in mind that one authority claims 100 per cent of all obese people have a fatty liver, it is necessary again to recapitulate the importance of choline in the formation of lecithin from phospholipids as the mobilizing factor of the fat deposited in the liver. The choline also enters into the body metabolism in a number of other ways. Acetyl-choline is one of the chemicals necessary for the integrity of the synaptic resistance at the myoneural junction of the parasympathetic nervous system. So choline is a highly important product both from the standpoint of defatting the liver and of maintaining normal integrity of the parasympathetic nervous system.

The breakdown of fat, achieves the production of carbohydrate, and this same process is accomplished by the breakdown of protein. This function is known as gluconeogenesis. Glueconeogenesis is a normal function of the liver, but when there is an involvement of sugar metabolism or when there is over-activity of the pituitary-adrenal axis, there is an excess of gluconeogenesis with a consequent breakdown of fat and increase in the production of ketone bodies which are picked up by the urinary assay. In the protein field the very severe depletion of protein material from the peripheral

tissue of the body in order to supply carbohydrate through liver functions is of considerable consequence. We have indicated the importance of the liver function in protein and in fat metabolism.

The sugar physiology is quite complex, but you will find it more interesting perhaps in that sugar metabolism is a physiological phenomenon peculiar to every cell, and it is the area from which we gain energy and heat. It is absolutely necessary to life processes, and the liver plays a tremendously important part in the metabolism of sugar. In order to understand sugar physiology, we have to realize the importance of Krebs cycle, which is the supply house of carbohydrate to the body metabolism. We must understand adenosine triphosphate which is the energy bond to make these phenomena occur. The combination of understanding adenosine and the action of phosphorus leads us into an understanding of phosphorylation and the highly important function of the liver in the entire setup. Metabolism of sugar is necessary to each cell in the body. Sugar is used in the peripheral tissues and it is stored in the liver. In order that the sugar, ingested as carbohydrates in our food, be utilized by the liver, it is necessary that a process of conversion from glucose to glycogen be accomplished. Glycogen is glucose with phosphorus added. Just as in the chemical laboratories it is necessary to use heat or electricity or ionic transfer to cause interaction between different substances, the tissue of the body also requires a source of energy to accomplish this. The source of energy is from the adenosine triphosphate.

Adenosine triphosphate is in all cells of our body but it is more abundant in the liver, because here this process goes on over and over again. When glucose is in the blood stream it passes through the liver cell membrane where

adenosine triphosphate adds a molecule of phosphorus which is a high-energy molecule. It takes energy to make one substance become another and this phosphorus bond is the energy molecule. The energy bond here releases energy or causes the release of energy very slowly as compared with the combustion in a chemical laboratory but, nevertheless, it is responsible for combustion transferring glucose to glycogen. In the removal of the phosphorus bond from the adenosine triphosphate, adenosine diphosphate is formed. As glycogen proceeds along the way to become pyruvic acid within the cell, and in the muscular cell, the peripheral cell, pyruvic acid is the material used in carbohydrate metabolism. In the liver it is stored in this fashion.

As the glycogen becomes converted to pyruvic acid, the adenosine diphosphate releases more energy bonds to become adenylic acid. When the demand of the periphery is such that more sugar is needed and the liver is expected perhaps to supply this sugar, the process reverses itself. Then adenylic acid becomes adenosine diphosphate and the pyruvic acid becomes more like glycogen. As the process continues and glycogen is formed and then released into the blood stream as glucose, the other phosphorus energy bond is picked up and adenosine diphosphate again becomes adenosine triphosphate. There is a tremendous reciprocal action in the catalytic action of adenosine triphosphate.

During the period of rest when this process perhaps is not going on, the excess phosphorus bonds that are picked up by the cells to be used in this phosphorylizing procedure are stored first as adenosine triphosphate and then as creatinine phosphate. Creatine phosphate and creatinine phosphate are closely related to creatine. Creatine is the hydrolized product of creatinine. Creatinine, of course, is found mainly in muscle

tissues and it is the storage warehouse for the energy phosphorus bonds that enter into the adenosine triphosphate cycle. The whole procedure is called phosphorylation.

In the process of phosphorylation, it is absolutely necessary that co-enzymes, co-factors, and enzymes be present. One of the co-enzymes is diphospho-pyridoxine nucleotide, which is derived from pyridoxine, thiamine, riboflavin, niacin, pantothenic acid. All of the B complex factors are necessary in the conversion of glucose to glycogen and then to pyruvic acid. Pyruvic acid can be oxidized or it can be utilized by the cells of the body without oxygen; it can be aerobic or anaerobic. So actually the utilization of the pyruvic acid in the muscle tissue can be accomplished without oxygen and as a method of measuring pyruvic acid or muscle activity, the measurement of oxygen would not be a definite dependable criterion. It is called the respiratory quotient, this measurement of oxygen, but it is notably inaccurate in determining any specific knowledge of phosphorylation or of utilization of the pyruvic acid.

The mechanism of sugar maintenance in the blood stream is a very complex one. Most of our education was achieved when the method for determining sugar was based on a normal of 80 to 120 milligrams of sugar to 100 c.c. of blood and while it is slightly different now, we can still transpose in our mind to correspond with the way it was taught. The blood sugar is maintained between 80 and 120 mg per cent normally. When the concentration falls in this range the liver is relatively inert, it does not do anything particularly because the sugar is within normal range. When the person ingests carbohydrate, the blood sugar lever naturally rises as shown in a normal sugar tolerance test curve. The postprandial rise in sugar will go up only so far before

the liver becomes active in withdrawing this circulating sugar into itself and storing against the time when the blood sugar level might drop below 80 mg at which time the process is reversed and the liver then releases sugar back into the blood stream. The relationship of stored sugar is very important in that liver damage can occur very easily during times when it is low in sugar. The liver can be depleted of sugar in most hypoglycemic people who have an excess insulin production. The administration of glucose and dextrose postoperatively is used to accomplish a greater protection of the liver because anesthetic agents are notably toxic to the liver.

Many times problems involve the endocrine gland system in relation to the sugar metabolism. Any time there is an excess of insulin produced, whether it is due to pituitary drive, or to vagus nerve overstimulation, or whatever the mechanism may be, the excess insulin again tends to regulate the blood sugar level; but it is held at a point below the needs of the body. Adequate oxidation can not take place, the cells can not metabolize normally. Hunger symptoms occur and if carbohydrate or sugar is not administered, the next result is a headache, sweating, faintness, and dizziness. This can progress even to the point of coma, which as you know is nothing more than insulin shock. It can be produced though without exogenous insulin being administered.

The effect of insulin on blood sugar is solely, as far as can be determined, in the regulation of phosphorylation. In sulin stimulates or speeds up phosphorylation. If no insulin is administered, cells of the body are still capable of metabolizing sugar but so much slower that by the time they would have used it, the sugar has been filtered out by the kidneys.

As we mentioned before, some of these patients are storing a great deal of water in the cells especially with the retained sugar and more particularly in the hyperpituitary person. They look solid and firm, as compared to those who are merely holding fluid in the tissues, making them seem soft and flabby. It is thus possible to differentiate between interstitial and intracellular fluid. The liver is a supply house of the raw material, sugar. The glandular system can be likened to the thermostat setting the balance for blood sugar level. The thermostat, of course, in a house could be set anywhere, and if it were set for a thousand degrees, the furnace would make an attempt to produce the thousand degrees of heat, even though it would burn up the house. The furnace would never shut off and it would be detrimental to the residence. If the gland system is set without limitations as it well could be in the failure of the pancreas to manufacture insulin, the effect is a rising blood sugar, which is as it was with the thermostat, detrimental. If on the other hand there is an excess of insulin, it would be relatively the same thing as setting the thermostat at a very low level, perhaps 50 degrees of heat, which would be cold. In the same way an excess of insulin would maintain a low blood sugar.

The thyroid and the adrenal enter into this picture also. The thyroid, by assisting the selective activity of the intestinal tract for sugar, increases the blood sugar. A glucose tolerance curve in a hypothyroid individual is quite flat, not showing a post-prandial rise because of the inability of the intestine to select and assimilate sugar from the content. The adrenal gland through glucocorticoids as well as the effect of epinephrine in releasing sugar from peripheral tissues causes a rise in blood sugar.

Liver function in the control of sugar metabolism is

highly important and can be tested in the office and examined laboratory wise by you, the physician, questioning what process is occurring. One of the best means is the glucose tolerance test. The patient is brought into the office in the morning without having eaten. Fifty grams of carbohydrate are administered, through orange juice, lemonade, or a coke; or something containing approximately 50 grams of sugar. Before giving the sugar a blood sample is taken from the patient. One half hour after the test meal another blood test is taken, repeated in one hour and again one hour later until 4 specimens are taken. They are marked so that you can identify them, but the report, when it comes in, should be approximately 80 mg per cent on the fasting stomach. After the administration of the test dose of carbohydrate, it will range somewhere between 80 and 150 mg per cent. Within the first hour usually it is back to the base line and it may run along subnormally here until about the second hour at which time it usually approaches a normal base level. The action here is that when the sugar was injected it increased the concentration in the blood stream. It was then removed from the blood by the liver, stored there and maintained at about this base line of 70 to 80 mg per cent generally.

The diabetics may start out around 100 mg per cent on a fasting stomach, and have a tremendous, usually quite rapid, rise and a very slow decline. The decline is due to filtration of sugar by the kidneys. It is not due to liver storage because the liver is not storing sugar due to the fact that phosphorylation is so delayed by the lack of insulin. The blood sugar curve of liver damage is discernible, because it falls in between a normal and a diabetic curve. It may start at a normal level and rise slowly to a slightly higher level, then fall, much more slowly than the normal. At the

end of two hours, generally the liver damage curve is back to a base level, so was the normal sugar curve back to the base level in two hours. The diabetic curve never reached the normal line, so we can assume liver damage based on the angle with which this descending line meets the base line in two hours.

In another stituation sometimes there is a sugar curve that starts below normal and stays below all the way through. It is almost a straight line. That possibly can be due to hypothyroidism where the sugar is not absorbed from the intestinal tract, or it can be due to a hyperinsulinism where the liver has been so depleted of sugar over a period of time that the minute sugar is introduced into the system it avidly reaches to that sugar and takes it within the liver. In that case of course, the sugar test does not show any rise.

Whenever somebody enters our care in whom we have a legitimate reason to suspect fatty metamorphosis in the liver, it becomes necessary to follow that up mentally with the consequence of fatty degeneration; and fatty degeneration is the first step of cirrhosis of the liver. We probably have no way to know what degree of fatty degeneration or of cirrhosis is present, but it is entirely possible this patient might have a cirrhosis of the liver at the moment of interview. The cirrhosis of the liver then can conceivably be due to dietary indiscretion because if the lipotropic factors are not administered, lecithin is not formed in the liver and fatty degeneration takes place. Fatty degeneration is simply an imbalance between lipogenic food and lipotropic food. Severe and prolonged fatty degeneration resulting in cirrhosis usually ends in death. Chronic mild cirrhosis is compatible with life but at a much reduced rate of activity.

Portal hypertension may be concomitant with cirrhosis

of the liver. The cirrhotic manifestations in many instances make it necessary for the circulation to the liver to seek other channels through anastomosis. One of these channels, which is not of any importance to us because it is found only in autopsy, is the postperitoneal blood vessels; but another one that is of interest is the abdominal veins, which distend and engorge in the effort of this portal circulation to seek a pathway to the suprahepatic blood channel. This peculiarity is noticeable on the abdominal wall of many patients as a distention of blood vessels known technically as caput Medusae.

The second effect and perhaps a more important reaction is the production of varicose veins or varicosities in the esophagus and in the rectal area. The rectal area helps to point a clue in diagnoses though not particularly significant as far as life and death are concerned. The esophageal varicosities are very important. They can be determined by proper x-ray diagnostic service. Many times these varicosities rupture and hemorrhage occurs, and consideration must be given to a liver that is not producing protein substances. Fibrinogen and prothrombin may not be present and the bleeding will go unabated without clotting, causing death.

Hepatic insufficiency is the result of two things, one of them the liver damage itself, and the second the anastomatic relationship of the circulation wherein the cell does not get adequate circulation. We can list several things here and it might be well to do so relative to liver damage. Liver damage is responsible for jaundice, the failure of the liver to empty the bilirubin and biliverdin into the biliary system. Liver damage can be responsible for hepatic coma with relationship to the ammonia production in the liver. The liver damage itself can further perpetuate the situation and with

cirrhotic liver, there are blood sugar problems. One of the effects of the liver damage is ascites, the filling of the abdominal peritoneal cavity with fluid. There are several mechanisms here. One concerns the oncotic pressure of the venous and the arterial segments in the capillary, and the relationship of a low albumin to this fluid production. We can just as well have the fluid production in the abdominal peritoneal cavity, as perhaps ankle, lung or semi-circular canal edema. Due to the effect on the hematopoietic system of liver damage, there is an anemia of macrocytic normochromic type. Due to failure of adequate production of protein products necessary for blood coagulation, there is a tendency toward capillary fragility with hemorrhagic spots on the body.

Along with this failure, when the liver cell is damaged it does not inactivate gonad hormones. The result is symptoms referable in either sex to the excess gonad hormone. In the male there are spider nevi, hemorrhagic spots in the tissues generally of the neck, shoulders or upper arm, that have a central arteriole with smaller vessels leading away from it just like a little star. The male may show pectoral alopecia, his chest is getting bald. He is developing large amounts of fat tissues on his chest wall (gynecomastia). There is altered distribution of the hair, as on the escutcheon, and the tendency is for the distribution to follow female lines. These men with hyperestrinism have a redness in their hands on the thenar and hypothenar eminences, and possibly testicular atrophy.

Liver damage can be present without portal hypertension, but in most instances there is portal hypertension with an identifiable series of symptoms. As mentioned before, esophageal varicosities, enlarged spleen (splenomegaly), the

caput Medusae or abdominal vein distention, and ascites can be ascribed to portal hypertension, as can ankle edema. Since there is damage to the spleen and its functions symptoms are set up from the spleen side of the picture, mainly bone marrow changes, leading to an anemia, thrombocytopenia and a leukopenia. All of these symptoms and signs should lead to a suspicion of the presence of cirrhosis of the liver with or without portal hypertension.

The laboratory tests that are of practical value are the blood analysis for determination of liver function. The primary one is the glucose tolerance test. The cholesterol level is very intimately related to liver functions. Cholesterol is manufactured in the liver and faulty liver function leads to improper use of cholesterol and hence a consequent rise in cholesterol level. As for thyroid activity, cholesterol level is in inverse proportion to thyroid function and, therefore, should be proof that thyroid therapy itself is very beneficial to liver function. The albumin-globulin ratio and the albumin and globulin separately are highly indicative of liver functional abnormalities. A rise in globulin can be experienced in some forms of liver damage, more often the problem is failure of the Kupffer cells of the liver to manufacture albumin, and that results in a low albumin on the blood test. As a compensatory reaction, globulin is increased. Therefore an albumin-globulin serum test gives a quantity of information concerning liver function.

There are tests based on the color comparisons to determine concentrations of bilirubin and biliverdin in the blood stream. One of these is the icteric index, which is simply that the bilirubin in the blood is compared to a standard, and a normal standard reading is 3 to 6. Readings of 6 to 15 indicate latent or subclinical jaundice. Clinical jaundice

appears when the icterus index is greater than 15. The van den Bergh reaction or test is of two types, the direct and indirect. The direct method measures the presence of the product of hemoglobin destruction and it has an immediate and a delayed reaction. The direct method of examining means that the blood serum is examined directly without any chemical process being accomplished on the serum. The indirect method has a chemical reaction of alcoholic precipitation before the quantity of chromic substances is measured in the blood. The test is primarily related to the biliary tract system. The indirect test gives more information concerning hemorrhagic problems, whereas the direct test shows more response concerning hepatic damage.

There are numerous dye filtration tests, some not too practical in our offices simply because they involve administration of the dye and immediate checking of the results. However, there is one method of testing or detecting the detoxication power of the liver, known as the hippuric acid test. Six grams of sodium benzoate are administered in 30 c.c. of water one hour after a light breakfast. Prior to the administration the patient is asked to void urine and then drink one half glass of water and the urine is collected for 4 hours thereafter. The total hippuric acid excreted in 4 hours should run between 2.6 to 3.3 grams. The filtration of the hippuric acid, which is formed by the benzoate preparation in the liver is a very helpful test in determining liver function. Filtration of hippuric acid through the kidneys indicates that the liver is adequately breaking this benzoate down into hippuric acid.

The serum alkaline phosphatase test is not exactly a test of a product from the liver. Serum alkaline phosphatase is manufactured in the bone cell. It is intimately related to

calcium and phosphorus metabolism, but it is filtered out of the blood stream by the liver. It is inactivated and excreted through processing by the liver. So the serum alkaline phosphatase examination indicates whether there is a rise in alkaline phosphate above normal, because the liver is not inactivating the alkaline phosphatase and it is accumulating in the blood stream.

One other test is the transaminase test. The transaminase test is based on the appearance or the presence of necrotic material in the body. It is not solely a liver function test because it is as frequently used to determine the presence of infarct in coronary conditions as it is to detect liver damage. Readings under 50 are considered normal for a transaminase test. Above 50 is indicative of a pathological process, wherein there is necrotic tissue in the body this could be a thrombus in a blood vessel elsewhere than in a coronary blood vessel. In a coronary condition, as early as six hours after the coronary attack the transaminase concentration rises and reaches a peak in about three days. It is of value in this way: if electrocardiographic examination of that patient can not be made at the time, then a transaminase test on blood drawn from the patient's arm could be done. If the electrocardiograph does not pick up a cardiac infarct but the symptoms of a coronary attack are present you have further proof that there is or is not necrotic tissue in the body by the results of the transaminase test. If the interpretation of an electrocardiograph is in doubt, the transaminase test again helps to clarify and frequently it is not possible to depend on the electrocardiograph as much as on the transaminase test. The transaminase test is both diagnostic and prognostic. The level of the transaminase test drops progressively from the third day post attack to normal

as the necrotic tissue is absorbed, excreted, organized, and healing takes place. Generally a cardiac infarct will show between 250 and 500 in the transaminase test. It can go much higher but that is the average range. In hepatic damage, the range of the transaminase test runs around 2,500 so there is a tremendous elevation in the transaminase reading with hepatic damage. It is a dependable way of determining if the patient has metastatic carcinoma, because a metastatic carcinoma in the liver leads to damage with necrotic tissue. There may be malignancy some other place with no necrotic tissue present, in which case the transaminase test is within normal range, but immediately that metastasis starts, tissue cell damage occurs and the transaminase test rises.

There are many facets of liver physiology that must be given consideration when discussing and evaluating therapy for the return to normal of liver function. All of the considerations are based upon the physiology. It is obviously necessary that an adequacy of carbohydrate be supplied to this patient, that the liver be given protection when the sugar content is low since the tissue is very susceptible to toxin action or the action of debilitating diseases. The sugar ingested also relieves to some extent potential gluconeogenesis. Sugars that are best for this purpose are those of natural origin since it has been reported that the refined granulated sugar has a tendency to stimulate the pancreas and produce more insulin.

Concurrent with the administration of sugar it is necessary to provide sufficient protein material. It is primarily important that the liver cells be given their normal requirement of amino acids. The supplementing of protein provides the liver with a raw material in the event that gluconeogenesis

is taking place at an excessive rate. It then becomes a protective mechanism to the rest of the body in that the need of the liver to receive protein to break down into sugar is alleviated by the administered protein and thus the cells of the periphery are not drained of their protein. The present day reducing diets so rigidly restrict carbohydrates that many of these people have been forced to undergo gluconeogenesis, the burning of protein to supply sugar, because the sugar was not provided in the diet. They therefore have reached a state of sugar and protein depletion. Rather than restrict further their food intake, it is recommended that they ingest adequate sugar and protein.

The great preponderance of fatty degeneration in the liver makes it advisable to suggest materials that have been proven in their ability to mobilize the fatty deposits and thus defat the liver. In this capacity choline is of proven value. The use of choline is here recommended with an adequate supply of the amino acid methionine which in turn is a precursor of choline. There are available many products containing methionine, choline and inositol. The product used should be enteric coated, as it is to be desired that the choline, methionine, and inositol be deposited in the intestinal tract. This will prevent any hydrolyzing or degenerating effect of the stomach acidity upon the product. Our recommendation for a high protein intake was based partially on the fact that the protein foods are lipotropic in nature due to their content of methionine and cystine.

The excessive gluconeogenesis that we consider present in many liver conditions must be traced back to its origin. The adrenal cortex, throwing out an increased amount of the cortical steroid groups, stimulates gluconeogenesis in the liver. To go one step farther behind this additional adrenal

production, it must be recognized that the adrenal overactivity is due to excitation by a driving pituitary gland, which is further evidence of endocrine imbalance. The use of one grain of thyroid with each meal may depress the pituitary and will balance to some degree the deranged endocrine gland system. It has the further beneficial effect of stimulating the hepatic cell. This is evident in the cholesterol-PBI relationship.

In all stages of phosphorylation there is a need for the vitamin B complex factors. An effective means of supporting liver physiology is the administration of vitamin B complex. This can be accomplished by either tablets or injection. It is recommended that the tablets be given in fairly high dosages, such as one with each meal, and if injections are preferred that they be given three times a week for two weeks and then dropped to twice a week for two weeks. This will depend to some extent upon the individual formula of the injectable, but on the average 1 c.c. intramuscularly three times a week at the inception of the therapy is of great benefit.

In order that the biliary function of the liver be sustained without any stagnation in the gall bladder, relaxation of the bile ducts and their sphincters has been found advisable. For this purpose it is possible to use a tablet composed of phenobarbital one-quarter (1/4) grain and belladonna one-eighth (1/8) grain. This tablet administered with each meal will cause relaxation of the sphincter of Oddi to relieve any potential back pressure from the bile ducts that might be due to spasm at this location. Furthermore the product relaxes the intestinal tract and the pyloric sphincter. In addition it decreases the excess stimulation through the parasympathetic nervous system, the vagus nerve, to the

pancreas, which might be conducive to maintaining high insulin production. Since we are already considering a potential endocrine gland imbalance, it should be recognized that upon the failure of the endocrine gland system to manage itself properly, the hypothalamic area of the brain takes part of this balancing effort over into the parasympathetic nervous system, in which case an overactive or an overly stimulated vagus system would lead to excess insulin production and spastic reaction of the biliary sphincters.

In many instances there is a desire to thin the bile and to augment bile production. When this is the case dehydrocholic acid and desoxycholic acid will be of assistance. The products available may contain a combination of dehydrocholic acid, desoxycholic acid and the lipotropic factors, methionine, inositol, and choline, with bile salts and pancreatin added. These tablets generally are enteric coated and can be given three times daily provided there is not an excess of laxative effect. Should there be too much laxative effect, the dosage must necessarily be cut down to comply with a normal physiological bowel activity of from two to three bowel movements daily.

A very high percentage of people displaying liver malfunction have a concurrent anemia, and it is advisable to use an anti-anemic preparation, such as liver and iron. In many products liver, iron, and the vitamin B complex are combined, in which instance the product will serve to stimulate hematopoiesis and supply raw material for the function of phosphorylation. Liver substance is also a source of protein.

When balancing the therapy against the results of liver treatment it must be borne in mind that patience is essential. The physician must administer both to himself and to the patient a compound essence of tincture of time. The liver

physiology has been perverted over a considerable length of time if it has reached the stage where it can be detected clinically. Consequently, it can not be corrected overnight; nevertheless, with therapy based upon the physiology, the correction of an abnormality of physiology, and a reasonable length of time very gratifying results can be achieved.

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Glandular Relationships

This concept of endocrinology embodies interrelationships between the endocrine gland system, the brain, and the autonomic nervous system. The hypothalamus is the mediating center between the rest of the brain and the lower body. It also controls the endocrine gland system through its relationship to the pituitary gland. The pituitary gland, especially the anterior portion, is the control center of the entire endocrine gland system. For the purposes here, we will often refer to the anterior portion of the pituitary simply as the pituitary gland.

The pituitary gland secretes and elaborates tropic hormones stimulating and activating the other glands of the endocrine gland system. There are manufactured in the anterior pituitary the thyrotropic, the adrenocorticotropic, and the three gonadotropic hormones: follicle-stimulating hormone, luteinizing hormone, and luteotropic hormone (prolactin). Although the gonadotropins are named from their effects on the ovary, it is an established fact that the follicle-stimulating hormone and the luteinizing hormone also influence the testes.

The interrelationship of the pituitary with the target glands is maintained in a state of equilibrium by the fact that as the target gland secretes its product into the blood stream and thence to the pituitary gland, the demand of the pituitary is satisfied and the tropic hormone production from the pituitary is decreased or depressed. In this fashion the

pituitary gland is relatively inactive when the hormones from the target glands are brought to it in sufficient concentration, just as a thermostat is satisfied when the heat answers the setting of the thermostat. When the heat level falls below the setting of the thermostat, the furnace is activated to throw out more heat. When a specific target gland fails to produce its particular hormone, causing an absence or a relative lessening in concentration of this hormone in the blood stream, the pituitary gland, not being satisfied, elaborates the particular tropic hormone designed to arouse the sluggish target gland.

Tropic hormones elaborated by the pituitary gland are mainly specific for the target gland designed to receive them. Thus, thyrotropic hormone will act more forcefully on the thyroid gland than on any of the other endocrine glands. In the event that it is not possible for the target gland to respond to this tropic hormone from the pituitary gland, for example a gonadotropic hormone in a castrate female, and the pituitary gland is not satisfied by receiving in return the particular hormone from the target gland, there is no restraint of the pituitary gland activity. The pituitary is capable of stimulating the adrenal cortex, or the thyroid, or the pancreas causing in these instances an overactivity and increased rate of function. This response is due to the lack of balance of the pituitary production of tropic hormones by the gonad hormones. However, this can be corrected.

Just as hormones from the thyroid gland have the capacity of managing the pituitary gland activity, thus will thyroxin control the pituitary gland in its production of thyrotropins. Cortisone and its derivatives will restrain the pituitary gland in its production of ACTH and the gonads will by supplying their specific hormones balance the pituitary production of gonadotropins. Therefore there is an interrelationship between the pituitary and each separate gland of the endocrine gland system. Some of the target gland hormones are capable of influencing the pituitary gland more than others. The gonad hormones are very powerful pituitary depressants as is thyroxin. Later in this book, each gland will be taken up separately, as to its function, its relationship to the pituitary gland, its symptomatology, and the therapy therefor. At this point the discussion will hinge particularly upon the overall picture.

In the event that the anterior pituitary gland is unable to function due to either exhaustion or injury, the second in command is the adrenal cortex. The adrenal cortex will manage the gonads and to some extent the pancreas, but it is not capable of managing the thyroid gland. This is not invariably the case, for in many instances of pituitary failure the adrenal gland is unable to conduct the symphony in any degree.

After a period of time during which the pituitary gland has set up drives to various target glands and has been unable to synchronize, or reestablish glandular relationships on a normal plane, the hypothalamic area of the brain takes part of the effort into the autonomic nervous system. The divisions of the autonomic nervous system are the cranial and sacral parasympathetic outflow and the lumbo-dorsal sympathetic system. The vagus nerve being the cranial outflow of the parasympathetic nervous system is the portion most involved in this mechanism.

When the pituitary gland is unable to balance the endocrine gland system and the effort is shunted into the autonomic nervous system, the endocrine gland system still will

not be stabilized. It is not capable of being synchronized through the nervous system; moreover, the increased stimulation to the nervous system sets up its own series of symptoms.

When the autonomic nervous system, parasympathetic division, is overstimulated there are symptoms in all parts of the body. Chief among these are an additional secretion of hydrochloric acid in the stomach, pylorospasms, intestinal musculature spasms, such as accompany spastic colitis, and kidney and bladder symptoms usually accompanied by mild cystitis. When the stimulation through the vagus to the pancreas is in excess, there is an increased production of insulin with a resultant low blood sugar or hypogylcemia. In the event that the sympathetic division of the autonomic nervous system is more particularly affected by the effort carried through the hypothalamus, its connections to the adrenal medulla cause an additional production of epinephrine, with a fast pulse and hypertension. It is further conceivable that due to the excess epinephrine in the system, there can be a high blood sugar or hyperglycemia.

There are many, many more symptoms related to the parasympathetic-sympathetic balance and probably all of them make their appearance in one patient or another. Since this book is being read by one trained in the functions of the autonomic nervous system, it is not necessary to elucidate in detail each symptom of each division of the autonomic nervous system. It might be advisable to point out that people classed as vagotonic or parasympathetic types, as well as those who might be typed as sympathetic or sympathomimetic, mediate their preponderance of effect through the hypothalamus of the brain conceivably related to the endocrine gland balance or imbalance.

With the above relationships in mind it can be seen that the most important factor in the maintenance of health can be considered perfect balance in the endocrine gland system with its interrelationship of one gland to another, the perfect correlation of the parasympathetic-sympathetic nervous system, one division to the other, and the maintenance of the autonomic nervous system equilibrium with the hormonal balance of the endocrine system. Deviations on either side, individually or concurrently, will lead to a specific set of symptoms, chemical aberrations, and the resultant disease related to this imbalance.

It becomes obvious therefore that in the castrate female the pituitary gonadotropic drive, being unable to influence ovaries that are no longer present, may be accepted by the adrenal cortex with a consequent production above normal of the adrenocortical steroid hormones influencing the liver to a greater excitability and response in the field of gluconeogenesis. The overall result is a depletion of protein in cells of the body wherever the protein may be given up due to the sustaining of the gluoconeogenesis. The effect in so far as the patient complains could as well be an arthritic syndrome as it could be a gastric or duodenal ulcer. Symptomatology may run the gamut of known symptoms related to protein depletion. The hot flashes that commonly accompany surgery of this type emanate from the autonomic nervous system, but are still due to inability of the pituitary gland to be regulated because gonad hormones are absent.

It then becomes imperative that a given symptom be traced back to its origin which will in many, many instances be found to be an endocrine gland imbalance. Most of these endocrine gland problems are not the frank endocrinopathy discussed in text books on endocrinology wherein pictures

are presented of an advance case of a specific gland dysfunction. The patients who enter our offices are found to be suffering from an endocrine gland disorder which has manifest itself in other systems and is not the extreme occasional acromegalic case or the hypopituitary cachexia that is so often illustrated in texts on endocrinology. The majority of people suffering from disease entities when thoroughly examined and diagnosed can be found to have a condition related directly or indirectly to the endocrine gland-autonomic nervous system balance.

The therapy advocated here is primarily the balancing of the endocrine gland system with emphasis upon the supplementation of the missing or inadequate hormones of a target gland evidently not producing its own secretions. It then becomes necessary before specific therapy is advocated that each gland be evaluated to determine which gland or glands are causing an aberration physically and chemically. We will attempt in the following discussions of the individual glands to point out symptoms of each gland imbalance, as well as symptoms of a general nature that can be related to the glands, and recommend appropriate therapy.

It must be remembered that the music produced by the balance of gland functions is a symphony and when one gland fails to function properly, the entire symphony is one harsh discord. Physicians are expected to untangle this myriad of symptom complexes, to follow through with detective work far more exciting and interesting than fiction writers have ever conceived, to the ultimate point of discerning which gland is the offender and then to administer therapy designed to make the unconforming tissue function once again in harmonious collaboration with its fellow members of the endocrine society.

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Pituitary Gland

The pituitary gland is the master controlling gland of the endocrine system. It manages the activities of the thyroid, parathyroid, pancreas, adrenal and gonads. In turn the pituitary gland is managed by glands of the endocrine system. Whenever blood contains adequate hormone secreted by the target gland, the pituitary gland is at rest and hence is controlled by secretions from the other glands. Due to deficiency of secretion from target glands the pituitary gland elaborates tropic hormone to be carried from it through the blood stream to the target gland for the purpose of stimulating greater activity in that target gland and greater production of its particular hormone. There is a fine point of reciprocity between the pituitary and the target gland. Whenever a target gland fails to produce its secretion and the pituitary gland is called upon to provide greater stimulation the pituitary can be considered as being in a state of increased or overactivity.

The state of overactivity manifests itself in many different ways. First of all, since the problem presents itself during the initial examination of the patient, we should begin with the more obvious discernible signs. The body contour is one criterion upon which to base a suspicion of pituitary gland status. In measuring the patient, if an ordinary seamstress tape measure be used, measurement of the abdomen just below the last rib will give an arbitrary point of stability. Mensuration at this level at each examination means

the measurements can be used for comparison. Measurement of pelvic area should be done at the widest part of the pelvis. It is well to measure from the crest of the ilium downward to the point at which circumference was gauged. Most pituitary type individuals carry the greater part of spread fairly well down below the head of the femur. Measurements of 9, 10, 11, 12 inches below the crest of the ilium would be in keeping with pituitary type padding. Whenever a measurement of the pelvis exceeds that of the waist by more than 10 inches, it is considered due to pituitary gland derangement.

Pituitary type patients, whether overactive or underactive, are classified into hereditary and acquired type. The hereditary type pituitary person gives a history of having a brother, sister, mother, aunt, or close relative who is built along the same line, i.e., wide hip, narrow waist contour. These people have always been pituitary type and ordinarily are attractive, magnetic, enthusiastic leaders. They excel in business ventures, dramatics, activities of parenthood and society. These are people who have many irons in the fire and are extremely active. The acquired type pituitary person has not always the body contour typical of a pituitary problem, however, due to accidents, high fevers, infections, or surgical procedures such as thyroidectomy, oophorectomy, etc., the patient has lost function of some member of the endocrine gland system. As compensatory reaction, the pituitary gland has become increasedly responsive and the patient presents symptoms of hyperpituitarism.

Pituitary patients are further divided into hard tissue and soft tissue type. The hard tissue type presents firm solid tissue when palpated. Their tissue does not easily compress and appears very solid, oftentimes this is accompanied by a florid flushed countenance. The soft tissue type person is

the extreme pituitary case pictured in many textbooks presenting a redundancy of tissue. They have a very pendulous abdomen, thighs, forearms and upperarms are covered by tissue that hangs in folds. These people feel very soft and it does not take much pressure to indent a finger into their tissue. For our purposes, we consider these patients to be hypopituitary. Practically all pituitary types have long slender fingers. Generally they have small wrists and ankles.

The first part of this discussion will concern itself with the hyper, or overactive pituitary case. When one of the glands of endocrine system has diminished its production of hormone, the pituitary gland emits a tropic hormone designed to activate the sluggish target gland. In so doing, the pituitary may either create all tropic hormones or a specific tropic hormone delivered may cause a response in other glands than that gland for which it was intended. Research has not made clear exactly which tissues of the pituitary elaborate each tropic hormone. It has been found that extirpation of a specific target gland causes changes in the cellular makeup of the anterior pituitary tissue. In any event the patient presents an overactive endocrine gland system. Their body is dominated by excited pituitary function.

Unless the thyroid gland is not functioning, thus causative of an energized pituitary, the hyperpituitary person will have an overactive thyroid function as can easily be determined by protein bound iodine analysis. Pituitary activity arousing the thyroid gland to produce an augmented amount of thyroxin, therefore, may be responsible for thyrotoxicosis or exophthalmic goiter with signs and symptoms connected thereto. Increased rate of oxidation is responsible for excessive utilization of protein which in turn may be obtained by the blood stream from peripheral tissue. This patient may

present symptoms indicative of protein depletion or exhaustion, such symptoms as were discussed in the chapter on protein metabolism. The person with the problem of hyperpituitary-hyperthyroidism will display rapid pulse, possibly hypertension, may be thin, nervous, short-winded, and demonstrate other symptomatology associated with hyperthyroidism.

The pituitary drive will extend into other areas of the body. The pancreas often reflects this overactivity and possibly this could be due to the fact that the pituitary gland is under the control of the hypothalmic area of the brain. When pituitary effort is not successful in regulating the endocrine gland system the hypothalmic area calls upon the autonomic nervous system both sympathetic and parasympathetic outflow to aid and assist in an effort to balance the endocrine system. In this event stimulation through the vagus nerve directed to the pancreas, or picked up incidentally by the pancreas, would induce greater amounts of insulin.

It is entirely possible that a tropic hormone from the pituitary may influence creation of insulin. Hyperinsulinism will take many forms, one of which is low blood sugar as determined by either simple blood sugar examination or by glucose tolerance tests. Over sustained periods of time excess of insulin in the blood stream means that sugar deposited in the liver is unavailable for release with consequent production of fatty metamorphosis in the liver. These patients often have periods of weakness, exhaustion, headache, nervousness, tremor, loss of equilibrium, instability of gait, very frequently they show palpitation, short-windedness, and profuse sweating. This patient will have a tendency to crave sweets, starchy foods at certain time intervals such as 10 a.m.

and 4 p.m. at which time their blood sugar level drops. They experience headache, weakness, and dizziness unless they ingest some form of carbohydrate.

The increased drive from the pituitary gland affects the adrenal gland in both medullary and cortical areas resulting in overproduction of epinephrine with consequent rise in pulse rate and potential hypertension. Relationship of epinephrine to sugar metabolism is such that sugar is released from muscle and from the liver in increased quantities helping therefore to combat hypoglycemia of pancreatic origin. Eventually this results in loss of sugar stores of the liver leaving the liver susceptible to toxin, bacteria, poisons, anesthetics, and other noxious substances, developing hepatic disease in some form or another. Release of sugar from muscle tissue due to increased quantities of epinephrine might conceivably result in muscle tremors and muscle exhaustion. The tendency of epinephrine to cause vasoconstriction when present in excess in the blood stream will be capable of promoting a rise of blood pressure. Momentary flooding of the system with epinephrine will increase the pressure, but constant drive from the pituitary is capable of causing prolonged steady hypertension.

Excess cortical secretion both mineralocorticoids and glucocorticoids have individual characteristics referable to symptomatology and more thoroughly discussed in the chapter on adrenal function. At the present point suffice it to say that mineralocorticoids exert their influence in the field of electrolyte balance. There may be sodium and chloride retention with excess potassium excretion and symptoms pertinent thereto of weakness, fluid retention, exhaustion, hypertension. Glucocorticoids actuate gluconeogenesis (breakdown of protein into glucose). Excess generation of glucocorticoids stimulates the liver to form sugar. It becomes necessary that the blood stream supply the liver with an increased amount of protein which can be robbed and withdrawn from peripheral tissues for this purpose. The overall effect is protein deficiency at the peripheral cell level. Arthritis, neuritis, bursitis, tendino-synovitis, myositis, arteritis, colitis, or symptomatology referable to any point from which protein is withdrawn becomes apparent, not the least of which is sinusitis. As additional sugar is produced through gluconeogenesis it is deposited in cell protoplasm, carrying with it water and causing the cell to enlarge and become very firm. This is intracellular fluid retention not edema and is responsible for the hard, firm consistency of tissue.

The increased drive to the adrenal cortex fabricating excess androgen and estrogen will manifest itself in numerous ways. One of which is the achievement of hirsuitism in the female, additional and more masculine distribution of hair on the body. This is difficult to pinpoint as being strictly adrenal in origin, however, in many of these women there will be increased growth of hair in the axilla on pubic area, on upper lip and cheeks. They further evidence coarsening of voice, loss of female contours, and menstrual irregularities. Many times there is an enlargement of the clitoris due to the superfluity of androgen. In the male loss of libido, gaining of female contours with adipose tissue being deposited on the chest, tendency for the voice to become high pitched, and broadening of the hips are often seen. Excess adrenal cortical function can be determined by a laboratory examination of urine for the 17 keto-steroid group which will be high in instances of over activity.

Expanded production of tropic hormones by the pituitary gland will enter into gonad functions. An intensified drive

to the ovary will cause early and profuse menstruation, possibly menorrhagia and metrorrhagia. Many times because progesterone production does not keep pace with estrogen dysmenorrhea occurs. In the male, the effect is exacerbation of activity of the testicle in its formation of androgen and as a consequence this male is oversexed. A preponderance of testosterone will lead to extremely heavy distribution of hair, a basoprofundo voice, aggressive personality traits, and in young people precocious development of the secondary sex characteristics.

In management of hyperpituitarism, due to low blood sugar, appetite can be used as a criterion of progress. Since the hyperpituitary patient exhibits an extreme appetite, and particularly for starches and sweets, it will become manifest that as the pituitary drive subsides production of insulin will be somewhat diminished allowing a normal level of blood sugar. This in turn will cause abatement of the patient's appetite. A patient who has presented an extreme appetite, placed under management, again displaying evidences of increasing appetite, would indicate to the physician in charge that the pituitary gland is still not fully controlled.

It is our policy when treating younger women to explain that because their pituitary is overactive, we must depress it. In all probability their ovaries have built up tolerance to an extreme drive from the pituitary gland, now necessary for normal ovarian function. As we inhibit the pituitary gland, they may expect scanty periods, or even miss menstrual periods with a protracted time interval between cycles or the development of mild dysmenorrhea. It is advisable that they be informed in order that they do not become alarmed. The ovary itself will cycle regularly with balanced pituitary action, but there will be a time interval during which adjustment must take place. At this period we wish to forestall any anxiety on the part of the patient. Some girls have been slow to start menstruating and have not had satisfactory chronological development of female characteristics, thus perhaps showing a reason for the pituitary drive. Because of an effort to cause maturation of ovaries, and hence development of secondary sex characteristics, the pituitary has strengthened its support. The ovary may have been causative originally of hyperpituitarism and has reached a point of requiring a superabundance of stimulation through the follicle stimulating hormone in order that it perform normally. In the event that the PBI and 17 keto-steroid production is normal or increased, we often attribute excess drive of the pituitary to slow development or faulty development of ovarian functions.

This same method of thinking can be applied to young males who disclose precocious development of secondary male sex characteristics. Early development of phallus, scrotum, and hair distribution with change of voice, and development of male aggressiveness can be due to the fact that the thyroid gland is not providing full measure of thyroxin. The pituitary gland endeavoring to excite the thyroid has energized the entire endocrine gland system motivating early or overdevelopment of testicular secretion, accounting in those cases for precocious development of this young boy.

In further discussion of reciprocal actions of the pituitary, with target glands it might be pointed out that hyperthyroidism could be due to the effort of the pituitary to invigorate a recalcitrant ovary or testicle. A thyroid gland being dominated by this drive produces copious thyroxin accounting for thyroid overbalance.

It is necessary in all instances here mentioned and insinuated that there be protein available in the blood stream. Since each individual target gland, and the pituitary gland as well, require protein in formation of their specific hormones it is imperative that serviceable protein be present in the blood stream. These people are predominately overactive and are very rapidly exhausting their supply of protein. Couple with this, the tendency of gluconeogenesis and there are provided all the essential factors necessary for the patient to develop hypoproteinemia.

Many cases of hypopituitarism are the subsequent result of a previously overactive pituitary gland. With continued drive and excess utilization of protein, eventually the pituitary gland exhausts. The patient's characteristics change from hyperpituitarism to hypopituitarism. There are other causes of hypopituitarism and this may be divided into the hereditary and the acquired type. The hereditary type of hypopituitarism is born with a pituitary gland incapable of normal function. The acquired type may have pituitary gland damage due to surgery, trauma, high fevers and toxic aftermath. The hypopituitary usually has impoverished peripheral cells of protein to the extent that they have literally eaten themselves and these cells are vacuoles containing water and electrolytes, but the protein part of cell protoplasm is sadly depleted.

The hypopituitary person generally speaking is slow mentally, apathetic, and presents every appearance of being utterly exhausted, many times having pallor indicative of anemia, often having edematous ankles and feet. This type of problem is the exact counterpart of the hyperpituitary. Patients show evidence of shortage of competent stimulation from the pituitary gland. PBI examination will demonstrate deficient concentration of protein bound iodine in the blood stream, the patient presenting frequently a myxedemous appearance with dry coarse skin, loss of hair, brittle flaking fingernails, low pulse rate, and a history indicating that in their prior care thyroid administration was beneficial. Females may present menstrual irregularities even to the point of amenorrhea and many times with a history of miscarriages.

The pancreas does not function in a typical manner. There is a tendency to an excess concentration of glucose in the blood stream, i.e., hyperglycemia, the patient has insufficiency of appetite. There are often symptoms of gastrointestinal disturbances conceivably due to inefficacy of the pancreas to manufacture digestive enzymes coupled with failure of the intestinal tract to selectively absorb sugars, referable to the hypothyroidism present. In any event regression of insulin production combined with inadequate thyroid formation superimposed upon fatty degeneration of the liver leads to obesity in its most extreme form.

The adrenal gland without sufficient excitation from the pituitary in hypopituitarism will not secrete adequate epinephrine and norepinephrine into the blood stream thus leading to deficiency of energizing the anterior pituitary from this source and in addition the tendency to low blood pressure and pallor. The cortical secretion incomplete in production or concentration leads to symptoms of imbalance of electrolyte concentration, such as a disturbance of sodium, chloride, and potassium. Extreme failure of the adrenal cortex leads to symptomatology similar to Addison's disease, such as malaise, asthenia, exhaustion, low blood pressure, lack of appetite, fluid retention. In addition development of symptomatology similar to any arthritis, joint aches

and pains, and muscular weakness are often accompaniments of adrenal cortical insufficiency. The condition may progress to the point of the patient displaying pigmentation similar to bronzing of Addison's disease. As a rule during the age bracket wherein normal activity of gonad tissue would be expected, failure of the adrenal cortex to produce gonad hormones is not particularly discernible.

The gonad tissue in the absence of follicle stimulating hormone and luteinizing hormone normally elaborated by the pituitary gland, reflects all stages of disturbance. In the younger person without satisfactory pituitary drive gonads do not mature and hence the patient does not produce gonad hormones. This may precede failure of epiphyseal fusion at the chronologically expected age. The patient will become tall and eunuchoid in appearance.

If the pituitary gland falters after maturity women then lack normal estrogen-progesterone concentrations in the blood stream which are responsible for normal uterine engorgement and deciduation, thus the cycle of menstruation is disturbed, the degree depending upon the relative amount or absence of pituitary drive. This varies from complete amenorrhea to menstrual periods 3 to 5 months apart with prolonged bleeding at the time of menstruation. Protein metabolism is very dependent upon the anabolic effect of gonad hormones and in their absence there is a perversion of protein physiology. Often the patient will present symptoms primarily of hypoproteinemia and it is only by thorough investigation into menstrual history that hypogonadism is discovered.

Hypopituitary patients may be difficult to immediately diagnose as being of subnormal pituitary activity. A thorough history may disclose the fact, but if in undertaking

management of the patient, it becomes necessary to sustain the thyroid gland in its function, and support is needed for the gonads which benefits the patient, with the exception of a mild arthritis and in the clinicians estimation it would be of value to use a synthetic corticoid to control the arthritis, it should then become apparent that target glands are being bolstered in all processes and the diagnosis of hypopituitarism is obvious. Examination of protein bound iodine finding it low, coupled with 17 keto-steroid examination which proves subnormal, and detection of depressed estrogen level either by examination of blood or by papanicolaou smear, or if preferred a check on gonadotropic hormone level all indicating subnormal activity of the target gland is direct evidence of hypopituitarism.

In the management of the hyperpituitary type patient, it is advisable to correct in any instance of its presence hypofunctioning of a target gland. For example, if the thyroid gland is not functioning competently as determined by PBI evaluation, attention should be directed to correcting this faculty. The chapter on thyroid discusses various reasons that the thyroid gland might not be performing even in the presence of abundant pituitary stimulation. Briefly to preserve continuity of thought, it can be said that insufficiency of protein or lack of iodine as determined by a screening test would be evidence that the thyroid gland could not act due to the inadequate supply of raw material. Therefore treatment would be directed toward reestablishing normal thyroid physiology.

Thyroxin is a powerful pituitary gland depressant. Addition of thyroid to this patient's blood stream in the form of desiccated thyroid (orally) will help control an overactive pituitary gland. Fairly heavy doses of desiccated thyroid

substance produce this consequence. Oftentimes we find it takes 9 to 15 grains of thyroid per day to help control an overactive pituitary gland.

Further mastery of the pituitary gland can be achieved through administration of gonad hormones. Estrogen and testosterone are powerful pituitary depressants. They should be administered according to indications discovered during a thorough examination of the patient and with particular regard to past history of gonad function. It may be mentioned here that to have progesterone produced from the gonads, thyroxin must be present. Many times the pituitary gland in a drive to cause secretion of progesterone from the ovary can be assisted by concurrent administration of thyroxin.

Giving phenobarbital one-quarter (1/4) grain and belladonna one-eighth (1/8) grain as a single tablet will be effective in depressing the overactive parasympathetic nervous system, the vagus nerve and thus relieve the pancreas of its extreme stimulation. This in turn allows the blood sugar to return to normal thereby depressing the craving for carbohydrate. As this is accomplished, a mild diuretic such as ammonium chloride may be administered since with normal sugar metabolism reestablished, fluid will be released from peripheral cells into the blood stream. A mild diuretic at this stage assists filtration of fluid through the kidney and counteracts a tendency toward high blood pressure from increased fluid in the blood stream.

There are a few patients on whom all of the above is not enough to control their pituitary overactivity. In those instances it is advisable to use one-quarter (1/4) grain tablet of desiccated pituitary substance daily. The administration of pituitary substance will depress the pituitary gland by

substitution therapy. As a rule we consider that pituitary substance is effective unless the patient gains weight. If this occurs it is due to increased gluconeogenesis as an end result of pituitary stimulation to the adrenal cortex from the administered desiccated pituitary substance. There is some question relative to the merit of desiccated pituitary substance but although it often has been claimed the material in this form is inert and accomplishes no result, desiccated pituitary substance where it is not indicated, will cause the patient to retain fluid, to burn in excess their protein supplies and to gain weight. Conversely, where desiccated pituitary substance is indicated and is properly given results are quite apparent. Pituitary drive is decreased, the patient does not show a tendency to low blood sugar, the menstrual cycle readjusts toward normal, and all evidences point to the fact that the pituitary gland was regulated by this means. In our experience it has not been necessary to exceed one-quarter (1/4) grain tablet of desiccated pituitary substance daily in the hyperpituitary patient.

In treatment of the hypopituitary patient, all target glands must be supported. It is necessary to sustain gonads as discussed in the chapter on gonads. It may be necessary to use small doses of glucocorticoids. That desiccated thyroid substance be used is the essence of this therapy. As a rule our management starts with 3 to 5 grains of desiccated thyroid daily, increasing as the need may indicate. In all cases of hypopituitary gland function, we suggest that the patient be started with one-quarter (1/4) grain tablet of desiccated pituitary substance daily and increase until satisfactory results are obtained, in some instances even to the point of 10 grains daily. As a rule however, it is not necessary to use this level of dosage of anterior pituitary sub-

stance and more averagely 2 to 4 grains daily will suffice.

During management of both hypo and hyper pituitary patients attention must be given to protein metabolism. Without ample protein support these patients cannot balance glandular functions, cannot respond with return to normal function basically due to shortage of raw material. Both hypo and hyper pituitary people have undergone some form of protein metabolic disturbance, to consider their level of protein metabolism, and to correct it if necessary is one of the most important facets of treatment.

The hypopituitary person can often be restored to more normal degree of vigor by use of an amphetamine product. We use 5 grains of dextro-amphetamine with one-eighth (1/8) grain amobarbitol one hour before each meal in an effort to excite the adrenal medulla. Since amphetamine is a sympathomimetic medication, the sympathetic system is aroused, thus the adrenal medulla enlarges its output of epinephrine and the patient feels more energetic while being thus supported.

Pituitary type patients are very perplexing to manage because as a rule they have been from one clinic to another. Clinicians that can recognize pituitary problems feel they are very intricate to manage and as a consequence do not care to supervise the correction of these problems. When the physiology and the patients' problem are thoroughly understood, because these are people who often times present emotional and environmental entanglements management of their case is not too arduous and results are most gratifying. It must be explained to the patient in some detail. When patients realize that you are thoroughly familiar with their dilemma and with the correction of it, they are happy to have found someone who will take an

interest in them and who will manage their recovery properly. It has been their experience that those who would attempt to manage have not been too interested, nor had reasonable success, so the patient as a consequence is quite discouraged. It behooves you as the physician, to instill in that patient faith and confidence that their case can be normalized and that they can look forward to a time when their health is restored, their appearance is better, their disposition is improved, and to all intents and purposes they are attaining successful results. They are quite slow to respond. In the majority of instances their dysfunction is not a new one, but they have had difficulty over a period of years and it will as a consequence take time to correct and reverse the processes. There is a great deal of personal gratification in witnessing correction of pituitary functions based on proper management. This supersedes other considerations and personal enjoyment you will derive from returning this patient to a normal person is priceless.

Pituitary Gland References

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Thyroid Gland

The thyroid gland occupies the same position in the endocrine circuit as do other members of the system. Pituitary gland elaborates thyrotropic hormone which in turn compels the thyroid gland to elaborate its secretion thyroxin. Concentration of thyroxin in the blood stream controls rate of secretion of thyrotropin from the pituitary gland. The thyroid gland, through its products, regulates oxidation. Thyroxin is a combination of iodine and the amino acid tyrosine. Combinations of tyrosine with iodine are named according to number of iodine molecules united with tyrosine; thus, monoiodotyrosine, diiodotyrosine, and triiodotyrosine.

Activity of thyroxin, insofar as can be determined, takes place in each individual cell and within cell protoplasm. Rate of cell metabolism is thus excited. The thyroid gland is susceptible to influences of cold, heat, excitement, fear, anger, and physical exertion. Diet and food intake are highly important in regulation of thyroid physiology. Thyroxin is a vasodilator and cardiac stimulant, increasing cardiac output and circulation time. It is a diuretic. The rate of oxidation is quickened by thyroxin, which simultaneously provides impetus for gastric secretion, motility and assists the intestinal tract in assimilation. Dominance of thyroxin on hepatic cell activity should not be underestimated, and thyroxin is quite instrumental in motivating bone marrow to originate erythrocytes.

The authority of thyroxin upon the liver is very helpful

in maintaining concentration of gamma globulin and enhancing resistance to infection. Whenever there is bacterial invasion there is defiant response of the thyroid gland in an effort to strengthen patient's defense. Thyroxin exerts beneficial effect on the integument, in its absence there are many skin conditions that become apparent. It is quite essential that thyroxin be present for customary ovarian and testicular function. Paucity of thyroid secretion prevents or decreases efficiency of copora lutea to form progesterone and is related to miscarriages.

There is some opinion to the effect that thyroxin is antagonistic to insulin. This is not truly the case. Thyroxin and insulin both require protein as raw material in their formation, and profuse thyroid production would mean less protein available to the pancreas to prepare insulin. An exceptionally active thyroid state could cause reduced secretion of insulin due to lack of raw material. Rather than term insulin and thyroxin antagonistic, it would be more accurate to term them "competitive."

There are imbalances of thyroid gland operation, both on under and overactive planes. The hypothyroid person may experience symptoms involving any tissue of the body: constipation, vertigo, shortwindedness, hyper- or hypotension, anemia, pallor, skin diseases, allergies, fatigue, exhaustion, malaise, hypo or achlorhydria, hypoproteinemia, menstrual irregularities and miscarriages, edema; and in an extremely hypothryoid patient there may be a generalized edematous appearance which is known as myxedema. All or some of these varied symptoms are found in hypothyroidism.

Competency of the body to protect itself against atheromatus depositions in blood vessels depends to some extent upon thyroid gland status. Relationship of thyroid secretion

to liver functions as determined by cholesterol measurements indicates that in euthyroidism cholesterol level of blood serum is within normal range, i.e. between 150 and 250 milligrams per cent. The hypothyroid person presents increased cholesterol, and hyperthyroid people low cholesterol concentration.

Among other symptoms of hypothyroidism may be found alopecia, thinning and brittleness of hair, dryness of scalp, loss of eyebrow hair on the lateral third of eyebrow, and frequently obesity. Many hypothyroid people have dry, coarse skin, blunt fingers and brittle, flaking fingernails, are asthenic and lack libido; some are mentally depressed and morose. Digestive disorders, cardiac enlargement, mild deafness, frequent headaches, and large flat tongue may accompany hypothyroidism.

Body build of the hypothyroid is quite typical in that weight and bulk are carried in the middle. Waist and abdomen are large, the trunk is full, and waist-hip measurements differ by less than 10 inches. These people give the appearance of mental dullness, are often stoic, and are sensitive to cold; frequently a very young person, an infant, presents mongoloid physiognomy.

In this connection we had opportunity to manage a three year old boy diagnosed by several different clinics and their pediatricians as mongoloid. This child was too young for satisfactory blood examination but to all intents and purposes seemed to be a hypothyroid problem. The child was placed on ½ gr of thyroid daily for one month, following which dosage was increased to 1 gr daily. This child, at the present, is on 4 gr of thyroid per day. Results of this therapy are absolutely astounding. The child is intelligent, capable of taking care of itself, helps its mother with minor housework.

Even slant of the eyelids has corrected. It is my opinion this abnormality was due to the mucoid deposit of myxedema in the upper eyelids. There are probably many patients who have been diagnosed as mental dullards who would be benefited by thyroid administration.

The incidence of coronary accidents and angina pectoris among myxedematous patients is so frequent it would lead to a conclusion that the fat-clearing factor of thyroxin and effect of thyroxin on cholesterol production is of great significance and during failure might often be instrumental in causing coronary atherosclerosis.

The thyroid gland and its relationship to pituitary can be expressed in this fashion and termed the "thyroid factor." The pituitary gland, anterior lobe, elaborates thyrotropin, which in presence of adequate available protein empowers thyroid gland to develop protein bound iodine, provided sufficient iodine is present. In this formula, the thyroid gland acts as manufacturing plant using raw materials of protein and inorganic iodine. Available protein and inorganic iodine are bound together by processes within the thyroid gland. The pituitary gland, when overactive, animates thyroid gland to produce an extravagant quantity of protein bound iodine. In hypopituitarism there is not enough thyrotropin produced to uphold normal PBI. Causes for the disturbances of pituitary function are discussed in the chapter, "Pituitary Gland."

There are people, born without competent thyroid colloid tissue, who are destined to be hypothyroid. These patients can be sustained and managed by exogenous thyroid substance. There are other instances wherein the thyroid gland has been removed surgically, damaged by toxic agents, or depressed by radioactive iodine, and it is necessary to sustain the thyroid with exogenous thyroid substance. The

average patient will present hypothyroidism due either to deficiency of available protein or lack of inorganic iodine.

Insufficiency of suitable protein can be a multifaceted problem. A person can become hypothyroid because of effort to diet, in which case, to conserve life on restricted food intake the thyroid gland has decreased its action. Maybe it has become inhibited because of scarcity of usable protein. There is faulty gastrointestinal function, achlorhydria or hypochlorhydria, and decrease of stomach motility in any hypothyroid person. Appetite is poor and food cannot be properly digested. The stomach empties slowly because pH of the stomach is too alkaline and the pyloric sphincter consequently sluggish in opening. The intestinal tract becomes ill-fitted to execute its role of digestion. The pancreas is not prompted to pour its secretions of fluid, electrolytes and enzymes, into the duodenum because of low gastric acidity. Assimilation of nutritive material through intestinal mucosa is impeded when it reaches the small intestine. The large intestine does not absorb food and the latter is wasted. Processing functions that depend upon normal healthy liver are impaired if this patient has developed fatty metamorphosis of the liver.

To return to the thyroid—without potent thyroid function gonad tissues do not produce their hormones. Since protein employment is very dependent upon sex hormones, it is easy to see why a person may lack protein essential for normal thyroid function. Protein deficiency will cause symptoms. It would be wise to prescribe laboratory assistance in the field of protein analysis, such as total protein, serum albumin, serum globulin, A/G ratio and cholesterol in the event that the symptomatology is not tangible.

There are people whose hypothyroidism is due to in-

sufficiency of inorganic iodine or colloidal iodine is not present. This can be determined by laboratory examination for inorganic iodine of blood serum. Normal reading should be 2.5 to 3.0 gamma per cent. There is not enough iodine present to sustain thyroid function when inorganic iodine falls below 2.2 gamma per cent. Inorganic iodine is a cumulative mineral and it does not require very much to replenish low concentrations. It is not recommended that inorganic iodine be administered for longer than three months unless repeated blood checks are made. When inorganic iodine concentration exceeds 3.0 gamma per cent it becomes a thyroid gland depressor. It is used in this capacity to control thyrotoxicosis and therefore it is not advisable in maintaining adequate iodine to exceed 3.0 gamma per cent. We would prefer not to have this concentration drop below 3.0 gamma per cent were the objective to depress thyroid overactivity. The present discussion hinges around hypothyroidism and is concerned with adequate supply but not a supply sufficient to depress.

There are specific peculiar symptoms relative to low inorganic iodine concentration. Among these will be found a sensation of choking. Many asthmatics need inorganic iodine. Leg cramps and muscle cramps can be precipitated by iodine deficit. Patients may come in frightened by pains in their chest fearful that they are suffering from a cardiac problem. If costocartilages are palpated and found to be extremely tender to light pressure, this may be due to iodine deficiency. It is necessary that protein and iodine both be present in order to have normal thyroid function. Frequently the PBI is within compliance—the patient is euthyroid—but the inorganic iodine is not ample. This patient will not stay at euthyroid levels very long, having provided it at the expense

of inorganic iodine. Any inorganic iodine supplement will replenish quite rapidly: Lugol's solution, or any commercial preparation.

Only with normal erythrocyte count and hemoglobin concentration can vital protein be convenient to tissues of the body. PBI examination may be low as a compensatory response of the body to severe dysfunction of tissue in some other field. Nature by prescribing the rate of oxidation and metabolism attempts to protect the involved area by reducing activity. Therefore thorough analysis of a patient should precede any effort to animate his thyroid gland assignment. Occasionally nature has endeavored to extenuate work of a heart suffering from mitral or aortic valve lesions by decreasing the rate of metabolism. It would not be advisable to return PBI to normal level in an instance of this type.

The PBI has been used to the exclusion of basal metabolic rate in this discussion. There are several reasons for this. The B.M.R. is notably inaccurate. Five or six different readings should be made and the mean of these readings used. B.M.R. takes into account only rate of oxidation. It is more accurate in cases of overactivity of the thyroid and quite inexact in cases of underactivity. The rate of oxidation can be influenced by so many factors that reading B.M.R. is not truly an interpretation of thyroid status.

The laboratory analysis of blood specimen for protein bound iodine is very precise and especially so in hypothyroid conditions. PBI analysis is true appraisal of thyroid gland function. As with any laboratory test, the blood or serum concentration of material in question fluctuates through a normal range. The specific instant that blood is withdrawn may catch the concentration of material in one extreme or the other of this normal swing. Our evaluation of normal

or euthyroid reading is that the level of PBI in blood serum fall between 5 and 7 gamma per cent. Low normal is 3.5 to 5 gamma per cent. Low thyroid is between 2.5 and 3.5 gamma per cent, and myxedema is below 2.5 gamma per cent. Seven to 9 gamma per cent is considered mildly overactive thyroid and above 9 is an extremely overactive condition. Normally pregnant women carry readings of 9 gamma per cent and this is not pathological. Extremely high PBI levels are considered to be within surgical or radioactive iodine fields. Below that and below the normal level are all amenable to less drastic treatment.

Patients exhibiting really low PBI are extremely sensitive to exogenous thyroid substance and should be started very conservatively. One-half (½) grain daily should be the maximum starting dose for a person showing PBI below 3 gamma per cent. The euthyroid, with a level between 5 to 7 gamma per cent can take tremendous amounts of thyroid substance without changing this concentration. As a patient leaves hypothyroid level and enters euthyroid state it is necessary to increase his dose of desiccated thyroid many fold, often as high as 10, 12, 15 grains per day to influence a PBI level of between 5 to 7 gamma per cent.

Considering exogenous thyroid substance it should be pointed out that U.S.P. thyroid substance contains a percentage of inorganic iodine. Increment of inorganic iodine may reach a level wherein it acts as thyroid depressant, inhibiting natural production of thyroxin when administered for periods of time. There are several pharmaceutical houses that manufacture thyroid substance in which inorganic iodine is buffered and not capable of being assimilated. There is no danger of accumulating too much iodine from those products.

Thyroid substance with buffered inorganic iodine stimulates the thyroid gland when administered in small doses; when given in large doses it suppresses thyroid secretory function. Restraint of the thyroid gland over long periods of time by use of external desiccated thyroid substance fulfills its purpose and when exogenous supply is withdrawn between six weeks and three months are necessary for the thyroid gland of that person to resume normal operation. There is no danger of permanently depressing the thyroid gland under this type of management so the overall picture resolves itself into supplementation of the patient's tissue and tissue production with the use of exogenous desiccated thyroid gland free of inorganic iodine, or with a buffered inorganic iodine.

The dosage depends upon the level of PBI but the rule of thumb is the lower PBI the less thyroid is administered until such time as the level of PBI has been raised, indicating enhanced tolerance.

Secondly, consideration of inorganic iodine is absolutely indispensable and when the patient's inorganic iodine level is low repletion can be effectuated through any inorganic iodine product on the market but must not be maintained too long. Excess inorganic iodine may have hindered thyroid activity in the event that inorganic iodine level is too high and PBI is low. It is necessary to employ large amounts of protein in order to use excess iodine. When protein is administered in large quantities there is biological action between inorganic iodine and albumin, forming iodinated protein, which has very little physiological activity.

Thirdly, consideration of protein metabolism is imperative. Despite pituitary stimulation competent thyroid colloid tissue, and presence of commensurate inorganic iodine, pro-

tein bound iodine cannot be formulated without ample available protein. Deprivation of paramount available protein or when availability is borderline, stimulating the thyroid gland may deplete protein dangerously. This deprives other glands, such as pancreas, of protein requisite to create their secretions, conducive to symptoms of dysfunction in those glands.

It is also important that when laboratory work is done there should be broad enough analysis to insure the interpretation is not being made upon basis of one laboratory procedure. PBI will almost invariably be high when there is chronic or acute infection in the body. Judging by PBI alone inference would be false, whereas if all factors were considered and infection ruled out deciphering PBI would be less subject to error.

There is much hyperthyroidism directly due to vigorous activity of the anterior portion of the pituitary gland. Very frequently some symptomatology is difficult to differentiate from that which might accompany hypothyroidism, nevertheless hyperthyroid people are as a rule thin with rapid pulse rate and hypertension; exophthalmos may or may not be present. When present, it is generally considered to be due not to thyroid but to pituitary gland potency. Exophthalmos is due mechanically to accumulation of fatty mucoid type tissue behind the eyeball pushing it forward. The origin behind the pituitary drive must be ascertained and appropriately treated to place it under control when the hyperthyroidism is due to pituitary gland compulsion. Some hyperthyroidism will be found in the presence of normal pituitary function. Present day therapies, with thiouracil, propylthiouracil, tapazole, inorganic iodine, radioactive iodine and surgery have the problem well in hand.

For a more enlightening discourse on hyperthyroidism the reader is referred to any standard textbook which will go into more minute detail concerning this subject.

There are colloid goiters, found generally in younger women, in which PBI is normal or below and colloid tissue of the thyroid gland greatly enlarged. This can be considered an effort of colloid tissue to expand to present greater surface to the blood stream in order to capture all available inorganic iodine. Therapy is generally successful and consists of supplementation of thyroid gland with exogenous desiccated thyroid as well as inorganic iodine. Properly treated these goiterous enlargements usually disappear in from three to six months.

There is no age contraindication to treatment with thyroid, in fact senility is delayed if we consider aging to be slowing of the glandular system. With proper attention to iodine, protein, PBI, use of thyroid substance will not cause cardiac palpitation, nervousness, extreme perspiration, or toxic symptoms commonly associated with excess thyroid.

Proper thyroid management is very effective in maintaining balance of the autonomic nervous system and glandular system. One of the most frequent causes of excitation of the pituitary is hypothyrodism and this is rectified with proper management, crutching of the thyroid gland. Thyroid function is absolutely essential to synchronism of other endocrine glands. Thyroid gland not operating properly, or removed, without substitution therapy, leads to severe imbalances in other tissues and organs.

Abundant thyroxin to enrich normal ovarian function is not a new facet of physiology but is certainly a highly important factor, relating to menstruation, pregnancy, and delivery. Normal thyroid gland function is likewise neces-

sary for the adrenal gland to perform properly. A hypothyroid condition causing increased pituitary production of tropic hormones may result in an highly overactive adrenal cortex. The consequent gluconeogenesis results in protein depletion to the extent that the sluggish thyroid gland becomes even more deficient. Protein is being excessively utilized in the liver in the process of gluconeogenesis. The pancreas will be maintained at reasonably normal activity by normal thyroid function. The inability, with hypothyroidism, of the intestinal tract to assimilate sugar means that even normal amounts of insulin cannot be properly utilized due to lack of sugar. The liver is the storehouse for sugar and failure to assimilate it can cause depletion of sugar stores of the liver leading to increased susceptability of hepatic cells to anesthetic, toxic, and noxious substances.

Importance of normal healthy function of the thyroid cannot be overemphasized, whether natural or achieved by substitution therapy. The level of the patient's health when these factors are given consideration, will be so improved that enthusiasm will be aroused for use of thyroid substance in situations seemingly remote from thyroid surveillance. However, every area can be influenced by thyroid activity, since it controls metabolism of each cell in the body. Take for example coronary heart disease. Research has proved that fat molecules circulating in the blood stream, generally considered to be part of cholesterol content, are related to etiology of this cardiac disease. Effect of thyroid regulation upon the liver, as judged by cholesterol-PBI relationship, indicates that euthyroids maintain these fat molecules at minimum level. Normal thyroid function re-established after a period of hypothyroidism is capable of promoting and maintaining efficient liver physiology. Thyroid therapy, because

it stimulates reabsorption into the blood stream of fat deposited on the inner lining of blood vessel walls, is one of the finest preventives of coronary heart disease yet discovered.

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Pancreas

The pancreas enters the endocrine system with responsibility of supervising, through one of its products, the utilization of glucose. The individual peripheral cells are dependent upon functional integrity of the pancreas in this domain. Since the liver is the storehouse of glycogen, which in the blood stream becomes glucose, there is an interrelationship between the liver and the pancreas. The pancreas, in producing its secretions, is sending an interoffice memo to the storehouse (liver) to deliver into the blood stream its stored sugar. The liver can act upon this directive only when it is in a state of normal good health. The pancreas can produce its order upon the slightest provocation. Whenever the president of the company (pituitary) decides that for the best interest of the company (body) he must act in a decisive manner to control any of the company's employees (endocrine glands) the pancreas is influenced through this activity. For example, with conscious mind to recognize fear or danger and be called upon to protect itself, the effort would be mediated through the hypothalamus and hence through the pituitary gland. The pituitary gland stimulating the adrenal would cause production of epinephrine and norepinephrine, further stimulants to the pituitary gland, and the adrenal corticoid secretions. Simultaneously since epinephrine liberates sugar from liver and muscle tissue, the pancreas will be called upon to supply more insulin in order that body tissue be able to properly utilize this new supply of heat and energy.

Another example of this same process is when the pituitary gland over sustained periods of time attempts to influence a particular target gland and is unsuccessful, the hypothalmic area calls upon the autonomic nervous system to help manage the target gland in question. Vagus nerve being part of this autonomic nervous system, stimulated, causes the pancreas to compound insulin. Function will continue relatively normal with liberal nutrition for supply of raw material and provided reasonable exertion is demanded of the pancreas. In the event that there is insufficiency of raw material or that the pancreas has been asked to work overtime continuously, the gland may regress, and the level of blood sugar becomes uncontrolled. The entire endocrine gland system through the pancreas, governs the supply or source of blood sugar from the liver.

The pancreas produces two types of secretions, one external, the other internal. Internal secretion is the hormone insulin. External (intestinal) pancreatic juice is composed mainly of enzymes. These consist of trypsin, a powerful proteolytic, acting best in alkaline medium, hydrolyzes proteins into polypeptides; amylase converts all forms of starch rapidly into maltose; lipase, splits neutral fats into diglycerides, monoglycerides, free fatty acids and glycerol. Bile actuates lipase which may be secreted in the form of an inactive precursor, prolipase.

The pancreas is under control of vagi and excitation from the mouth (as accomplished by food ingestion) produces response of secretion, sending forth enzyme-rich juice. Introduction of certain substances in the intestine is influential to pancreatic proficiency. These substances are acids, fats, and bile. Acid, .5 per cent hydrochloric, is very effective and pancreatic juice secreted in response is highly alkaline with lower enzyme content than that excited through vagus nerve activity. Fat is as effective as weak acid, and bile salts also encourage pancreatic juice. Water and irritants are ineffective; alkali inhibits pancreatic secretion. There are certain hormones developed by the intestinal mucosa which are very vital to formulation of pancreatic juice. Secretin is one, pancreozymin is another.

It is quite conceivable that a person with endocrine gland dysfunction such as caused by removal of an ovary, would have a compulsion from the pituitary gland. This over an extended period would be shared by the parasympathetic nervous system. Vagi, the cranial outflow of the parasympathetic system, would carry excess or increased stimuli, energizing secretory response of the pancreas. Cells producing pancreatic juice would exhaust and become dormant were this continued. Thus, impaired digestion and proteinemia would run rampant.

Production of insulin is believed to be from beta cells of the islets of Langerhans. Insulin is a soluble protein with molecular weight of 48,000. It has been isolated in pure crystalline form and considerable progress has been made in determining the arrangement of amino acids along the peptide chain. It is destroyed by proteolytic enzymes in the gastrointestinal tract if administered orally and therefore has to be administered parenterally.

The domain of insulin is related to phosphorylation, the process whereby glucose in the blood stream enters peripheral cells. Glucose is united with a bond of high energy phosphorus derived from adenosine triphosphate. This is taken up in detail in the chapter on liver physiology. Insulin facilitates phosphorylation, expediting sugar utilization by peripheral cells. Absence of insulin delays or stops phosphorylation,

allowing glucose to remain in the blood stream to be filtered through the kidney.

There is a delicate balance between the service of insulin in phosphorylation, sugar metabolism and the liver, which acts as both a storehouse of excess blood sugar and a source for sugar when needed. This fine balance is maintained intact in normal good health. However, since pancreatic secretions are influenced by the vagus nerve there can be overproduction of insulin with consequent hypoglycemia. In the presence of intensified concentration of insulin the liver may be unable to return stored sugar to the blood stream. The effect becomes more pronounced hypoglycemia, results of which become quite serious.

Symptoms of hypoglycemia are principally cerebral in origin. First there is a feeling of hunger and a great sense of fatigue. Walking becomes difficult, the patient may become anxious, worrisome, excitable, or behave as if he were intoxicated or demented. Then tremulousness develops and fine movements cannot be carried out. Following this, vasomotor disturbances occur, i.e. flushing, and profuse perspiration, which may soak the bed clothes. There may be pallor and chilliness, probably due to compensatory secretion of epinephrine. Later there are more serious mental disturbances, delirium, and convulsions. Coma then develops with loss of deep reflexes. The first symptoms may occur either at a blood glucose level of 75 milligrams per cent, or not till much lower level such as 30 milligrams per cent is reached. In chronic diabetics with high blood glucose, symptoms may occur when hyperglycemia is suddenly reduced so the blood glucose is still above normal, perhaps at a level as high as 150 milligrams per cent.

Symptoms of hypoglycemia are relieved by administration of glucose. Adrenalin helps by mobilizing liver glycogen. This response of the liver is more marked in well fed persons than in starved or diabetic subjects in whom glycogen stores of the liver are low. The hypoglycemic stage can be considered prediabetic. It is often due to mental, emotional and starvation conditions, but in an appreciable group of people is more deep-seated and relates to endocrine dysfunction.

Hyperpituitarism is quite capable of triggering secretion from the pancreas. This would release more insulin and is commonly due to dysfunction of a target gland goading the anterior pituitary gland to produce one or all tropic hormones in the effort to bring a recalcitrant target gland back into synchronization. The effect arises directly from the pancreas and secondarily through the parasympathetic nervous system. This, over long continued periods, results in chronic hypoglycemia.

Among other factors precipitating hypoglycemia is ingestion of large quantities of carbohydrate, particularly granulated sugar. In people with this condition, (and this may be an amazingly high percentage of the general population, determined in your individual practice by glucose tolerance tests) the diet should include carbohydrates from natural sources. Excess production of insulin eventually exhausts the beta cells of the islets of Langerhans. The pancreas fails to form insulin when this occurs leading to diabetes mellitus.

That proper amino acids be provided is essential for preparation of insulin. All endocrine glands use protein in perfecting their secretions, there will be demand from many areas. Expanded competition may cause relative insufficiency of amino acids necessary to the pancreas for creation of insulin. It would appear possible that diabetogenic qualities

of pituitary and thyroid activity might be based on their obligatory use of protein competing with the pancreas.

The phenomenon that many diabetics show high cholesterol readings would manifest inadequate protein physiology. In most instances of protein aberration there is a concurrent high cholesterol level. This level may be on the high side of normal. Many endocrine glands use cholesterol as precursor in manufacturing their secretion and may fail to do so because of insufficient simultaneously present protein. There would be accumulation of cholesterol in the blood serum detectable by laboratory methods. Likewise, acquisition of cholesterol may be due to faulty liver physiology.

Excess of insulin prior to onset of exhaustion of the beta cells of the islets of Langerhans may inhibit the liver from discharging its stored glycogen into the blood. Stored glycogen is capable of being transformed into fatty deposits causing pressure impingement of hepatic cells upon each other and upon liver circulation causing hepatic damage with resultant high cholesterol production. Whatever the mechanism may be there is usually a high cholesterol level accompanying diabetes. This is correlated to atherosclerosis, thromboses, gangrene, or myocardial infarction.

It is most desirable that these problems be discovered in the stage of hyperinsulinism, at which time they are correctable. The etiological endocrine gland disorder must be found, using whatever laboratory methods are necessary, and therapy instituted to abate pituitary drive. The vagus overactivity may be controlled by one tablet of one-fourth (1/4) grain phenobarbital, and one-eighth (1/8) grain belladonna with each meal.

Competitive action of the glands for available protein is

keen, and especially when some members of the endocrine system are using protein to excess. It is of primary significance that concentrated attention be directed to the protein metabolism. If it is necessary to use the entire armamentarium of therapy in this field it is most advisable to do so to prevent occurrence of diabetes. Once diabetes mellitus has developed, it is no less necessary to direct our attention to protein metabolism; but since fatigue, exhaustion, and necrosis have begun in the beta cells likelihood of recovery is much decreased. It is absolutely necessary to give insulin to these diabetic people and under no circumstances is the context of this chapter to be construed as disparaging to use of insulin.

Many cases of diabetes are associated with the climacteric and protein in the blood will unite with cell protoplasm only in the presence of sex hormones; administration of these is discussed in the chapter on gonads.

Research has disclosed in a great series of autopsies on diabetics 80 per cent of microscopically apparent pathology was present in the liver. This is conclusive proof that liver physiology is badly damaged and impaired either due to diabetes or causative of diabetes. All forces available must be brought to bear upon maintaining normal liver physiology. They consist of liver, iron, and vitamin B complex. Thyroid therapy must be prescribed designed to maintain a normal level of PBI in the blood stream. Activity of the thyroid is stimulatory to hepatic cells both in oxidation and augmented circulation. Stimulatory effect decreases the level of cholesterol, improves transamination, transmethylation, and deamination in the liver cells to provide a normal level of amino acids in the blood stream. It is recommended that

one (1) grain of thyroid substance be administered with each meal, if necessary this amount can be multiplied many fold.

Thyroid therapy by its corrective regulation of the intestinal tract enhances selective ability of the gut and allows more normal assimilation of sugar from intestinal contents, thus playing a part in the pancreas-liver management of carbohydrates. Laboratory determination of PBI level can be used as a guide in correlating dosage. Since heart muscle is sensitive to changes of glucose levels in the blood and uses glycogen in its activities, many cardiac abnormalities of rate and rhythm can be modified by thyroid administration through its efficiency in assisting carbohydrate metabolism. This must be determined through the laboratory.

Use of digestive enzymes and pancreatin plus bile salts in enteric coated tablets is to be highly advocated. One tablet with each meal is beneficial. Therapy of diabetes is more successful if attention is given to diet. Daily caloric intake should be equivalent to 10 times the patient's ideal weight. For example, if the ideal weight of the patient is arbitrarily given as 120 lbs., daily caloric intake should be 1,200 calories. These 1,200 calories should be divided into fat, protein, and carbohydrate calories. Not over 300 calories of fat should be ingested, preferably unsaturated in form, but in any event not to exceed 300 daily. The protein intake should be not less than 300 calories daily and more if possible. The balance, which would be roughly 600 calories more or less, depending upon fat and protein intake, is from carbohydrates and, as before emphasized, preferably in the form of natural sugar. This entire regimen is subject to variations depending upon type of energy expenditure and requirements of the individual patient.

I shall make no effort to discuss intelligently the new products Orinase ® or Diabinese ® in the therapy of diabetes since experience to date is limited.

There are numerous tangents of diabetes that could be discussed, pertaining to all fields, anatomy, histology, biochemistry, physiology, and therapy. However, there are innumerable treatises relevant to this condition, the clinical application of which is being carried out daily by the reader. The standard textbooks and reference works present background details for further review.

Control and management of the pancreas can be accomplished by means of rectifying the patient's demand for sugar. This may entail balancing of the endocrine gland system through the pituitary gland, pituitary adrenal axis, thyroid alone or pituitary thyroid axis, gonads alone or pituitary gonad axis, but the specific target gland to be managed will present its own individual peculiar symptomatology which can be traced back into affiliation with the endocrine gland system. Chapters on each target gland will indicate in which manner these tissue functions can be modified.

Concurrent with this approach the phenobarbital-belladonna tablet is instrumental in depressing vagus nerve stimulation to the pancreas. Amphetamine-amobarbital products can be used to raise the level of blood sugar through their sympathomimetic action similar to epinephrine causing release of tissue glycogen into the blood and the same product by exciting effect on the adrenal cortex is capable of influencing blood sugar level (through action of corticosteroids upon liver physiology stimulating gluconeogenesis). Management of the pancreas will follow organization and establishment of synchronous function between separate glands of the endocrine gland system. Nutrition as mentioned, par-

ticularly in the protein field, must be given intelligent consideration. Dietary response in so far as increased or decreased appetite is concerned will provide an indication as to the progress of control of pancreatic function. Increased appetite indicates low blood sugar and decreased appetite indicates a more appropriate level of blood glucose.

Function of the pancreas is an integral part of target gland response and does not have independent characteristics inherent in some of the other glands. Every performance of the endocrine gland system and many other tissues of the body manifest themselves in relationship to blood sugar which in turn is supervised by pancreatic function.

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Adrenal Gland

The adrenal gland occupies a position in the endocrine gland society of considerable interest and prominence. It controls electrolyte equilibrium, protein, carbohydrate and fat metabolism and supplies gonad assistance. Function of the adrenal gland is essential to maintenance of life. There are numerous hormones secreted by the adrenal medulla and the adrenal cortex which we intend to discuss. In order to prevent confusion and with awareness that this book will be read by physicians conducting a general practice rather than by biochemists, physiologists and endocrinologists, chemical formulae and discussions concerning chemical differences of specific compounds elaborated by the adrenal cortex will be omitted.

The adrenal gland can be considered second in command of the endocrine system. This gland will take over the direction of the system in the event of hypothalamic-pituitary inability. It is capable of a certain degree of independent action, controlled perhaps through external environmental stresses and strains. When the necessity arises and the adrenal gland does take over endocrine management the pituitary and thyroid are not included within scope of control. Pancreas and gonads are capable of being influenced by adrenal gland management. In this exigency (pituitary failure) rate of oxidation, stimulation to liver physiology, regulation of selective assimilation of the intestine as well as secretory and motility capacities, are not governed

through the thyroid gland since thyrotropic hormone is not present and adrenal control does not include the thyroid. The functions of balancing hormonal responses of target glands when lost due to pituitary failure are not regained through management by the adrenal tissue. It can be seen then that symptomatology resulting from adrenal gland disturbances will be somewhat bizarre and confusing.

The adrenal medulla secretes epinephrine and norepinephrine. The function of epinephrine is pituitary gland stimulation, vasoconstriction, acceleration of cardiac rhythm, initially mild diuresis and liberation of glycogen from muscle and liver cells tending to raise the blood sugar level. Dilation of bronchioles occurs, and the sympathetic division of the autonomic nervous system becomes energized through potency of epinephrine and norepinephrine. The effect of pituitary response from epinephrine as well as other sources, results in an addition of ACTH. Response elicited is an accession of adrenal corticosteroids.

The adrenal corticosteroids are divided from the standpoint of function into two classes; the mineralocorticoids govern and control electrolyte balance in the blood stream, interstitial tissue and intracellularly. Glucocorticoids regulate and manage protein, fat and carbohydrate metabolism. In addition, gonad hormones are also produced from the adrenal cortex. They are the sole source of female hormones to the male whereas androgen, and progesterone which is often considered as precursor to androgen, are likewise elaborated by the adrenal cortex and supply male hormones to the female.

The correlation of electrolyte balance is based on antagonism of adrenal mineralocorticoids to the anti-diuretic hormone from the posterior pituitary gland. Anti-diuretic

hormone is to a great extent responsible for reabsorption of water from the convoluted distal tubules and reabsorption of sodium is due to adrenal products. The antidiuresis which frequently follows administration of certain narcotics, sedatives, and anti-diuretics probably results from urging the posterior pituitary to produce anti-diuretic hormones. Morphine, codeine, barbiturates, quinine, quinidine, anti-pyrine, aminopyrine, acetanilid, acetophenetidin, have this action. With the use of any of these agents there may be decreased excretion of water from the distal tubules.

Presence of aldosterone from the adrenal cortex influences reabsorption of sodium and chlorides, which is the primary anti-diuretic mechanism resulting in the secondary reabsorption of water and has been shown to occur in response to ACTH. This pituitary-adrenal axis may be accountable for a major part of anti-diuresis induced by stress situations.

In the absence of aldosterone and perhaps other adrenal corticoids, diuresis may occur to the extent of seriously unbalancing electrolyte equilibrium in the blood stream. When the chloride and sodium are excreted and not reabsorbed from the distal tubules, carrying water with them, a general dehydration occurs. This dehydration appears first in the vascular compartment of the body. Changes in osmotic pressure cause sodium and chloride from the interstitial tissues to enter the vascular compartment, thus attempting to balance electrolyte concentration in the blood stream. As the process continues, potassium will be drawn out of intracellular protoplasm to replenish osmotic balance in the interstitial compartment. This would be evidenced by increase of potassium concentration and decrease of sodium and chloride level in laboratory analysis of blood serum. Should the process

continue unabated, there is a possibility of deranging potassium concentration of the blood stream to the extent that the myocardium becomes involved, discernible by electrocardiographic tracing, and in some rare instances thought to be causative of cardiac arrest.

Conversely, an increase of aldosterone may be responsible for excessive retention of sodium and chloride occasioning an over hydration of the blood stream first, then secondly interstitial tissue and eventually the intracellular compartment. If this were concurrent with an elevation of epinephrine from the adrenal medulla, there is in the making a potential hypertension with expanded fluid volume, vasoconstriction effectuating peripheral resistance and insufficient diuresis. Both aldosterone and the anti-diuretic hormone are filtered and inactivated through liver processes. In instances of hepatic insufficiency, decreased filtration and oxidation reduction (redox function) allows excess circulating level of both hormones with the aforementioned consequences.

It is possible for the patient to maintain an existence by augmenting salt intake in the absence of the mineralocorticoid. Many people evidence desire for a great deal of salt on their food and may be forced into this procedure due to diminution of mineralocorticoid secretion. Desoxycorticosterone acetate (DOCA) can be used to reestablish electrolyte equilibrium if necessary.

Glucocorticoid seretions govern protein, fat, and carbohydrate metabolism and as a consequence are termed sugar hormones. Effect on glucose levels is to elevate concentration in the blood stream, in this manner they have an antagonistic effect to insulin. Insulin is more concerned with utilization of blood glucose at the cell level, whereas glucocorticoids are instrumental in raising glucose level in

the blood stream. This is accomplished by means of gluconeogenesis in the liver.

The liver is capable, under compulsion from adrenal cortex secretions, of provoking the breakdown of protein to carbohydrate. This increases coincidentally production of ammonia urea, carbon dioxide, and water. The carbohydrate radical thus liberated enters the mechanism of Krebs cycle (common metabolic pool of carbohydrate) and hence becomes glucose in the blood stream when the liver is called upon to supply sugar.

Protein metabolism of the entire body may be affected by this procedure since it will be necessary for the blood stream to carry protein to the liver to sustain enhanced gluconeogenesis. The protein thus used may be derived from ingested food in which case no great harm is done. More commonly and detrimentally it can be obtained from the blood stream. When the blood stream releases protein for this purpose it must be replenished and is capable of raiding protoplasmic stores of the vascular system or reticulo endothelial system such as lymphoid tissue and synovial membranes as well as extracting this protein from muscle tissue, mucous membranes including those of the gastrointestinal tract and sinus cavities. In many instances, the nervous system is called upon to release protein and since stores are very meager in the nervous system, it requires very little depletion to precipitate neuritis, neuralgias, or nervous system failure, such as nervous exhaustion and nervous breakdown. We have in this physiology very basic etiology for arthritis, hypertension, vascular insufficiencies such as coronary atheromatoses, arteriosclerosis, gastric and duodenal ulcers, colitis, and probably the least serious but most uncomfortable problem of skeletal muscle spasms. Calcium

and phosphorus imbalances, as well as endocrine gland derangements based upon protein depletion may be precipitated in this fashion.

In absence of glucocorticoids as well as mineralocorticoids, hypotension, asthenia, malaise, weakness, fatigue, pigmentation (origin unknown) arthralgia, nausea, anorexia, vomiting, and diarrhea may occur. As will be recognized these are typical symptoms of Addison's disease and in true fact, the absence of mineralo and glucocorticoids is responsible for the condition described by Addison in 1857 whose description of the characteristic syndrome can not be improved. The fact that he attributed the etiology to tuberculosis has been to some extent modified. Approximately 50 per cent of Addison's disease patients have been proven not to have tuberculosis. It can be readily appreciated that this percent of people with the condition, might have hypopituitarism in which instance the adrenal cortex would not function due to deficiency of adrenal corticotropic hormone.

Therapy for profuse supply of corticoids must be relegated into proper management of the pituitary-adrenal axis. In the absence of tumor formation in the adrenal cortex, the causative factor of increased adrenocortical response would be inexorable compulsion from the anterior pituitary gland. Behind this might lie hypothyroidism, hypogonadism, heredity or as discussed in the chapter on pituitary any cause capable of exciting an aroused response of pituitary secretions. The therapy must be approached on the basis of managing and stabilizing pituitary function.

Adrenal cortex discharge of gonad hormones is often responsible for symptomatology in this field. When testicular function declines and androgen production subsides in the male, there may be compensatory conduct of the anterior

pituitary, producing gonadotropins, which in turn empowers the adrenal cortex. Reduction in androgen concentration from testicular production (because of its counterbalancing effect to estrogen of adrenal origin) may be unable to negate female hormones (from adrenal cortex) in the blood stream, in which event the patient will display characteristic symptoms. Among these are widening of hips, softening and smoothing of skin, adipose deposition in buttocks and thighs, as well as often in the pectoral area, change in pitch of the voice, decline or loss of libido, thinning and sparsening of hair in the axillary and pubic areas with personality changes and physical actions accepted generally as being effeminate in character. Conversely, in the female whose ovaries no longer secrete estrogen, the pituitary will be called upon to increase its activity and excitation to the adrenal cortex oftentimes shows a predominate increase of androgen. Without estrogen present to counteract androgen secretion of the adrenal cortex in these women, symptoms relate to androgen predominance. These patients demonstrate growth of hair on face, axilla and upper lips, loss of female contours with hips slimming and atrophy of breasts, muscular mass of their body may become more solid, voice may deepen and become coarse, skin will thicken, and she will adopt masculine aggressive attitudes.

The estrogen and androgen secretions both of the natural gonads and of the adrenal cortex, are inactivated through function of the liver. Liver impairment or hepatic insufficiency of even mild degrees may be responsible for many of these symptoms despite normal function of target glands. Nevertheless, the combination of abnormal target gland response coupled with hepatic insufficiency is often seen clinically and requires considerable diagnostic acumen in order to administer restorative treatment.

The adrenal cortex is expected to mature in its estrogen-androgen production at approximately the same time of life as gonads retrogress. With normal equilibrium the adrenal cortex will take over these gonad activities, especially in the field of protein anabolism, without undue symptomatology or inconvenience to the patient. Inability of the adrenal cortex to assume its responsibilities at this chronological age results in exacerbation of the pituitary-adrenal axis and resultant spillover of effort (through hypothalamus) into the autonomic nervous system thus promoting symptomatology of the climacteric such as hot flushes, cold chills, sweats, nervousness, headache, insomnia, and mental depression.

Many patients who have adrenal problems appear to have an extra collar or double chin since the adipose tissue has predilection for depositing on face and neck, they appear moonfaced, often the female showing excess hair or a mild beard and mustache, the male loses hair and may have smooth facial tissues with softness normally considered female in type. The supraclavicular area of these patients may show fat deposition and the shoulder girdle and upper body appear heavy. The characteristic "buffalo hump" at areas of the sixth and seventh cervical and first dorsal vertebrae is considered related to adrenal irregularity. These patients often show edematous accumulations of fluid in ankles, pretibial, abdomen or may complain of intractable coughing due to fluid collecting in the thoracic cage, or vertigo which might be construed as abberrant fluid in the semi-circular canal of the ear. Oftentimes the patient enters our care for therapy of arthritis at which time it is discovered that he is suffering from hypoadrenalism.

Laboratory aids in this field are not perhaps of as much value as they are in other problems. Seventeen ketosteroid urinary evaluation is of some benefit since hypodrenalism

is characterized by low production of the 17 ketosteroid but this is not pathognomonic for the condition. The laboratory analysis of gonadotropic hormones may be of value in determining that the pituitary gland is definitely overactive, or underactive and in the presence of intact adrenal cortices it may be inferred that pituitary activity has commensurate effect upon adrenal corticosteroid response.

Research investigation has disclosed that vitamin C and cholesterol are ordinarily present in the adrenal cortex but under influence of ACTH the supply becomes depleted—insinuation being that adrenal fabrication of corticosteroids causes utilization of cholesterol and vitamin C. Cholesterol determination on the blood serum denoting high cholesterol content might be representative of failure of the adrenal cortex or the anterior pituitary or gonad tissues to consummate their respective hormones.

There are tests relative to fluid retention which have been used to determine adrenocortical activity. The water loading test is one wherein copious quantities of fluid are given to the patient followed by measurement of fluid excretion. This test is not without danger and excessive hydration may precipitate convulsions on the order of petit or grand mal and even comatose conditions. There have been several deaths reported from this type of examination. It is not here advised. ACTH test is based upon the fact that eosinophil count is decreased by production of the corticoids, hence an eosinophil count is made prior to injection of ACTH. After 4 to 6 hours another eosinophil count is made. With intact adrenal cortex of normal functional ability, the eosinophil count will drop in the second reading. The laboratory in evaluating adrenal function can not take the place of a meticulous history and physical examination.

History of a patient who has undergone severe emotional and physical stress, or perhaps infectious toxic conditions concurrent with high fevers, would indicate that their effort to recover and to maintain apparent good health, caused exhaustion of the adrenal cortex with resultant hypoadrenalism. There are a certain percentage of people who have adrenal function compatible with normal activities, yet who are unable to get proper adrenal response to exceedingly stressful strain, such as major surgical procedures. This may not be apparent until the patient post-operatively fails to recover or the surgery may precipitate an adrenal crisis. Patients who have been maintained on corticosteroid medication for a period of time may fall into this category. Exposure to stress of patients with steroid induced depression of the pituitary adrenal system, may foment an adrenal crisis. Occurrence of otherwise unexplained shock during or following surgery should lead one to consider the possibility that pituitary-adrenal response to stress has been inadequate. Intravenous hydro-cortisone may be life saving under such conditions especially when the patient is unresponsive to transfusion of blood or to the use of vasoconstrictor drugs.

Sudden peripheral vascular collapse in the patient with chronic adrenal insufficiency may of course be the result of gradual depletion of sodium, chloride and water. Under these circumstances hyponatremia, hyperkalemia, acidosis and hemoconcentration are found. There are other circumstances under which acute adrenal crisis develops without prior renal loss of electrolytes and water. Sudden vascular collapse may be due to acute insufficiency of hydrocortisone manifesting itself as loss of vasoconstrictory response of small blood vessels. Circulatory collapse, shock, coma, and death are pre-

ceded by extreme lassitude and weakness, nausea, vomiting, costovertebral angle pains, restlessness and confusion. Hypoglycemia and hyperpyrexia are frequently associated findings.

The objectives of corrective therapy for adrenal crisis are:

1. Rapid expansion of the circulating fluid volume, if low, by intravenous infusion of two liters of physiologic saline and administration of desoxycorticosterone (10 milligrams intramuscularly or preferably fluorohydrocortisone (1 milligram) intravenously. In the presence of acidosis an electrolyte solution containing both sodium chloride and sodium bicarbonate (150 mEQ sodium per liter, 100 mEQ chloride, and 50 mEQ bicarbonate) is preferable.
2. Correction of hypoglycemia by the concomitant infusion of 5% glucose.
3. Rapid elevation of blood steroid concentration by the rapid administration of 50 milligrams of hydrocortisone, thereafter 10 milligrams of hydrocortisone per hour are given by continuous intravenous infusion. At the time intravenous steroid therapy is begun, it is well to inject 50 milligrams of hydrocortisone intramuscularly.

Therapy is continued with intramuscular and, as soon as practical, with oral doses in decreasing amounts until a maintenance level is reached. Blood plasma and norepinephrine are indicated if hypotension persists. Antibiotics are used for treatment of any underlying infection. The patient with well controlled chronic adrenal insufficiency will be in severe difficulty under conditions of stress, since he cannot increase the amount of corticosteroids as the situation demands. The same principle applies to the patient with

no pituitary insufficiency and the patient with steroid induced depression or latent efficiency of the pituitary-adrenal system. For exposure to spontaneously occurring or planned stressful situations, such patients must receive additional amounts of corticoids. The amount required depends upon the magnitude and duration of the stress.

The patient with chronic adrenal insufficiency may be maintained comfortably on small amounts of corticosteroid preparation. Prednisone or prednisolone are satisfactory for this purpose and will help balance the electrolyte ionic equilibrium. Optimal dose must be determined by starting at reasonably high dosage and reducing until reoccurrence of symptoms at which time the vicinity of dosage has been established. If excessive corticoids are administered over prolonged periods of time, the patient assumes the characteristics of hypercortical activity such as polyphagia, obesity with body fat distributed in a characteristic way, the face becomes rounded particularly in the preauricular region giving rise to so-called moon facies, the mouth appears small, the upper lip has a cupid bow configuration with rolled up upper border. An increase occurs in the cervical dorsal (buffalo hump) and supraclavicular fat pads. An apron like deposition of fat encircles the base of the neck. All four extremities seem to be withered in comparison with robust appearance of face, neck and trunk.

In consideration of therapy for adrenal conditions it must be noted that the adrenal gland will respond in those cases of vigorous activity to decrement of the adrenal corticotropic hormone (ACTH). The adrenal corticotropic hormone will be intensified in any functional change involving strong response of the anterior pituitary gland. As discussed in the chapter on pituitary, there are numerous and diverse

stimuli activating the anterior pituitary gland. Among the principal methods in the effort to depress the anterior pituitary, would be subsidizing any and all target glands not producing their secretions and therefore the etiology of the overactive pituitary. The pituitary gland can also be inhibited by the use of gonad hormones and thyroid substance. Reestablishment of endocrine balance is the essential purpose of any therapy and consequently should be employed by whatever mechanism or medication is capable of accomplishing this.

Hyperadrenalism stimulates gluconeogenesis. In an effort to prevent protein depletion of cellular protoplasm of the body, it is necessary to give definite and thorough consideration to protein metabolism.

Discussion of therapy in the chapter on protein should be reviewed on this point. Many symptoms relative to adrenocortical overactivity are due to protein exhaustion of various tissues.

Management of adrenocortical hyperfunction should take into consideration electrolyte balance. Sodium retention and potassium excretion may be managed by administration of potassium salts, such as potassium citrate 4 to 8 cc of 20% solution 2 to 3 times daily in fruit juice. The majority of newer synthetic corticosteroids do not have any appreciable sodium retention associated with their use, however, in natural overproduction of adrenal corticosteroids the increase of aldosterone is capable of considerable sodium retention.

In every case of adrenal involvement the liver plays a central important part. That normal liver physiology be established and maintained is prerequisite in order that proper filtration, reduction, oxidation be present to inactivate the pituitary anti-diuretic hormone (ADH), aldosterone,

estrogen and androgen secretions and the corticoids. In any patient evidencing symptoms diagnostic of adrenocortical overactivity without other concurrent symptoms of hyperpituitarism, it is imperative that neoplastic conditions be differentiated from functional problems herein discussed. The most common etiology of adrenocortical overactivity of an organic nature being tumor formation.

Therapy and management of adrenal hypofunction is today simplified by availability of commercial synthetic corticoids. Mineralocorticoid deficiencies that were previously managed by high salt intake and desoxycorticosterone acetate implantation today can be controlled and maintained by use of corticoid commercial preparations. Profusion of these products induce symptoms of hyperadrenalism and hence are discernible by development of moon facies, hirsuitism, psychotic manifestations and in long continued administration by symptoms of protein insufficiency. Nevertheless, with dosage tailored to the individual patient these conditions (hypoadrenalism) can be sustained indefinitely with long termed therapy as compared to progress prior to the advent of commercial corticoids, wherein life expectancy of the patient was considerably shortened. It is best to consider the medications as substitution therapy and carry the level of dosage on a very low plane. This is to be differentiated from pharmacological effect of corticoids with their relationship to urticaria, angioneurotic edema, dermatitis, such as psoriasis, eczema, and many other conditions wherein pharmacodynamic action is required of the drug.

There are numerous products manufactured differing from one another in their chemical formulae. Common to all of these formulae is the phenanthrenene ring, but differing in the placement of fluorine molecules, methyl groups, or

hydroxyl radicals. The cortisone and hydroxycortisone preparations were among the original products available but have been supplanted in later years by prednisone and prednisolone, which recently are being replaced by fluorine containing medications such as Deronil ® and Aristocort ®. While most of these products are expensive, the results obtained by their use more than justify their cost. Aristocort ® is started in many instances at a level of 4 tablets daily of 4 milligrams each. Within 36 to 72 hours averagely, results are seen in the patient's symptoms. As these results become evident dosage is reduced by 2 milligram steps until minimum maintenance dose is established. Deronil ® having more potent biological activity, requires less dosage and as a consequence, one Deronil ®tablet of 0.75 milligrams is considered in effect to be the equivalent of 4 milligrams of Aristocort,® therefore it would require less medication when using Deronil.®

Exogenous administration of corticoids has restraining effect on the pituitary production of ACTH as does the natural hormone. Long continued administration of corticoids depressing secretion of ACTH consequently presents potential atrophy of the adrenal cortex. This can be offset by the use of injectable ACTH for several days at levels of between 40 to 80 units per day at 6 month intervals. Withdrawal of exogenous corticoid must be done very slowly and under supervision lest an adrenal crisis occur. In the consideration here, of using corticoids due to already present adrenocortical insufficiency plus atrophy of the adrenal cortex, concurrent with long administration of corticoids, may make withdrawal of this medication a very problematical procedure. Protracted administration of corticoids may under certain circumstances be necessary in order that life be sustained.

Should the hypoadrenal condition be secondary to hypopituitarism, it is advisable prior to inception of corticoid therapy to administer desiccated anterior pituitary substance. This may be started with a 1/4 grain tablet of anterior pituitary substance daily and increased to levels of 10 grains daily before its use would be abandoned. Desiccated anterior pituitary substance in many instances is capable of energizing target glands, among which are adrenal cortices, with resultant increased response and removal of the necessity for exogenous corticoid therapy.

In hypopituitary patients administration of thyroid is beneficial. There are a few instances in which the adrenocortical performance is at such low ebb that adding to the load by giving thyroid substance is capable of precipitating an adrenal crisis. This book will evidence the authors considerable use of desiccated thyroid substance and in the many many patients treated by thyroid substance we have never seen an adrenal crisis occur. Benefit of thyroid therapy offsets other considerations in that the blood sugar is improved giving the patient more strength, vitality and very definitely protecting against an hypoglycemic syndrome. Since there is no other nutrition to the brain, this organ is very sensitive to sugar levels. Damage of hypoglycemia occurs first in the brain. All symptoms are related to hypoglycemia and anoxemia of this organ which if continued longer than 3 minutes may result in irreparable and irreversible brain tissue damage. Patients with Addison-like symptoms experiencing faulty sugar metabolism and hypoglycemia are in great danger of hypoglycemic coma, serious enough to be terminal. Therefore, administration of thyroid for improving blood sugar levels is here advised.

It is recommended that (1) grain of thyroid be admin-

istered t.i.d. and raised or increased as the patient's condition warrants. Electrolyte balance in patients handled by other means than exogenous corticoid can be managed by augmenting salt intake. Sodium and chloride being lost through kidney tubules due to paucity of aldosterone, results in deficit of sodium in the plasma and interstitial tissues which in time becomes replaced by intracellular potassium in order to equalize osmotic pressure. This results in dehydration of the blood stream and interstitial tissue first and later results in over hydration of the cell. With loss of sodium and chloride the osmotic pressure is altered and rather than diuresis occurring, more frequently intravascular and interstitial fluid enters the cell itself. Potassium exodus from the cell leads to a high potassium level in the blood serum with its concurrent dangers. Administration of table salt in considerable quantities prevents this electrolyte shift.

Protein metabolism is involved in considering treatment of all adrenal dysfunctions whether on the hypo or hyper level. Incited gluconeogenesis in hyperadrenalism results in depletion of peripheral cells, of protoplasmic protein and as a consequence this must be replaced. The failure of normal amounts of gluconeogenesis and other related activities of protein metabolism in hypoadrenalism must be corrected. Protein therapy becomes a primary factor in management of any adrenal disturbance. The protein metabolism should be considered from the standpoint of ingested protein and protein food supplements, gastric digestion with the realization that the first stage of hydrolysis occurs in the stomach through effect of hydrochloric acid, intestinal factors with consideration to proteolytic enzymes from the pancreas and intestinal mucosa, assimilation through intestinal walls and its relationship to vitamin factors, liver physiology and

finally relationship of protein in the blood stream to conversion into cell protoplasm being dependent upon presence of gonad hormones.

The presence of vitamin C is essential to the adrenal cortex in formation of its hormones. It therefore is advisable to use products high in vitamin C content, either natural vitamin C or ascorbic acid can be given and dosage must be fairly high in some instances 600 to 1200 milligrams daily. The philosophy of bioflavonoid factors combined with vitamin C as treatment for colds, allergies, impotence, and infections, stems from the necessity of these factors to the adrenal cortex for its creation of the corticosteroids. In some instances this type of treatment has been very beneficial and under any circumstances there is necessity for vitamin C. To date no known undesirable side effects have occurred from its use.

Functional hypoadrenalism and hyperadrenalism will respond to government of the pituitary gland. In hyperadrenalism depression of the pituitary through use of thyroid and gonad hormones, with consequent decreased elaboration of ACTH, allows adrenocortical activity to assume a more normal balance. In hypoadrenalism substitution by use of desiccated anterior pituitary substance provides energizing effects to the target gland and thus will stimulate more normal adrenocortical function. The adrenal cortex can be considered as an integral part of the endocrine system and will respond satisfactorily to establishment of equilibrium of target gland hormones. Neoplastic conditions must be differentiated by suitable diagnostic procedures.

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Gonads

Gonad tissue occupies a very important position in the endocrine gland society. Ovaries and testes exert positive and powerful control balancing the performance of the pituitary gland. Patients presenting no discernible disturbance of gonads during physical examination may have an aberration of function due to involvement of gonadotropic hormone from the pituitary. In regulating endocrine functional disturbances often it is necessary to provide gonad hormone. Gonad hormones are among the most powerful of the pituitary gland inhibitors.

Part A. Ovary

At the age of approximately 12 years, ovaries begin to mature and onset of menses occurs. In the cortex of the ovary are embedded thousands of tiny sacs called graafian follicles, each containing an ovum. Normally ova mature at the rate of one follicle per month and in alternate ovaries. Vitality to the ovary causing maturation of the graafian follicle is supplied by the anterior pituitary gland through the follicle-stimulating hormone. Gonadotropic hormones elaborated by the anterior pituitary gland are follicle stimulating hormone (FSH), luteinizing hormone (LH), and interstitial cell stimulating hormone (ICSH). As the follicle-stimulating hormone activates the graafian follicle to mature, the ovum enlarges. During the first 14 days of

development membranes around this ovum form estrogen. It is the province of estrogen to prepare the body of females to accept and nurture fertilized ovum.

Preparation is accomplished by promoting engorgement of the uterine body with blood, and by causing enlargement and engorgement of breasts.

Upon completion of development the ovum is expected to leave the ovary. This is the time of ovulation. During the first 14 days time in which estrogen is produced, its presence in the blood stream regulates activity of the anterior pituitary gland in manufacture of FSH. Optimum levels of estrogen restrain expansion of FSH while inadequate concentrations cause amplification.

During ovulation, the graafian follicle ruptures, allowing ovum to enter fallopian tube which it must traverse to reach uterine mucosa. The graafian follicle then fills with blood. Within very few days blood thus contained becomes organized, forms the corpus luteum, which under influence of luteinizing hormone (LH) secretes progesterone. Function of progesterone is to prepare the uterus to either accept a fertilized ovum or to cause deciduation of uterine mucosa known as menstruation. This preparation takes the form of limiting engorgement of breast tissue, of uterine mucosa, softening of musculature of the cervix, and generally relaxing pelvic ligaments. During this second 14 days, estrogen is regressing while progesterone is increasing. Effect of progesterone in the blood stream is to curb the anterior pituitary gland in making gonadotropic hormone, the luteinizing hormone (LH). Balance between estrogen and progesterone is absolutely necessary for well-controlled anterior pituitary behavior.

As the female matures progesterone-estrogen relationship

becomes much more important. Many girls at this age develop an acne condition. Acne generally is due to deficiency of progesterone, and poor liver function, which in turn relates to protein metabolism. It is essential that thyroxin be present to operate in synergy with the gonadotropic hormone. Progesterone will not be formed in the absence of thyroxin. Should the ovum become fertilized, progesterone is manufactured by the placenta. Purpose of progesterone at this stage is to insure retention of fertilized ovum by uterine mucosa.

Estrogen likewise is formed by placental tissue, and provided normal liver proficiency is present, the embryo can be developed and carried to term. During the first three months of pregnancy most miscarriages occur and at this time hypothyroidism must be considered. Progesterone will not be formed in the absence of thyroxin and consequently the uterus will expel its contents. During the last 14 days of the ovarian cycle, if progesterone is not sufficient the uterine mucosa will continue to engorge, the cervix will not relax nor will pelvic ligaments. The end result is menstruation before 28 days have passed, sometimes an acceptably heavy flow generally associated with cramping known as dysmenorrhea. If, in addition to this, headache accompanies this menstrual cycle, it is evident the pituitary gland is making an effort to supply more progesterone by elaborating progressive amounts of luteinizing hormone (LH). This process causes the anterior pituitary gland to swell and engorge, generating pressure on intracranial membranes, thus precipitating severe headaches.

There are symptoms referable to imbalances in estrogen-progesterone ratio. In the event of too much estrogen the patient will have large breasts, earlier and heavier men-

struation, gain in weight because estrogen is a protein-anabolic hormone; when protein is taken into cell protoplasm it carries water, causing fluid retention and weight gain. With a deficiency of estrogen, the patient will have late periods, small breasts, possibly dysmenorrhea, and scanty flow. In any ovarian hormone imbalance fat is likely to accumulate between trochanter and iliac crests. The patient has deposition high on the pelvis evident as a waist-hip measurement differential in excess of 10 inches which would indicate overactive pituitary gland. However, gonad pituitary deposit is typically high on the pelvis, being above the head or trochanters of the femur, probably within the first five or six inches below the crest of the ilium. Excess progesterone is indicated by late menstruation without dysmenorrhea, scanty menses and small breasts. Deficiency of progesterone has the same symptoms as surplus of estrogen; however, it is associated with miscarriages and dysmenorrhea. Menstruation will also be scanty in hypoproteinemia. Therefore it is wise in any case of light menses to run complete blood counts.

There are a few instances in which there will be history of pain between menstrual periods. This is known as "mittelschmerz." Pain at this time will be due to rupture of the graafian follicle with consequent expulsion of ovum, hemorrhage into the graafian follicle and distention of ovary. It is an innocuous condition but is quite uncomfortable. There may be associated with this a show or spotting of blood but it is not to be considered a menstrual period.

In this physiology there is explanation for amenorrhea, dysmenorrhea, metrorrhagia, and menorrhagia. Amenorrhea is failure of maturation of the graafian follicle which would be due to reluctance of the anterior pituitary gland to elaborate follicle-stimulating hormone. Menorrhagia, or profuse bleeding at the time of menses, is a sequel of excess estrogen without counterbalancing presence of progesterone. Metrorrhagia, bleeding between menstrual cycles, can be due either to ovulation or failure on the part of the corpus luteum to supply progesterone. Dysmenorrhea is definitely failure to produce progesterone.

It is our policy to administer estrogenic substances either by hypodermic or orally as treatment for insufficient estrogen. It is more practical to substitute products of the ovary than it is to use anterior pituitary gonadotropins. One reason is at the present time pharmaceutical houses do not have satisfactory anterior pituitary gonadotropins for use on human patients. We therefore substitute with estrogen. Estrogen will act not only on the functioning uterus during its cycles, but will serve to depress pituitary overactivity. It can be administered by mouth and there are a multitude of products of this type. We generally use ethinyl estradiol in 0.05 milligram strength and depending upon the patient will use ethinyl estradiol 1 tablet every day—if need is not so great 1 tablet on alternate days. It is apparently overdosage when there is an anovulatory menstrual period, since ethinyl estradiol is capable of causing uterine and breast engorgement. Frequency of the dosage is naturally decreased when this occurs.

Ethinyl estradiol can also be used to stimulate onset of menses if the girl has reached the age of 14 or 15 without menstruating. Ethinyl estradiol is used for 20 days. On the fifteenth day, in addition, 10 milligrams of progesterone are administered by means of a buccal tablet once daily. At the end of 20 days all medication is discontinued. This cycle is continued for 3 to 4 months if menstruation occurs,

until she can manage her own menstrual periods. The medication is repeated starting on the thirty-second day if no menses occurs. It may be necessary to repeat for several months before menstruation occurs. Ordinarily it requires five to six months, after which the patient is able to continue without further support. If the situation is that of a younger girl, only 20 tablets of ethinyl estradiol are dispensed and the patient reports back to the office for further medication. The periods are brought closer to a 28 day cycle by judicious use of ethinyl estradiol, should the patient be having scanty periods more than 28 days apart. These people require small dosages such as perhaps two 0.05 milligram tablets per week. This program can be transposed into injectable therapy by recognizing that 1 milligram is equivalent to 1,000 units of estrogen.

Progesterone can be used when the patient is suffering from dysmenorrhea, presents small breasts, large hips, perhaps irregularities of cycling. One tablet of 10 milligrams can be dissolved sublingually daily for 5 days starting on nineteenth day following first day of previous menstrual period. There are times when this is not adequate and must be increased therefore dosage is started one day earlier and two more tablets are given. It is started another day earlier and carried another day longer, if dosage needs to be further supplemented. An excess of progesterone is apparent when interval between menstrual periods is prolonged beyond 28 days, reaching maybe 32 to 35 days from previously normal 28 day cycle. It then becomes necessary to decrease the amount of progesterone. Progesterone is a powerful biological stimulant and ordinarily a great quantity of it is not necessary. Progesterone likewise can be administered hypodermically. The philosophy of treatment for

these problems is to substitute hormones at times when they normally should be present. Therefore, with ovulation occurring at the fourteenth day, progesterone will be present from the fourteenth day on, probably reaching a peak in four or five days. It is during these four or five days that we prefer to have progesterone available.

In patients with severe intractable headaches accompanying dysmenorrhea, it is often necessary to use a quarter (1/4) grain tablet of desiccated pituitary substance daiiy for six weeks to two months. This helps to limit pituitary gland excitation. At the same time substitute progesterone to further retard pituitary drive. The patient with ovarian dysfunction may be suffering from hypothyroidism and it is recommended that thyroid therapy be instituted, one (1) grain of thyroid substance with each meal. It is advisable to consider protein metabolism in therapy of ovarian imbalances. A patient in the state of hypoproteinemia will not menstruate normally, for the body is attempting to economize in all protein expenditures and blood expelled through the menstrual period is of such importance to the body efficiency that she will conserve this blood.

It is necessary to reconsider physiology of the ovary at time of the climacteric. The ovary will decrease or even cease so far as reproductive potential is concerned, at approximately 45 years of age. Normally at this age the adrenal cortex will have matured and be able to produce estradiol, estrone, and 17 beta estradiol. Elaboration here of female sex hormones is for the purposes of protein anabolism, primarily, and secondarily control of the anterior pituitary gland. It seems a very high percentage of women have failure at this point. There results progressive stimuli from the pituitary gland if the adrenal cortex does not

produce female gonad hormones when the ovary is retiring from active service. Since no estrogen is present, the patient is likely to put on weight at very rapid rates, have mental depression, crying spells, and become extremely nervous. The hypothalamic area of the brain takes part of the effort of the pituitary into the autonomic nervous system and consequently hot flushes are apparent.

Adrenal cortex, in the female is the source of male sex hormone. It is necessary that these hormones be present in the female body. Since the female hormones which counterbalance androgen have become depleted in the menopausal patient under consideration presence of male sex hormone may lead to symptoms of masculinization such as hirsuitism, deepening of voice, coarsening and thickening of skin, loss of female contours. It is beneficial to administer ethinyl estradiol or natural estrogenic substances provided there is a good liver function. Ethinyl estradiol can be used in 0.05 milligram tablets on alternate days. This can be continued throughout the month since there is no further cycling of menstruation, and it will serve to control the pituitary gland. Very occasionally this dosage will cause an anovulatory period then the dosage should be reduced. This contingency may arise immediately at the onset of the climacteric. There are times when progesterone will control hot flushes and it can be used in 10 milligram sublingual tablets starting two times per week, and, if necessary, building up to alternate days. Progesterone however will not function in absence of estrogen, and when progesterone is used it should be with intent to balance estrogen-progesterone concentration. Whenever estrogen is not present, progesterone is inert, unless used as a precursor of androgen manufactured by the adrenal cortex; and that is not desirable when the

patient is already displaying evidences of surplus androgen.

There are further instances where the patient either has endured symptoms of the climacteric for a period of years or does not enter our care until in the early and middle fifties. To this patient we give a combination of testosterone and estrogen in relationship of approximately 20 parts of testosterone to one part of estrogen. This is for purpose of controlling the anterior pituitary drive; besides, many of these patients have developed signs discernible by x-ray of osteoporosis, and it is necessary to use a protein-anabolic substance to enhance protein metabolism. Products of this nature do not cause anovulatory menstruation nor do they cause masculinization. The combination balances itself and does not overact either on masculine or feminine side.

Surgical castrates have gone through artificial menopause and are experiencing pituitary drive trying to balance estrogen and progesterone, but not being able to do so develop symptoms of too much pituitary activity. Many times these patients have lost ovaries surgically, because a large engorged, purplish discolored distended ovary was seen and excised as a pathological specimen. In true fact the ovary was in the stage of containing a large corpus luteum and was a physiological normal for that time of its cycle. Nevertheless, these patients apply for help and it is advisable to crutch their system with ethinyl estradiol. Usually they are not at an age when the adrenal cortex would be expected to manufacture female hormones; accordingly, it is helpful to use ethinyl estradiol one tablet daily, 0.05 milligram strength, if they will tolerate medication at this dosage. Ethinyl estradiol by itself may not be balancing with androgen or with any progesterone and hence there will still be an imbalance causing an overactive pituitary gland. Ethinyl estra-

diol can be given daily and two times weekly a sublingual tablet of progesterone, when that is the problem. Generally this will control the pituitary gland.

If the pituitary gland is controlled by ethinyl estradiol alone, and there is complaint of breast tenderness it is advisable to decrease dosage to one (1) tablet every other day. Drop the dosage, should soreness persist, to two times per week. One tablet daily may control the patient for a period of months. However, as time progresses she will not need so high a dosage. It should then be decreased, particularly and especially if severe headaches occur. It is possible to gain easement from severe headaches even in cases that are not relieved by demerol, morphine, or milder analgesics by resorting to intramuscular injection of 50 milligrams of testosterone and repeating the following day. Rationale of this is that testosterone being a powerful pituitary gland depressant will temporarily dissipate congestion and engorgement. However, it does not answer the purpose of controlling the pituitary over a reasonable length of time. Thorough investigation is demanded as to gonad hormones not in balance, and supplement of the same should then be provided.

Premenstrual tension is a common complaint and is due to surplus estrogen with insufficiency of progesterone activity. Suffice it to say that estrogen-progesterone ratio is out of balance. The protein-anabolic effect from an excess of estrogen can cause water retention, nervous tension and weight gain prior to menstruation due to pituitary drive attempting to make an ovary secrete progesterone. The treatment of this condition with five tablets of progesterone, 10 milligrams, 1 daily starting on nineteenth day after first day of previous menstrual period, will generally manage to

modify estrogen-progesterone ratio. Ammonium chloride 7½ grains t.i.d. during the week prior to menstruation in addition serves as a diuretic to relieve tension and engorgement.

Women past menopause who are suffering disturbances due to lack of female hormones and who must be crutched with exogenous products, can expect the adrenal cortex eventually to supply the necessary sex hormones. The pituitary is so depressed if crutching is too enthusiastically administered, that it will not cause the adrenal cortex to respond as early as would otherwise be the case. Young girls and women at menopausal age often experience itching, burning, and discomfort of the vulva. This is the result of insufficient estrogen present in the blood stream and can be successfully alleviated by estrogen creams or estrogen suppositories.

Poor or faulty ovarian function may be due to hypopituitarism. Ovaries are failing to get proper gonadotropic stimulation from the pituitary gland. These are patients who will need, besides sustaining of the ovary with ovarian secretion, help in the field of pituitary activity. They should be given a quarter (¼) grain tablet of desiccated anterior pituitary substance daily, increasing as might be necessary.

When controlling the anterior pituitary by depression through use of gonad hormones, it is well to recognize the fact that ovaries may have been performing, but only at expense of a highly excited pituitary gland. It has been necessary for the pituitary gland to function at an accelerated rate in order to keep ovaries supplying their hormones. This is more particularly evident when a patient, under our care for hypothyroidism, has been given proper amounts of thyroid substance and pituitary activity has been inhibited, only to lead to the discovery of aberration in operation of the ovary. This need cause no alarm. The ovary has been con-

ditioned to receive excess gonadotropic hormones and depression of the pituitary gland has diminished this supply, naturally it will take a period of several months before the ovary is again able to function normally. The ovary is thoroughly capable of responding to proper amounts of gonadotropins; all that has been done in this instance is to remove superfluous stimulation; time is essential to allow the ovary to adjust to the change.

Progesterone, in addition to other effects mentioned, causes the uterus to secrete an alkaline mucoid discharge which probably protects viability of sperm by reducing acidity of the vagina. Thus, progesterone enhances pregnancy.

Part B. Testes

The testes consist of seminiferous tubules which form sperm and interstitial cells which secrete androgen, testosterone. Testes descend into the scrotum in the first few years of the male child. This is evidently under jurisdiction of the anterior pituitary gland. There are cases on record in which testes failed to descend but patients were given concentrates of anterior pituitary substance which induced testes to assume the expected location. If this descent does not take place the seminiferous tubules remain infantile. The person is sterile if the condition is bilateral, but as interstitial cells are structurally normal and continue to exude, secondary sex characteristics develop.

The term androgen is used to describe any substance which has masculinizing properties, i.e., which promotes growth of accessory organs of reproduction. At puberty testes increase rapidly in size and spermatogenesis starts. Interstitial cells begin to secrete testosterone and as a result accessory organs of reproduction (i.e. epididymis, seminal

vesicles, prostate, penis) begin to grow and secondary male sex characteristics make their appearance. Scrotal skin thickens, there is growth of hair of the face and axilla, pubic hair develops considerably with masculine distribution, growth of the larynx occurs and the voice breaks, muscular development, occasional erections and discharge of seminal fluid take place. Psychological changes begin to make their appearance. This is all accomplished through stimulation initiated at the level of the anterior pituitary gland. Gonadotropin manufactured by the anterior pituitary is known as interstitial cell stimulating hormone (ICSH). ICSH controls growth, functional integrity, and activity of testes. In turn the testicle influences efficiency of the anterior pituitary. Basophilic cells of the pituitary in castrated animals grow in size and in number and there is added secretion of gonadotropin. Since the mechanism of puberty depends upon the anterior pituitary gland it is conceivable that the hyperpituitary person may show precocious sexual development and vitality, whereas the hypopituitary person may evidence failure of normal maturation at the proper age level.

There are instances where young men develop wide hip-waist relationships, become somewhat egg-shaped while retaining a high pitched voice, fail to show normal hair growth or maturation of secondary sex characteristics. These young men may have a damaged testicle or an undescended testicle. When nothing of this type can be found, one must reconsider physiology of the endocrine gland system. It is essential that adequate thyroid function be concurrently present for normal development of gonads. There are instances where normal sex establishment has been brought about by administration of thyroid substance. Often it becomes neces-

sary to administer anterior pituitary substance to these patients and if this fails to use testosterone, the normal male gonad hormone. To enable the patient's own testicle to mature and become functional, it is helpful to make an effort first with thyroid and anterior pituitary substance. Testosterone can be used in doses of 10 milligrams, even as high as 30 to 40 milligrams daily, if the specific patient demands that level of dosage. However, there is some question as to whether the testicle matures by this method of therapy or whether it is simply substitution therapy.

Since testosterone is protein-anabolic, and is a form of growth hormone, there is stimulation to epiphyses, hastening their closure. Consequently, when testosterone is administered to a youth who has not achieved his full physical height there is possibility of premature closure of epiphysis.

Adults who present retarded testicular growth or maturation give typical eunuchoid appearance. They generally are tall people, quite asthenic, very frequently showing bowed legs, and almost invariably long legs. Epiphysis in these people have not closed at the normal chronological time so their legs are longer than their trunk. Hair distribution is scanty and secondary sex characteristics may be severely underdeveloped. Treatment of these eunuchoid people is quite successful with testosterone and is evidenced by gaining weight, acquiring more masculine appearance, more normal development of scrotum and penis, and masculine distribution of hair.

A person may be eunuchoid due to hypopituitarism. He has not developed characteristics of hyperpituitarism and yet the pituitary is not being controlled by androgen, so there may be deficient anterior pituitary activity. It is well to treat these people with testosterone and anterior pituitary

desiccated substance. The pituitary substance is used here to get peripheral target gland effect. It is substitution therapy designed to assist the patient's own production of gonado tropin. The desiccated anterior pituitary substance is used for purposes of depressing by substitution activity of that patient's own pituitary gland in one becoming egg-shaped with wide hips and giving evidences of hyperpituitarism.

The male patient goes through a climacteric similar to that of the female. This can be so similar that vasomotor changes, hot flushes, chills, nervousness, weakness, fatigue, exhaustion, mental and emotional imbalances may be present. It is not as easily discernible in the male as in the female for there is no menstrual period to use as a criterion; nevertheless, there comes a time when the male displays symptoms of the climacteric. Oftentimes there will be insomnia, the patient remarking that he has recently stopped drinking coffee before going to bed because he feels that coffee exhilerates him to wakefulness. He may find his trousers becoming too tight at the hips and may be acquiring some effeminate characteristics, because in the male the adrenal cortex will manufacture female sex hormone. Since production of androgen is subsiding and regressing due to the climacteric, female sex hormones may come into more prominent role, causing symptoms due to preponderance of estrogen in this male patient.

Therapy at this time is testosterone 10 milligram sublingual tablets, one daily, continuing until symptoms have been relieved and then very gradually decreasing dosage. The adrenal cortex is expected eventually to produce gonad hormones. Naturally secreted androgen will handle the problem without exogenous testosterone being administered at that time. The male climacteric generally starts later in

life than does the female. Most males will enter this phase between ages of 60 and 65. There are patients who are benefited by treatment with testosterone and estrogen combined. These tablets ordinarily contain androgen and estrogen in ratio of 20 to 1. They can be given one daily over a period of many many months, provide an excellent protein-anabolic effect, and will assist this gentleman to more vigorous, comfortable, relaxed existence.

Use of these medications has not only the control of symptoms directly referable to decreased testicular activity as its purpose, but also control of the pituitary gland. As the male approaches the climacteric his pituitary gland becomes more and more aggressive, since androgen secretion is no longer a brake symptoms of this excess anterior pituitary activity are likely to occur. One of the chief disturbances is the intensified gluconeogenesis with consequent burning of the patient's own protein. He then holds water, gains weight, becomes tired and weak, and in true fact insomnia mentioned before is due to excitation of the pituitary gland. Coffee is one of the first things voluntarily eliminated because caffeine is a stimulant to the adrenal cortex; the patient is already undergoing undue persuasion of the adrenal cortex and has found any increase is detrimental to him. If this man is bordering upon hypopituitarism and his pituitary gland is not capable of responding, he should be given some anterior pituitary substance as well as thyroid substance. If the pituitary is not producing enough gonadotropins it also is deficient in thyrotropins. The patient will look and feel better if both the testicle and thyroid are crutched through this period of time when he may feel mentally depressed and without further ambition.

Gonads References

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Hypertension

Hypertension is abnormal elevation of arterial blood pressure both systolic and diastolic, ideal blood pressure being 120 over 80 mm. Hg. The upper normal limit of systolic reading for practical consideration is 110 plus one half of the patient's age. The upper normal limit of diastolic reading is 100 mm. Hg. The blood stream must operate under pressure for each cell to receive a suitable supply of food, oxygen, enzymes, hormones, vitamins and for drainage of waste products from cellular metabolism. Pressure is essential for proper circulation. This pressure is supplied by pumping action of the heart, changes of positive and negative pressures inside the thoracic cage, and by physical motion and exertion, i.e., muscular action. Pressure necessary to accomplish optimum circulation is dependent upon amount of fluid to be moved, fluid volume, and resistance against which it must be forced to travel. Cardiac output is the ability of the heart to force blood through the ventricle. Blood pressure is dependent in part on cardiac output, and therefore upon the state of muscular integrity of the heart, which in turn, is maintained by electrolyte balance and the glycogen stores of cardiac muscle.

Rate and rhythm of the heart beat are under control of the autonomic nervous system, the vagi nerves acting as brakes and the sympathetic nerves as accelerators. Volume of fluid being forced through blood vessels is dependent upon electrolyte balance. Sodium and chloride concentration

in abnormally increased amounts can be responsible for fluid retention within the blood stream thus enlarging fluid volume. State of sugar and protein concentrations may also increase or decrease fluid volume due to changes in oncotic pressure (fluid binding quality of albumin).

Peripheral resistance is a most important factor in blood pressure consideration. Increase in peripheral vascular resistance whether due to fatty deposition or to greater contraction of the vascular system forces the heart to work harder to overcome this opposition. Edematous accumulation in various parts of the body can also reenforce peripheral impediment, as can arteriosclerosis. Blood vessel musculature maintained in state of contraction implements peripheral resistance by obliterating vasculature elasticity. It is necessary that blood vessel walls have resiliency and elasticity to expand with systolic thrust of blood and to contract during diastole thus maintaining a reasonably normal level or head of blood pressure.

Blood pressure should be regarded as compensatory reciprocal activity where multiple demand of cells for food and raw material is met by higher pressure designed to meet requirements. Exercise, whether physical or mental, and mental or emotional strain are capable of extending this demand. Rate of metabolism and need for oxygen to maintain it are to be considered. Ability of the blood stream to carry oxygen may be of importance in evaluating a patient's blood pressure. When the blood stream becomes deficient in iron and hemoglobin and is thus unable to carry sufficient oxygen, circulation is accelerated so that oxygen carried will be more rapidly supplied to peripheral cells to prevent oxygen starvation. It is not too surprising then that anemic people may have hypertension.

Women in the menopause often experience hypertension. Endocrine affiliation here becomes apparent when it is realized that ovaries have ceased providing estrogen and progesterone. The pituitary gland in its effort to find gonad hormones has become overactive in production of gonadotropin as well as other tropic hormones. Effect then mediates through increase of corticosteroids, norepinephrine and epinephrine from the adrenal gland due to pituitary drive. Copious secretion of corticoids is capable of causing sodium and chloride disturbance and fluid volume expansion in the blood stream. A surplus of aldosterone from the adrenal cortex will cause fluid retention, while maximal production of norepinephrine and epinephrine is capable of causing vasocontriction. This can lead to insomnia, very possibly due to high blood pressure combined with excess of circulating epinephrine. Norepinephrine and epinephrine furthermore cause release of muscle and liver glycogen into the blood stream carrying with it fluid formerly held in cells in combination with glycogen thereby adding to the fluid volume.

Continued drive of the pituitary gland will stimulate thyroid gland to produce excess thyroxin, promoting the rate of oxidation, which raises demand of periphery upon the blood stream oxygen. Again we have potential hypertension.

Many times hypertension is found in patients with low PBI. One plausible explanation for this occurrence may be with low thyroid activity liver physiology is to some extent diminished. Impairment of liver physiology to support adenylic acid cycle, with particular reference to adenosine triphosphate, may mean absence or relative decrease in adenosine triphosphate to blood vessel walls. Adenosine

triphosphate and adenylic acid cycle are essential in conversion of glucose to glycogen and are related to sugar metabolism. Absorption of sugar through intestinal walls is often quite reduced in hypothyroidism. Furthermore, protein breakdown and hence nucleic acid metabolism from whence adenylic acid is derived may be involved due to faulty liver metabolism. The absence of adenosine triphosphate to blood vessel musculature is instrumental in the inability of blood vessel muscles to relax and thus absorb the systolic thrust of the blood stream.

Failure of relaxation of blood vessel musculature means increased peripheral hinderance to blood flow and various parts of the body are deprived of desired circulation. There is a substance released from kidney tissue, when this happens the effect of which is to raise blood pressure. Basically, this is an effort of the kidney to improve circulation to itself and if it is successful, reestablished circulation to the kidney depresses formation of this substance, consequently blood pressure drops back to normal. But in the event that blood volume to the kidney does not respond sufficiently due to local vasoconstriction of renal circulation, more material is manufactured in kidneys and blood pressure continues to heighten. The material formed in the kidneys is named hypertensin. In the mechanism of hypertensin, nature is protecting the life of the person. Release of hypertensin is a self-defense reaction and is designed to enhance blood pressure to augment circulation through the kidney and thus to preserve life. Presence of this action is more in the field of potentiality than actuality. The mechanism is present and available in extreme expediency, but very seldom, if ever, is presence of hypertensin in abnormal amounts encountered.

Edematous accumulation and fat deposition by simple pressure relationship to blood vessel walls intensify peripheral resistance and magnify blood pressure. Incidence of hypertension in obese individuals is roughly three times that in nonobese. Varicosities theoretically could be capable of implicating blood pressure in that return flow of blood through venous system is so slowed that the capillary beds are unable to empty properly necessitating amplified arterial pressure to force venous blood through capillary beds.

Endocrine dysfunction accompanied by high blood pressure, tends to verify the fact extended pituitary drive is instrumental in causing and maintaining hypertension. Whether greater activity of the pituitary gland is due to hypothyroidism, hypogonadism, or hypoadrenalism is not so important at this stage of consideration as is the fact that pituitary drive will impair sugar metabolism through the pancreas both directly and through the vagus nerve. This relates to the adenosine triphosphate cycle, fluid balance of the blood stream, and through the adrenal cortex will effect electrolyte balance and gluconeogenesis, again reflecting itself in fluid volume of the blood stream. High incidence of overactivity of the pituitary gland in obese people and relationship of hypertension to obesity indicate the role of the pituitary gland in its ability to instigate peripheral resistance to circulation.

State of protein nutrition pertains to endocrine physiology, fluid balance in the blood stream, and liver physiology, all of which are functional aspects of hypertension. It is conceivable with protein depletion and a blood stream seeking sources of protein to replenish its concentration a ready source of protoplasmic protein available for robbery will be present in the blood vessel wall. Were the cells of the blood vessel intima to release protein, these cells could then

become roughened, possibly inflammed and in turn attract deposition of fatty molecules from the plasma leading to atheromatous changes. It is even possible the vaso vasorum if called upon to surrender protein to the blood stream, could rupture beneath the intima of the blood vessel wall leading to roughening of intima and deposition of thrombotic material. Many autopsies disclose subintimal damage produced by hemorrhage.

Continued presence of hypertension with consequent demand upon the heart leads to ventricular hypertrophy, cardiac enlargement, and eventually cardiac decompensation. Frequently the individual patient is not given time to complete this cycle and atheromatous plaques in coronary blood vessels with cardiac infarction are responsible for sudden interruption of the progressive course of hypertension. In other instances nephrotic changes occur with their sequelae: continued release of hypertensin, ever increasing level of blood pressure with eventual rupture of cerebral arteries, and possibly fatal termination. The cycle with temporary recovery sometimes recurs at a later date with more final consequences. The problem of hypertension is not to be taken lightly, but in all instances, hypertension itself is but compensation of the body. Obstacles placed in the course of the blood's supply line of essential raw material to each cell force the pressure to raise and thus overcome the obstacle otherwise results are fatal.

In consideration of therapy for the hypertensive patient, our recommendation is first, thorough and complete evaluation and indicated therapy for protein metabolism as discussed in the chapter on protein. Secondly, desiccated thyroid substance for the purposes of vasodilation, hepatic encouragement, stimulation of assimilation of sugar from

the intestinal tract, augmenting cardiac output and diuretic effect. Thirdly, concurrent use of digitalis leaf for purposes of improving cardiac output, strengthening cardiac musculature, and diuretic effect to be achieved by this means.

Digitalis leaf is the safest form of digitalis since the toxic dose is far in excess of therapeutic dose and only 20 per cent of administered dose of digitalis leaf is assimilated. Combination of thyroid and digitalis is extremely effective in management of hypertension. Tablets are available containing two (2) grains of thyroid and one (1) grain of digitalis leaf. One tablet of this type can be given in the morning and one tablet at lunch. Further safeguard against digitalizing a patient or of toxic manifestations is available by use of belladonna and alkaloids. Concurrent with administration of digitalis and to prevent accumlative effect, a tablet containing one-eighth (1/8) grain of belladonna combined with a mild laxative can be prescribed at bedtime. This will allow full action of two (2) grains of digitalis leaf (of which only 20 per cent is effective) without any accumulative action occurring.

It is then advisable to supply ammonium chloride, 7½ grain tablets, one with each meal on alternate weeks. Effect of ammonium chloride for diuresis adds to that of thyroid and digitalis and when used on alternate weeks is more effective than is continual administration. As discussed in the chapter on liver, there is a potential source of amino acids possible by disintegration of ammonium chloride.

Some patients presenting hypertension complain of gastrointestinal disturbances, flatulence, indigestion, constipation, and spastic colon conditions. Treatment consists of a tablet of phenobarbital, one-quarter (1/4) grain, and belladonna, one-eighth (1/8) grain, taken with each meal to relax the

gastrointestinal tract. Failure of digestion of protein materials evidencing itself by gastrointestinal symptoms may be responsible to some degree for hypoproteinemia, which could be causative of hypertension.

There are many methods of treatment available today with newer medicinal agents that perhaps deserve some comment. Diuril ® and Diamox ® both are powerful diuretics and deserve honorable mention, but by themselves do not take into account protein metabolism of the individual patient—one major consideration in all hypertensives. Nitrites achieve their vasodilation at the neuromuscular junction, thus cutting out sympathetic and parasympathetic nerve influences to blood vessel muscles, however, toxic effect and overaction are dangers to be considered. Rauwolfia serpentina derivatives function, as do barbiturates at the hypothalamic area, causing relaxation or inhibition of both the endocrine system and autonomic nervous system by blocking control of the hypothalamus to each. They have such inhibition on other functions of the body without corrective effect other than symptomatic relief that we do not here advocate their use.

The mental and emotional state of the patient must be given consideration. The automatic nervous system can be unduly excited by mental, emotional, or physical strain, such as loss of sleep. Effect is mediated through the hypothalamus of the brain and both parasympathetic and sympathetic nervous systems, with consequent overproduction of epinephrine and insulin and can be considered therapeutically in the same category as hyperpituitarism.

It follows logically that patients with endocrine gland imbalance responsible for hyperpituitarism must be considered in the light of foregoing chapters. Whatever endo-

crine imbalance is present should be managed in such manner that the pituitary gland is relieved of necessity of driving to make target glands produce their secretions. The variety of causes of hypertension from this standpoint are numerous. Each individual gland is capable of precipitating hypertension and any combination of gland dysfunctions is capable of causing overactivity of pituitary drive.

It thus behooves the physician to thoroughly evaluate status of the endocrine gland system and use therapy designed to control or to reestablish balance. We feel that therapy here expounded is capable of correcting aberrations of function responsible for the symptom hypertension, and is designed to be corrective rather than palliative. Sedation alone or diuretics alone fall into the category of palliative treatment—they are perhaps capable of preventing severe vascular accidents but do not normalize basic imbalances. Adjustment of protein metabolism, endocrine physiology, and parasympathetic-sympathetic balance will remove the etiology of hypertension and thus are more advisable than simple palliation.

Hypertension References

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Arthritis

Arthritis is an inflammatory condition of synovial tissue or joint articular surfaces. Many classifications of the arthritides have been made depending upon time element as in acute or chronic arthritis. Other terms such as rheumatoid, hypertrophic, and atrophic arthritis are related to pathological process present in the joint. In this discussion, we do not intend to differentiate between various classifications, but will simply use the heading arthritis.

Primarily due to reaction of articular surfaces when depleted of their normal concentration of protein, inflammatory process occurs in joint tissue evident by joint enlargement and swelling, pain upon motion, in some instances disfiguration. Depletion of protein from the articular area reduces normal resistance of tissue. Tissue deprived of its natural immunity becomes sensitive to effects of toxin, bacteria, to oxygen insufficiency and external barometic pressure changes. The intra-articular fluid balance is disturbed by external pressure changes, which cause retained fluid to expand the capsule painfully.

Effect of normal motion of a joint, depleted of protein, is equivalent to trauma and movement ordinarily easily and comfortably performed becomes extremely painful. Fluid retention in the joint, thus magnifying the amount of synovial fluid is among the first effects when protein has been withdrawn. Protein is removed from the matrix of joint surfaces causing thinning and rarefication of bone components

as further withdrawal occurs. This can be demonstrated by x-ray and is one diagnostic criteria of rheumatoid arthritis. Calcium which has been held in combination with protein or albumin becomes separated and is precipitated, depositing upon bone tissues intensifying density of the calcium bone covering (periosteum) as more joint protein is removed. An excess deposition of calcium leads to spur formation and to "lipping" and is usually classified as hypertrophic arthritis. These changes are demonstrable on x-ray plates.

The patient may evidence sensitivity to various toxins determined clinically by intradermal testing with staphylococcus, streptococcus, or other bacterial vaccines, but since natural immunity of the patient is depressed, they may show positive reactions to any bacterial toxin. Most arthritis is accompanied by anemia, malaise, low PBI, and either hypotension or hypertension along with other constitutional symptoms depicting hypoproteinemia.

Hypoproteinemia may result from many different imbalances both physiological and dietary. The dietary imbalances are sometimes traceable to insufficient protein in the daily food intake. They may stem from faulty digestion from hypochlorhydria (which commonly accompanies mild anemia and hypothyroidism) or failure of suitable concentrations of digestive enzymes, faulty assimilation or even mild hepatic insufficiency. When the patient is thoroughly analyzed and the foregoing possibilities are eliminated, consider internal environmental disturbances capable of leading to or precipitating hypoproteinemia.

Arthritides are very commonly found during the ages of the climacteric. The pituitary gland elaborates more of its tropic hormones, particularly gonadotropins, to cause gonads to step up their productivity. These glands have retired or

are in process of retiring from active service, no longer capable of responding to this stimulation. Adrenal cortex, however, will respond with exaggerated production of corticosteroid hormones. They cause a drive of hepatic tissue which will further increase gluconeogenesis.

It is necessary that additional quantities of protein be supplied to the liver in the performance of gluconeogenesis. The first step of this occurs when blood stream delivers protein to the liver. The blood stream to compensate will rob other tissues of the body. Depletion may occur from any tissue or area. Obviously this is the state hypoproteinemia.

To carry the discussion a little further, consider the fact that highest concentrations of protein are in lymphatic and reticuloendothelial systems (synovial membranes). As search is made for available protein these tissues having high concentration of it are most likely to be tapped. The depriving of lymphatic and synovial tissue of their protein sets off the string of events that leads to an arthritic condition in each joint so affected. As the process continues—and it will continue since the gonad tissue is becoming more and more unable to perform its specific function—there will be less control of the pituitary and the course will be progressive. The inflammatory manifestation in the affected joint goes through stages of rheumatoid, hypertropic and atropic arthritis as depletion occurs. Administration of gonad hormones is capable of depressing pituitary drive, but will still not restore protein to the cells.

The foregoing statements are not applicable, of course, to the younger woman in early or middle twenties. She may be subject to an imbalance of estrogen-progesterone ratio. Gonads are still functioning, but are not controlling the pituitary gland which is attempting to promote better proportion of either estrogen or progesterone. The adrenal cortex is forced to supply excess steroid hormones, particularly glucocorticoid hormones.

There are instances in which the patient does not evidence clinical symptoms relative to estrogen-progesterone disequilibrium. She may be secreting gonad hormones only by virtue of a pituitary gland that has become overactive in its effort to regulate estrogen-progesterone relationship. The adrenal cortex again will be incited. The pituitary-adrenal axis when overactive increases gluconeogenesis, leading to hypoproteinemia. Effort to produce testosterone in young men may have an analogus effect in so far as pituitary-adrenal axis is concerned.

Hypothyroidism often present in arthritic subjects, causes its effect through decreased cellular activity and oxidation, impaired hepatic functions, circulatory insufficiency and digestive inability in the protein field along with diminished sugar absorption from intestinal contents. This results in hypoglycemia, and in the effort to combat it, the blood stream will supply liver with more protein to be used for purposes of manufacturing sugar, thus maintaining normal blood sugar level at expense of protein reserve. Carbohydrate has a protein sparing effect.

Adrenal gland relationship to arthritis has been discussed in instances of overproductivity of glucocorticoids due to pituitary drive; however, many arthritic patients display hypoadrenalism and arthritis is a very common accompaniment of Addison's disease. The concept in this situation is in relationship to liver physiology and pancreas function. The sugar hormone of adrenal cortex has antagonistic effect to insulin and a normal balance between the two maintains the relative constancy of blood sugar level. Failure to pro-

duce commensurate sugar hormone in hypofunction of the adrenal cortex allows insulin present to maintain low blood sugar. This is offset by effort of the liver to provide more sugar in answer to relatively excess insulin. Failure of supply of mineralocorticoids from the adrenal results in electrolyte imbalance and fluid deposition in joint areas. Decreased androgen and estrogen due to hypofunctioning adrenal cortex, tends to further upset endocrine equilibrium and deprives the body of protein anabolic hormones.

Inability of the adrenal cortex stimulates pituitary drive, reenforcing secretion of pituitary tropic hormones primarily ACTH but not confined to one tropic hormone, the effect being demonstrable upon thyroid gland as well as pancreas. Effect on the pancreas increases insulin concentration. The response of thyroid production causes a rise in PBI with consequent utilization of protein potentiating severe depletion.

These considerations can be applied to almost any age group. Younger people in their formative years are dependent upon pituitary for growth hormones, but excess leads to hypoproteinemia. During reproductive years, disturbances of gonad tissue and of lactation as well as expanded environmental strain may stimulate the pituitary gland to overactivity. Climacteric years require regulation and rebalancing of the endocrine system and the pituitary is very prone to become overenthusiastic in management of this readjustment. The patient in older years is generally slowing down, so also is elaboration of digestive juices and enzymes with resultant hypoproteinemia. Frequently these people do not secrete enough steroid hormones from their adrenal cortex and are subject to arthritis due to hypoproteinemia related to insufficient adrenocortical activity.

Management of arthritis appears complicated when not

properly related to endocrine equilibrium. Many things available for treatment attest too failure of any one product to give satisfactory results in every patient. Palliation of arthritic pain is relatively simple and aspirin in large doses has proved quite effective. Etiology of arthritis, however, continues rampant and is not controlled by this means. Use of vitamins and minerals has in some people proved effective and it would be our opinion that they suffered hypoproteinemia due to failure in the gastrointestinal tract and in liver physiology where vitamin and mineral combinations are essential to normal physiology. ACTH and cortisone derivatives and refinements have given relief in many instances, but manufacturers of these products recommend that while they are being used protein metabolism be carefully supervised.

The effect of ACTH is primarily to stimulate production of corticoids from the adrenal cortex. Whether ACTH is used or cortisone and derivatives, the response with relationship to arthritis will still be the same. Result of this corticoid treatment is to cause muscle tissue, mucous membrane, blood vessel walls, and the blood stream itself, to give up protein to resupply the liver and joints. This program of replenishing joints with protein has limitations, for side effects of materials used are not inconsequential. There must be an end eventually of the capacity of the body to transfer protein from other tissue to joints. Corticoids are of no benefit to the sufferer when that stage is reached, but by that time substitution therapy, has brought about atrophy of adrenal cortex necessitating continued administration of cortisone-like products in order to maintain life. Incidence of diabetes under corticoid management is related to the fact that protein is being transformed in liver to carbohydrate or glucose at a rapid rate, causing heightened

formation of insulin from the pancreas. Often this is capable of exhausting the beta cells of the isles of Langerhans, with consequent failure of insulin and hence a diabetic condition. Methods of managing arthritis at the present time carry with them an element of danger and sometimes it is debatable whether arthritis is not the lesser evil to be endured. Other tissues will be afflicted when the hypoproteinemia progresses and the patient is in dire circumstances with arthritis being only a minor part of the problem.

Recommendation here for treatment of arthritis is based upon actual general practice and has proved successful in many patients. Suffice it to say the very great majority of people thus treated, become comfortable, are relieved of arthritic pain, and in no danger of precipitating other consequences from changes induced by this therapy. The patients display some characteristic of hypoproteinemia. Even mild anemia accompanying arthritis can be accounted for by the fact that it takes raw material of protein to form erythrocytes. Admittedly there are other factors to consider. Normal blood count will not be maintained in absence of enough thryoxin or vitamin B-12 manufactured by intestinal bacteria, but their absence indicates hypoproteinemia. Protein intake will of necessity be given first consideration.

If the patient is ingesting a variety of protein food, based upon minimum daily intake of 300 protein calories, and still displays evidences of arthritis, we supplement in the form of one of the commercial products on the market on the basis that the patient's natural intake does not contain a sufficiency of all essential amino acids. One used in this office is Paramino,® manufactured by Lanpar Pharmaceutical Company of Dallas, Texas. There are, however, many acceptable products available. This provides an immediate source of available hydrolyzed amino acids and does not depend upon integrity of the digestive system for its success. We recommend the unhydrolyzed complete protein and have found Partein ® wafers to be eminently satisfactory in this field for patients who possess a satisfactory gastrointestinal function. These are also manufactured by the same company. The preference in determining which product to use, i.e., the hydrolyzed or unhydrolyzed products, is based upon the integrity of the gastrointestinal tract. Utilization is insured by concurrent administration of glutamic acid and pepsin tablets wherever the wafers are prescribed. One tablespoonful with each meal of paramino is recommended or two wafers of partein thoroughly chewed, with each meal, plus a tablet of five grains of glutamic acid and five grains of pepsin.

We use an enteric coated tablet containing methionine, choline, inositol, pancreatin, and ox bile one tablet t.i.d. in order to promote improved utilization of the patient's own food intake and supplements. This provides choline for adequate liver physiology and proper intestinal use of foods, methionine, precursor to choline and inositol, aids in the production of vitamin B-12, pancreatin and ox bile stimulate the pancreas to produce protease, amylase and lipase.

Liver, iron, and vitamin B complex combined in one tablet are often used in arthritic problems. Liver is an excellent source of protein and has stimulative effect upon hepatic cells. Iron insures adequate oxygen will be carried by the blood stream to cells and is necessary, perhaps as a co-factor in the adenylic acid-adenosine triphosphate cycle which is related to arthritis. Muscle spasm surrounding the arthritic joint without adenosine triphosphate cannot be dissipated or relaxed. Vitamin B complex is necessary in all

stages as co-enzymes and co-factors of sugar metabolism and liver cell physiology.

Patients often are given tablets containing 100 milligrams each of bioflavonoid and Vitamin C, one with each meal. This supplies an adequacy of vitamin C for production of adrenocortical steroids, necessary in physiology of all cells. It is combined with bioflavonoid factors to maintain cell membrane integrity, as preventive of cellular and capillary fragility, and to improve assimilation through intestinal mucosa.

Therapy must include consideration of gonad tissue. Cells will not use albumin from the blood stream without governing presence of sufficient gonad hormones. The specific type and quantity of these hormones being dependent on the symptoms and history of the individual patient. We supply the combination of testosterone and estrogen in relationship of 20 parts of testosterone to 1 part of estrogen for very powerful protein anabolic effect to those who are beyond active gonad function, either male or female. They are available in tablet form to be administered one daily.

As you will note from the discussion thus far, therapy of arthritis is the same as advocated in the chapter on protein. This is intentional and premeditated, in view of the fact protein physiology and hypoproteinemia are so closely related to arthritis. Patients will not show satisfactory improvement, until such time as their cells have been replenished with protein. They may have been robbing protein from joints for a period of years, so replenishment will not be accomplished with extreme rapidity. Patience and perseverance are essential yet if thorough analysis be made and treatment based on physiology of the endocrine system and protein

metabolism, the patient will feel better gradually until finally there is no discomfort. Results are slow, but are encouraging to victims of arthritis because they feel the difference.

The clinician undertaking responsibility of an arthritic patient should prescribe competent laboratory analysis. Tests recommended are red and white blood count and hemoglobin, cholesterol, PBI, inorganic iodine, total protein, serum albumin, serum globulin, albumin-globulin ratio and blood glucose. Results of these will indicate the severity of chemical aberrations and serve also as a yardstick for determining progress. There are a few instances in which improvement is slow in appearing, when the physician becomes discouraged, as well as the patient. It is reassuring to repeat the laboratory examination in such an exigency, and thus prove that progress is occurring.

Use of physiological small amounts of desiccated thyroid is advisable as the patient continues under management and relief from arthritic pain becomes apparent, however thyroid administration should be delayed until such a time as the serum globulin is 2.9 or less. For while diuresis and the increase in circulation, liver function, and sugar metabolism are often of benefit, whenever the serum globulin level is 3 gm or above, the patient does not have protein capable of supporting increased thyroid activity.

Obesity puts excess work upon articular surfaces and must of course be kept in mind. It was pointed out that with protein depleted joint surfaces even normal activity becomes trauma, and when work of the joint is aggravated by carrying excess weight, trauma is multiplied. Some patients will lose weight when protein metabolism is normalized. Most of them will release excess water. In those who

are obese and arthritic, treatment advocated above is still recommended in conjunction with the therapy discussed in the chapter on obesity.

We do not advocate to these people that any dietary restrictions be enforced. The average person in relatively good health usually eats but minimal amounts of protein. It has been our experience not to find anyone who eats an excess of it. Low blood sugar may stimulate use of protein further depleting stores, so carbohydrate is not restricted lest its protein sparing action be lost. It is often possible to restrict fat intake. However, if it consists mainly of unsaturated fats, we do not impose any dietary restraint on the arthritic person.

Striking frequency in general practice, of arthritis in conjunction with hypoproteinemia lends substantiation to this form of therapy. Results achieved through persistent concentrated effort toward normalization of protein physiology gives justification for expounding this aspect of management.

The total absence of undesirable side effects makes this the therapy of choice for every arthritic person. Joint deformities and bone depositions present will not be corrected. On the other hand many people are capable of carrying these deformities without pain. Presence of deformities, unless to point of fusion of joints, is inconsequential. There have been instances beyond record of hypertrophic arthritic spurs discovered on patients who had never experienced a single symptom from this source, but were being examined for some other problem. This is a frequent finding on x-rays made for chest or gastrointestinal analysis.

Arthritis can be halted at any stage and unless complete fusion has occurred, patient's daily routine can be followed in a normal fashion.

Arthritis References

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Obesity

Obesity is a neuroendocrine nutritional imbalance and should be treated as such. The theory promulgated by the popular press to the effect that all obesity is due to excessive eating and as a consequence can be controlled by restriction or withdrawal of food is erroneous. Necessity of protein to each and every tissue of the body was quite thoroughly explained in the chapter on protein. Extreme effects to physiology when protein is not present in sufficient quantity would demonstrate that necessity of protein is above equivocation. Fats are essential in management of intestinal excretory functions and are raw material for creation of hormones from the endocrine gland system. Carbohydrates are essential for supply of heat and energy within the body and in their absence the liver is forced to use protein to supply carbohydrate. They therefore have protein-sparing action. Practically all present day dietary approaches to obesity limit fat and carbohydrate intake.

Our recommendation is that if there must be a dietary approach to obesity, it be considered in the following light. Normal intake of all foods is mandatory for adequate physiology. Daily total caloric intake should be equivant to 10 times the ideal weight, thus if a person weighed ideally 120 pounds, the intake should be 1,200 calories. Calories should be divided into protein, fat, and carbohydrate categories. Fat intake should not exceed 300 calories per day. Protein should be equivalent to no less than 300 calories per day

and carbohydrates should make up the difference between total fat and protein calories subtracted from total daily allowable calories. This then would fall into classification of normal food intake and as such can be recommended unless more than average energy expenditure is anticipated. It is our practice not to suggest dietary limitations to patients entering our management for the purpose of losing weight.

Detrimental effects of obesity are so obvious and are so closely related to effects of endocrine system dysfunction that they are here pointed out only to connect endocrinology with obesity. The concept propounded, is that obesity is but a symptom of neuroendocrine dysfunction. Likewise the problem of leanness is also a symptom of endocrine disorder, and is generally accepted as such. It is not uncommon to hear that leanness is due to glands. The common concept seems to be that obesity is due to gluttony or some perverse desire on the part of people to eat to excess and thus provide an excuse for other shortcomings. Such philosophy appears to me untenable and even more so in light of the fact that management of obesity by normalizing neuroendocrine function is successful.

Approach to obesity is made by thorough physical examination of the patient with recording of age, past history, blood pressure, pulse rate, weight, measurements of chest, waist, hips, and height are likewise of importance. It is possible to use a rule of thumb with regard to ideal normal weight. We consider a height of 5 feet tall equivalent to 110 pounds adding 5 pounds for each inch above 5 feet. This is subject to variation of 10 per cent due to bony framework and hereditary factors peculiar to each case. Thorough physical examination is required since many endocrine gland derangements are apparent by examination. Palpation, per-

cussion, auscultation, and ophthalmoscopy all provide information of essential character. Previous history of the patient is of primary importance. Relationship of acute infectious conditions during childhood with possibility of high fevers damaging endocrine function, previous surgical experiences, condition of the cardiovascular system with association to hypertrophy, palpitation, arrhythmias, and valvular conditions, must be considered. Important also are questions relating to protein metabolism such as allergies, fatigue, aches or pains, constipation, indigestion, flatulence; as well as evaluation of resistance with regard to frequency of colds or other infections and ability to heal cuts, sores, and wounds.

History relative to menstrual background is of real importance. Age of onset, frequency, regularity and duration of flow, whether accompanied by breast tenderness, premenstrual tension or cramps, become significant. It is advisable to inquire as to presence or absence of symptomatology regarding menopause such as hot flushes, chills, headache, vertigo, and any other information pertinent to ovarian function, not the least of which is history concerning children, or miscarriages with due concern in those people who have not had children as to whether intentional or due to an inability.

The patient's weight during previous years prior to and after adolescence as well as at age of marriage and within the last two or three years is important. We must consider when obesity started and what correlation that time had to childbirth, menopause, acute infections with high fevers, traumatic incidents, or other external and environmental factors which might have had an influence on the inception of neuroendocrine imbalance.

Our procedure generally is to acquaint the patients with the fact that we do not expect them to lose weight with undue rapidity. The body can respond and adjust to weight loss of approximately 5 pounds per month. They may lose weight in excess of this, but will not retain the loss with any permanency or stability.

Hyperpituitary Obesity

Following the case history, physical examination and with thorough understanding of the background of the present physical condition, it is possible to evaluate in categories of endocrine probabilities on basis of the physical configuration. Pituitary type persons will have an excess of 10 inches difference between hip and waist measurement. Patients who had a pituitary problem in the preadolescent period of life will evidence some further interesting facts. Normally measurement from symphysis to floor will equal that of symphysis to vertex of the head. From the medial notch of the sternum to tip of longest finger will equal these measurements and span from the longest finger of right hand with arms outstretched to the longest finger of left hand will equal height.

During formative years the pituitary gland secretes growth hormone as well as gonadotropic hormone. When the pituitary gland does not produce gonadotropins, the target organ, ovary or testes, does not supply protein anabolic secretions in which event the epiphysis of long bones does not fuse as early as it chronologically should. Hypopituitary-hypogonad patients assume eunuchoid proportions of long legs with relationship to the rest of the body, i.e., from symphysis to floor is longer and arm span is longer than is measurement from symphysis to vertex. A person who has

an increasedly active pituitary gland during formative years producing both growth hormone and gonadotropins in profusion, may have early closure of epiphyseal plates and as a consequence will evidence shorter extremities generally with a longer trunk, i.e., from symphysis to floor is shorter than from symphysis to vertex as is also measurement of either arm and the arm span is shorter than the patient's height. These are interesting points of observation and may serve to indicate pathways through which treatment will be instituted.

The patient with pituitary problems will in all probability present difficulties and irregularities of menstruation which are evident on the case history. Overactive pituitary type presents a firm solid consistency of cells obvious upon merely touching the arm or discernible while taking blood pressure, is usually an alert, personable, interesting individual, embroiled in community affairs, and frequently of a high social calibre (this is not invariable).

Further confirmation of the hyperpituitary activity can be achieved through laboratory aids. We rely upon physical examination and history, but if warranted, perform laboratory screening tests consisting of cholesterol determination, PBI, inorganic iodine, total protein, serum albumin, serum globulin, albumin-globulin ratio, and sugar.

Cholesterol determination reading above normal with PBI below normal is the expected ratio. Normal or high PBI and high cholesterol indicate the patient's fat intake is evidently abundant and should be regulated to normal intake not to exceed 300 fat calories per day.

The hyperpituitary person may show PBI of normal or above since thyrotropic hormone from the pituitary is compelling additional production of PBI. Nevertheless, low thyroid function could be causative of hyperpituitarism and in such a patient balancing thyroid physiology will control pituitary activity.

Normal inorganic iodine (2.5 to 3 gamma per cent) requires no therapy. If the inorganic iodine level is below 2.2 gamma per cent, prescription should include a supply of inorganic iodine. Any inorganic iodine will suffice. Lugol's solution, Organidine,® potassium iodide, or others may be used. Inorganic iodine above 3 gamma per cent necessitates administering great quantities of protein to cause union of accumulated iodine with albumin forming an iodinated protein and thus using excess iodine. Normal level of inorganic iodine must be maintained to permit satisfactory thyroid gland performance (as discussed in the chapter on thyroid).

Total protein should be 7 gm per cent or above, but we do not intend to subsidize this field on this basis when the report indicates patient is maintaining a level of 6.5 gm per cent or above. Serum albumin of 4.5 gm per cent or above is acceptable but must be interpreted in conjunction with serum globulin. Serum globulin of 2.9 gm per cent or below is within acceptable range. Serum globulin above 2.9 gm per cent makes it necessary to subsidize protein metabolism. A reading of this level indicates hypoproteinemia. It is not possible for the thyroid gland or peripheral cells to receive usable protein in the presence of a high globulin reading, therefore low PBI and high serum globulin is neither unusual nor unexpected but indicates the necessity of subsidizing the protein field. The hyperpituitary person evidencing a response in the thyroid gland and producing high PBI may have rapid depletion of protein reserve and this can be causative of high serum globulin. Hyperpituitary people are prone to diabetic problems so blood sugar exam-

ination is important oftentimes disclosing unsuspected diabetes but in any event assuring the physician that he is not dealing with a borderline case and is not likely to precipitate diabetes by encouraging protein use through thyroid management.

Our proposed therapy on this patient is to use an iodine free preparation of desiccated thyroid for the purpose of restraining the extremely active pituitary gland. In addition to this the diuretic effect of thyroid will assist in the effort to cause reduction of weight. Improved motility, secretion, and assimilation of the intestinal tract will insure better utilization of food. Proper use of food to complete hydrolysis and oxidation rather than storage within the body is enhanced here by stimulatory effect of thyroxin upon liver physiology. Dosage of thyroid substance used varies with the patient, but generally speaking, the hyperpituitary person will require high doses of thyroid substance. Our routine is to initiate therapy on dosage level of around 6 grains of thyroid daily. One preparation that is used in our practice is a combination of digitalis with thyroid substance.

The rationale of using digitalis is predicated upon the following. Standard reference texts and pharmacology authorities are in general agreement that digitalis augments the output of the ventricle while prolonging the rest period of the myocardium. Decompensation of the heart, wherein the body circulatory needs are not met by the stroke volume, is definitely and unequivocally mitigated by the use of digitalis. Part of the effect of this medication is through its influence on the vagus nerve. The diuresis may be a response to improved renal circulation combined and concurrent with the return of interstitial fluid into the vascular

compartment. This expands fluid volume while renal activity based upon fluid volume becomes more efficient.

The evaluation of decompensation is quite arbitrary and it is apparent that a patient carrying fifty and more pounds in addition to weight considered normal for his height and bone framework would be unable to fully compensate without undue cardiac strain. Promotion of myocardial strength and enhanced stroke output can be accomplished without digitalization.

Most authorities agree that digitalis has little or no effect upon the normal heart, i.e., it is not contraindicated. The level of decompensation, being perhaps subclinical, will be corrected and the overall results of using digitalis in obesity are beneficial.

Dr. Israel Bram of the Bram Institute for Goiter and Glandular Diseases, Philadelphia, Pennsylvania, reported on 140 cases of obesity treated with digitalis in "Medical Record" of February 21, 1940, and further substantiates use of digitalis in this field. Digitalis supplies diuretic effect that is valuable. It has tonic effect on heart musculature and is synergistic with thyroid to augment cardiac output. Digitalis will induce mild subconscious nausea preventing excessive eating precipitated by activated metabolic processes coincident with use of thyroid. The preparation used is whole digitalis leaf of which only 20 per cent is assimilated. This is preferable because therapeutic and lethal doses of digitalis leaf are widely separated. Therefore, should any signs occur indicating too much digitalis, the margin of safety is sufficient and it can be withdrawn before any severe symptomatology appears.

Proposed benefits of digitalis are not dependent upon

digitalizing the patient. Many physicians regard use of digitalis as being confined to congestive heart failure or decompensating heart. There are cardiac problems found in obesity which indicate use of digitalis but frequently the level of decompensation is so borderline that the managing physician would not ordinarily suggest it. Digitalis combined with thyroid is extremely helpful. Medication used in our practice contains ¾ grain of digitalis and 3 grains of desiccated thyroid substance (iodine free). Normally, we start our hyperpituitary patient on one tablet of this preparation with breakfast, and one tablet with lunch, advancing dosage as required to achieve adequate weight loss.

Cumulative effect of digitalis is prevented in this therapy by a preparation containing belladonna. This preparation contains belladonna united with a mild laxative to be taken one tablet at bedtime. Patients who do not tolerate this, since it does contain a minimal amount of strychnine, capable of initiating intestinal irritation, griping, or an extra amount of bowel movement, can use instead a preparation of ¼ grain phenobarbital combined with ⅛ grain of belladonna at bedtime. Accumulative effect of digitalis is daily counteracted and is therefore not capable of causing heart block or digitalization.

Treatment of hyperpituitarism must contain hormone products to substitute for those glands not performing normally. Any target organ not operating sufficiently is capable of inciting additional activity on the part of the pituitary gland. Therefore, it is essential that this be evaluated and corrected by substitution. Gonad tissues are tremendously important in this consideration. Any lack of estrogen exciting to the pituitary must be corrected. Treatment with estrogen when indicated has a powerful pituitary inhibiting as

well as protein anabolic effect and is highly recommended. Many women, particularly younger girls and menopausal women, evidence shortage of progesterone. We advocate either estrogen or progesterone to balance estrogen-progesterone ratio as indicated in the chapter on gonads. This is advised in addition to thyroid therapy.

Absence of testosterone or androgen in males can be the precipitating factor to their obesity. Buccal tablets containing 10 milligrams each of testosterone propionate are administered one daily at bedtime. Many males undergo climacteric changes similar to those of females and testosterone propionate buccal tablets are quite effective in managing this syndrome. Testosterone may be administered to any male who evidences signs of failure in this field as discussed in chapter on gonads. Caution here is to the effect that a youngster who has not yet achieved full bone growth should be given testosterone only under most strict supervision of the physician in order to avoid premature epiphyseal fusion.

Patients who are postclimacteric and evidence symptoms of protein irregularity should be given one tablet daily sublingually of testosterone and ethinyl estradiol in combination of approximately 20 parts of testosterone to each part of ethinyl estradiol. Protein anabolism is here much desired and will impede robbery of joints, bones, muscles, mucous membranes and other tissues which conceivably might occur when metabolism is promoted by thyroid therapy.

Hyperpituitary patients progress so it becomes necessary to increase dosages and in very few instances to use one quarter grain tablet daily of desiccated pituitary substance. Any patient who is started on pituitary substance should start with ¼ grain tablet daily and in the event that they gain weight on this material, it should be discontinued since

the effect would be that of encouraging gluconeogenesis rather than restraining pituitary drive.

Laxatives may be used with this program since it is desirable that all excretory functions be maintained at high levels. A small percentage of hyperpituitary patients will do well by the administration, in addition to above, of 7½ grains of ammonium chloride with each meal on alternate weeks, thus again enhancing diuresis. Suggestions from the chapter on protein are applicable in any instance wherein protein metabolism is impaired. We are not desirous of stimulating metabolism above the ability of the protein level to support it. Supplementing to prevent protein depletion is advised by means of agents described in the chapter on protein, anticipating that great amounts of stimulation are to be applied in the effort to reduce weight and balance the neuroendocrine system.

Hypopituitary Obesity

Hypopituitary patients presenting themselves for weight reduction must be given the same meticulous physical examination and case history in order for thorough evaluation. These are usually extremely obese people. They display redundancy of tissue having a pendulous abdomen, folds of tissue on the thighs and upper arms and being very soft or flaccid. This flaccidity is evidence that there is a state of hypoproteinemia where in protein has been withdrawn from cells (muscle and soft tissue) leaving a vacuole of a cell containing predominately fluid. The patient is dull mentally, stoic in appearance, extremely exhausted, indicating little if any appetite, often constipated, and frequently gives a history of having been an hyperpituitary person, later becoming utterly exhausted with softening of tissue and redundancy becoming apparent. All stages of transition from hyperpituitarism to hypopituitarism are presented although some people offer no history of having been hyperpituitary.

The history may be surgical extirpation of one of the target glands leading to failure of the pituitary gland because protein metabolism was not able to support the pituitary gland in its effort to direct the endocrine and the diametrically opposite effect occurred. The pituitary gland deprived of protein instead of becoming overactive became underactive or failed entirely to function.

Therapy of the hypopituitary patient aimed at balancing the neuroendocrine system with the nutritional system to reduce obesity, is initiated with desiccated thyroid substance (iodine free). The thyroid gland not supplied with an adequacy of thyrotropins has become dormant as a consequence the patient will be sensitive to thyroid substance.

Initial prescription starts at low levels, in many instances a level of 2 to 3 grains of thyroid substance daily, combined with digitalis leaf for diuresis. Use of digitalis makes mandatory administration of the belladonna compound at bedtime. These patients are so full of water that we again recommend ammonium chloride 7½ grains one tablet with each meal on alternate weeks.

All target glands must be supported and gonad substances are used as indications may present for their crutching effect. Hypopituitary patients should be started with one quarter grain tablet of pituitary substance daily, increased as progress indicates to the extent of 10 grains per day. The entire program may be expanded according to response of the patient. Efficiency of liver physiology enhances filtration of these hormonal products and as a consequence it becomes necessary to raise dosages gradually to levels of around

10 to 14 grains of thyroid daily. There are instances where because of arthritic manifestations or other evidences of severe hypofunction of the adrenal cortex it is beneficial to give corticosteroids we do not hesitate to do so, but make every effort to protect the patient by specific attention to their protein metabolism.

Most hypopituitary patients are protein depleted at the inception of their treatment and almost invariably we find it necessary to subsidize protein metabolism as discussed in the chapter on protein. Every obese patient has fatty degeneration of the liver so it is practically routine to administer an enteric coated tablet containing methionine, inositol, choline, pancreatin, pepsin, and ox bile at least one per day and often t.i.d.

There have been several people in our experience who made satisfactory progress with weight reduction with exception of the lower extremities. These patients presented edema and fluid infiltration of soft tissues of the legs and ankles. Normal curvatures of the legs were obliterated even to the extent of tissue bulging over the shoe top. Reduction of lower limb was then accomplished by moist wrapping of a glycerine saturated gauze, covered by an elastoplast bandaging applied securely and renewed every 10 days for approximately 90 days, after which time the legs had regained their normal appearance and did not return to the previous state.

The concept of treatment of the hypopituitary patient is to subsidize if necessary all target glands and by substitution support pituitary physiology while replenishing protein stores of tissue. Extremely obese people can be reduced to a reasonable weight. It may not be possible to accomplish

complete reduction to ideal weight as determined by charts based upon age, sex, height, and skeletal measurements.

Evaluation of either hyper- or hypopituitarism may at first glance appear confusing. Familiarity with hormones elaborated by the pituitary will clarify such problems. Growth hormone, thyrotropic hormone, adrenotropic hormone and gonadotropic hormones are all originated from the pituitary gland. Overactive functioning will accelerate response of target glands and their secretion of hormones with consequent changes in peripheral tissue functions. Contrariwise, hypofunctioning pituitary gland results in decreased manufacture of target gland hormones with failure to arouse normal performance of peripheral tissues.

Laboratory aids serve to substantiate pituitary status as evidenced in peripheral tissue. Familiarity with expected or normal dates of ossification of long bones will assist in determining whether epiphysis and diaphysis fused at the anticipated time thus verifying the condition of gonad secretions and growth hormones. There are of course all degrees of abnormal pituitary function. The measures of weight reduction here delineated will point the way to either restraining pituitary overactivity or augmenting control of the target gland by substitution therapy when pituitary control is not sufficient. Obese patients will respond to astute management when all factors are considered.

Thyroid Obesity

Thyroid obesity carries weight distributed in the trunk and upper part of the body. Busts become enlarged through fatty deposition, shoulder, clavical and neck area expand due to adipose tissue and the abdomen grows to the extent

many times of equalling the hip measurements. Simple thyroid obesity is characterized frequently by the fact that there is less than 10 inches difference between waist and hip circumference measurements. Hypothyroid conditions may be due to previously limited food intake wherein the body in self defense decreased the rate of metabolism. The chapter on thyroid will indicate other reasons for failure of thyroid function. Not all hypothyroid people are obese. These people generally have sluggish appetite, dull mentality, thick coarsened skin, often complaining of cold extremities many times with an hypotension, and very often presenting a negative attitude. Hypothyroids usually have blunt, short fingers and wide palms. There may be thinning of hair with particular reference to the lateral third of the eyebrows. Some people in this category have a thick wide tongue. They often are anemic and the women give a history of menstrual irregularities, even with several miscarriages.

Laboratory reports will indicate a PBI reading below normal, the degree being commensurate with lack of thyroid hormone function. A blood count will indicate anemia. Inorganic iodine and protein evaluation often relate to the etiology of hypothyroidism.

Management of the simple hypothyroid is comparatively easy in so far as weight reduction is concerned. Patients do not have a driving appetite, many of them suffering hypoproteinemia due to insufficient appetite, and quantity of food intake presents little or no problem. Lower PBI values specify patients who are very sensitive to thyroid substance. Weight reduction of hypothyroidism should be started on a very conservative plane. We start these patients on 1 grain of desiccated thyroid substance (iodine free) with breakfast and with lunch. Great quantities of fluid are

retained so we prescribe 7½ grains of ammonium chloride to be taken t.i.d. on alternate weeks.

Most hypothyroid people present some degree of achlorhydria and initiation of therapy includes one tablet of glutamic acid 5 grains combined with 1 grain of pepsin taken with each meal. The glutamic acid is prescribed to combat hypochlorhydria and make protein accessible for the thyroid gland in its formation of PBI. Gastrointestinal motility will be subnormal due to hypothyroid physiology and it is suggested that a mild laxative be administered at bedtime.

One month or four weeks later we will expect to build up thyroid dosage and at this time administer 3 grains of thyroid plus ¾ grain of digitalis leaf, 1 tablet in the morning and 1 grain of thyroid substance at lunch. The time interval allows us to ascertain that the original 2 grains of thyroid daily will be tolerated. Patients are instructed on their initial visit to inform us by telephone if necessary in the event that any thyrotoxic symptoms occur, such as palpitation, excessive sweating, shortwindedness, exhaustion, nervousness or tremulousness. Absence of such report permits raising thyroid dosage as indicated by the patient's progress. Thyroid dosage may reach levels of 12 to 15 grains daily, however, these levels are approached gradually and cautiously and are based upon the patient's weight and inches change. Thyroid substance will reduce inches off the abdomen and chest even though weight has not decreased. We do not augment thyroid dosage until failure to show reduction in either weight or inches. Severe hypothyroid function indicates sensitivity to thyroid substances but as each dose raises the PBI there is progressively more tolerance to thyroid substance. A rule of thumb not infallible used in this office is that thyroid dosage will equal in grains the PBI read-

ing, i.e., if the PBI reading is 2 gamma per cent, it will require approximately 2 grains of thyroid per day to increase this PBI.

Ovarian function is very dependent upon thyroid activity. Menstrual irregularities, and miscarriages or infertility are often corrected by simply using thyroid substance alone. We do not immediately resort to subsidizing with gonad hormones in patients presenting such history, but rather allow the patient a trial period on thyroid to determine whether this approach will competently stir ovarian activity. Ovarian function failing to return to normal may require use of gonad hormones in addition to thyroid. Dosages and indications are discussed in the chapter on gonads. Possibility of hypopituitarism must be considered in that patient for whom we must substitute gonad hormone and thyroid substance.

Patients managed with this therapy often correct unreported conditions such as indigestion, constipation, inability to relax, eczema, neurodermatitis, alopecia. Visual and aural problems are corrected that generally are not considered as thyroid dysfunctions. Considering the functions of thyroid substance this phenomenon should be expected. Thyroid promotes better gastrointestinal and hepatic function in the field of secretion, motility and absorption and an increase in selective ability of the intestinal tract with special emphasis on sugar so it would be only logical that the nutritional status of the patient would be improved. Oxidation promoted through this therapy will enhance vitality of all peripheral cells and thus even skin should show definite improvement in texture, in temperature, in appearance and with consequent disappearance of the nonspecific dermatoses. Improved circulation and increased cardiac output concurrently will enhance the patient's vitality as well as adjust his sensitivity to cold. Add to this vasodilating and diuretic properties of thyroid substance and not only will weight be reduced but waterlogged tissues will resume normal function. Mental apathy will disappear and the patients will present normally active interest in themselves and their surroundings. It is characteristic of this type of therapy, that well being and feeling of aroused vitality are frequently expressed by patients.

Thyroid substance will reduce a high atherogenic index and thus prevent coronary episodes or arteriosclerotic problems. It may prevent diabetic conditions. It provides patients greater life expectancy. It makes them more useful citizens as well as more compatible mates who will be able to conceive, develop and carry to maturity normal embryos then raise these children to adulthood. All this should be adequate justification to the physician for very serious consideration of thyroid therapy. Use of this program as weight reduction is in a sense not commensurate with benefits derived. Nevertheless obesity is a problem with so many people that in fairness to these this therapy should be administered. Management of this type of obesity on the basis of dietary restrictions is not only unsuccessful, but actually adds to the degree of hypothyroidism and is more detrimental than obesity itself.

Hypogonadal Obesity

This type of obesity is characterized by fat depositions on the pelvis, below the crest of the ilium and above the head of the femur, within the first 4 to 6 inches below the crest of the ilium.

Patients whether male or female will almost invariably

present history of disturbed gonad function. Menstrual irregularities and disorders are common. Absence, in the male of secondary sex characteristics in varying degrees, loss or absence of libido, high pitched voice, abnormalities of hair distribution or growth are all indications of hypogonadism. Length of extremities as compared with either arm span or length of the trunk of the body indicate at least in the preadult area of that persons' life, the status of gonad function. Most instances of hypogonadal obesity are associated with hypofunction of the pituitary gland. Absence of pituitary gonadotropins acting as stimulants to gonad tissue, leads to faulty development of sex organs, which in turn promotes defective protein metabolism. Other reasons for hypogonadism can be mentioned among which are surgery, toxic effects, whether of medicinal origin or infectious, and high fevers. Not to be ignored is potential damage to gonads from a childhood attack of mumps. Hypothyroidism may be concurrent or causative of hypogonadism since thyroxin in the blood stream is necessary for development and operation of gonad tissue.

Therapy should be ethinyl estradiol 0.05 milligrams once a day, every other day, or twice a week depending upon indications for this and the relative degree of estrogen deficiency as discussed in the chapter on gonads. In the presence of sufficient estrogen production especially in young girls and menopausal women it often becomes necessary to use progesterone. This is done by use of one 10 milligram buccal tablet given the 19th day following the first day of previous menstrual period daily for five consecutive days. Indications include the complaint of breast tenderness immediately preceding menstrual periods, dysmenorrhea, cycles shorter than 28 days, heavy menses, acne, premenstrual tension, or hyperpituitarism. Dosage in extreme cases can be raised to one 10 milligram progesterone buccal tablet on alternate days.

Protein anabolic effect of gonad hormones can be achieved in post climacteric patients whether male or female through use of a tablet containing 20 parts of testosterone to one part of ethinyl estradiol taken sublingually daily. Subsidizing the androgen field in the male may necessitate use of one buccal tablet 10 milligrams of testosterone propionate daily. This medication may be effective as pituitary depressant or as protein anabolic stimulant. They should be used very sparingly on a patient who has not attained full growth since there exists the potential of hastening closure of epiphysis. Most hypogonadal obesity problems will require subsidization by gonad hormones. The hormone of choice should be determined on basis of the case history. The chapter on gonads presents their physiology and judging from that it becomes easy to determine which material is to be used.

Thyroid substance combined with digitalis leaf is here highly recommended in addition to gonad hormones. Initial dose should be dependent upon the patient as an individual. Most patients can be started with a minimum of 5 grains of thyroid broken into 3 grains in the morning and 2 grains at lunch. Morning medication is combined with ¾ grain of digitalis leaf. This combination will assist in removal of excess fluid which is typical of hypogonadal conditions, and consequently will serve to relieve premenstrual tension, dysmenorrhea, ankle edema, and other symptoms of fluid retention. Belladonna combined with a mild laxative is necessary at bedtime in order to prevent accumulative effects of digitalis. This dosage is gradually increased in order that constant weight loss be maintained. Mental depressions, anxi-

eties, melancholia, lassitude, headache, numbness and tingling of extremities are often relieved by this therapy.

Neither ethinyl estradiol nor any other estrogenic substance is advised in case of suspected or proven cell proliferation because protein anabolism enhanced by it might be beneficial to uncontrolled cell proliferation and hence be undesirable.

Adrenal Gland Obesity

Patients presenting themselves with adrenal gland obesity have certain characteristics. Generally, there is a moon-faced appearance, excessive hirsutism, a collar or chin of fat extending even into the supraclavicular areas, with typical buffalo hump in the area of sixth and seventh cervical and first dorsal vertebrae. The entire shoulder girdle, neck and face seem to be areas of predilection of fat deposits due to adrenal gland dysfunction. These people often have hypertension due to excessive epinephrine secretion and sodium retention. The female patient may disclose hypertrophy of the clitoris and masculinization due to increment of androgen. The male patient may acknowledge decreased size of genitals combined with diminished growth of hair on the face, higher pitched voice, and effeminate characteristics due to increased production of female sex hormone from the adrenal cortex. Addition of aldosterone from the adrenal cortex leads to retention of sodium and chloride and hence water, adding weight.

Glucocorticoid production in excess activates gluconeogenesis in the liver with increased sugar production. Insulin triggered by this sugar supplement causes storage of sugar resulting in enlargement of peripheral cells. Compelled gluconeogenesis demanding more protein from the blood

stream for its support will precipitate hypoproteinemia. The end result is buffalo type of obesity in the upper body. Excluding tumor formation and organic pathology, adrenal obesity is the result almost invariably of too much adrenocorticotropic hormone from the pituitary gland. Therapy of adrenal obesity is the same as of pituitary obesity.

The pancreas is intimately involved in all obesity as well as in many other conditions—it would be more proper to state in all endocrine imbalances. Pancreatic secretion of insulin is influenced by the pituitary, autonomic nervous system, adrenocortical steroids, liver sugar physiology, protein availability for formation of insulin and by conditions of stress or strain from environment. High level of blood sugar affects the pancreas triggering production of insulin. Blood sugar levels above normal, without the reaction of additional insulin, result in the blood stream holding water with sugar leading to gain in weight. Symptomatology of diabetes becomes evident as the situation continues. Insulin in response to higher blood sugar levels will cause storage in peripheral tissues of sugar and water thus enlarging peripheral cells. High insulin production resulting in hypoglycemia stimulates the liver to expel stored glycogen to offset it and in time leads to exhaustion and depletion of liver glycogen stores. This enhances susceptibility of hepatic tissue to deleterious influences and promotes the likelihood of hepatic insufficiency. Sugar ingested by mouth and assimilated raises blood sugar levels precipitating production of more insulin and the cycle continues. If the level of insulin remains high hunger increases and when not appeased, signs and symptoms of hyperinsulinism develop. These are discussed in the chapter on pancreatic function.

Appeasement of extreme hunger expands storage of

sugar and water in the periphery of the body and continued stimulation of production of insulin due to ingested carbohydrates. Obesity in these instances is inevitable. If carbohydrate is not ingested, the liver will utilize protein taken from the blood stream to form sugar and counteract the high insulin present. Eventually this will lead to hypoproteinemia. One consequence of hypoproteinemia is failure of endocrine and peripheral tissues to perform in an orderly and synchronous manner.

The process of gluconeogenesis is stimulated by high insulin levels, excess adrenal corticosteroids, and concentration of hormones from target glands in great excess of normal physiological range. Ability of the pancreas to respond to tropic hormones, parasympathetic stimulation, increased adrenal cortex activity, or hypogonadism as well as environmental and emotional stresses, indicate that it is concerned with every function of the body and must be kept in balance. Otherwise, obesity with hyperinsulin or diabetic complications will surely follow.

Management must be considered with all seriousness. In all types of obesity there is a parallel, concurrent, relationship of blood sugar. It is here proposed that management of blood sugar levels be regulated by means of either parasympathetic depression or sympathetic stimulation. Extreme excitement of secretory activity of the pancreas is restrained by use of tablets of phenobarbital 1/4 grain and belladonna 1/8 grain to be taken one with each meal. This tablet acts as a parasympathetic nervous system depressant (vagus nerve) and is especially useful in patients exhibiting gastrointestinal disturbances such as indigestion, gastritis, pylorospasm, flatulence, spastic colitis, a history of either gastric

or duodenal ulcers, or diarrhea. The tablets tend to decrease appetite by inhibiting production of insulin.

Amphetamine may be used to control the level of blood sugar by the patient who evidences no gastrointestinal disturbances, and especially the hyperpituitary type person. We use a tablet of amobarbital 1/2 grain and d-amphetamine sulphate 5 milligrams. This is usually administered twice daily, at 7 a.m. and 2 p.m. or one tablet at 11 a.m. and one tablet at 4 p.m. Should use of amphetamine at 4 p.m. be so stimulating that sleep is delayed, earlier dosage is preferred. Some patients may be placed on this 3 times a day at 7 a.m., 11 a.m., and 4 p.m. Medication here advised acts as a sympathetic nervous stimulant, causing the adrenal medulla to produce epinephrine to release stored liver glycogen offsetting low blood sugar. Appetite control is achieved in this fashion.

This tablet inhibits gastrointestinal secretion, further depressing appetite, but when sustained over periods of time has the capacity of so reducing gastric acidity that the first stage of protein hydrolysis is not accomplished on schedule. This drawback coupled with the tendency of amphetamines to induce nervousness, exhaustion and thirst, provide reservations to its employment. A percentage of patients, however, will do well on this medication. Blood sugar level in practically all of our obese patients is managed through either phenobarbital-belladonna or amobarbital-amphetamine compound. Sugar level is involved in all obesity, requires attention, and when neglected, satisfactory progress in weight reduction is not achieved.

Use of laxatives becomes necessary under this therapeutic weight reduction program. Improved physiology of the gastrointestinal tract and liver promotes increased protein

assimilation from the intestinal contents leaving a dry, dehydrated, fecal mass so in the interest of excretory regularity it becomes necessary to use laxatives. We regularly prescribe one tablet at bedtime of a combination of aloin U.S.P. 1/5 grain, belladonna U.S.P. 1/8 grain, resin podophyllin N.F. 1/16 grain and strychnine sulfate N.F. 1/60 grain. This tablet is given routinely at bedtime for the purpose of counteracting cumulative tendency of digitalis administered with thyroid substance. This tablet as a general rule is not sufficient to maintain normal bowel regularity and when indicated we use other laxatives of greater strength in addition. The mildest of these laxatives contains, aloin U.S.P. 1/4 grain, cascara sagrada U.S.P. 1/2 grain, rhubarb N.F. 1/2 grain, stramonium N.F. 1/16 grain, and ginger N.F. 1/32 grain. The next grade laxative is exactly double strength of this formula. A more powerful laxative is used when necessary containing phenolphthalein U.S.P. 1 grain, cascara sagrada U.S.P. 1/2 grain, pepsin N.F. 1/2 grain, aloin U.S.P. 1/4 grain, podophyllin N.F. 1/6 grain, diatase of malt 1/8 grain, ginger oleoresin N.F. 1/100 grain. These laxatives generally will suffice to manage bowel action. The first tablet mentioned containing belladonna is used in every instance unless the strychnine precipitates intestinal griping or cramping or excessive defecation. The phenobarbital belladonna compound can be used in its place at bedtime to provide the desired belladonna.

General procedure in all weight reduction patients is to increase dosages gradually in order to maintain continuous weight loss. Experience with many hundreds of patients of this type has brought to light a phenomenon wherein the patient will lose 40 to 60 pounds and then reach a plateau. At this point it is useless to step up dosage—the physician

must reevaluate the patient's physiology which has been altered in its effort to adapt to the weight loss. Plateauing occurs in approximately 10 per cent of our patients.

Numerous factors can be responsible for this plateauing, among which should be listed gonad dysfunction, hypoproteinemia, antihormone formation and oftentimes intercurrent surgery.

The most common fault seems to be failure to recognize need for gonad hormone substitution. The patient may have been under our care for approximately a year before attaining this plateau since we anticipate a loss of approximately 5 pounds per month. A gonad change that history and examination did not disclose is often brought to light in the period of one year. Furthermore, patients may have entered our care prior to the onset of menopause or climacteric, but may since have entered into this phase. It becomes important to reassess gonad function and to administer substitution in event of deterioration of tissue function.

If hypoproteinemia is blocking the patient's progress, it may have been induced by amphetamine. Administration of amphetamines continued for 6 months or longer may have depressed digestive secretion and involved protein hydrolysis to the extent of being an etiological factor of hypoproteinemia. Our procedure in this instance has been to prescribe a tablet composed of glutamic acid hydrochloride 5 grains, pepsin N.F. one grain to be taken before meals. This is particularly indicated in the event there are symptoms of pruritis ani. The patient who has developed hypoproteinemia will not be producing exogenous pancreatic enzymes and it becomes necessary to subsidize this field. The prescription in most patients of this type can include protein supplementation by protein hydrolysates,

capable of correcting protein deficiency and furthering weight reduction.

In the field of anti-hormones it is thought that enzyme production occurs in cell protoplasm in order that thyroid substance carried to cells may be made operative through splitting off of protein carrying molecules, freeing thyroxin for intracellular action. There is a paucity of enzyme manufacture in any protein depleted patient. The body in order to conserve, decreases its use of protein and may cease to form protein enzymes thus causing failure to activate circulating thyroxin.

Evidence in the literature concerning actual anti-hormone production does not conclusively prove the presence of such substances. Should this hypothesis prove true, anti-hormones would be manufactured from protein and stimulated by antigen hormone preparations. The advised technique in event of failure either of intracellular enzyme production or of anti-hormone formation would be to discontinue weight reduction therapy for a period of 10 to 12 weeks. Protein metabolism can be subsidized during this time as discussed in the chapter on protein. Reduction therapy can then be resumed at slightly lower dosage with universally successful continuation of weight loss.

When the patient has reached his ideal weight, it becomes a question of maintaining this level. Our experience recommends the following as a means of stabilizing endocrine physiology while our supporting therapy is being gradually withdrawn. Four weeks supply is routine in this office and is based upon one tablet each day of each medication or as many tablets as are necessary for individual medication to be taken more than once per day, counted out to exactly supply dosage for this period of time. The last effective dosage of medication is repeated in a four weeks supply. The patient is advised at this visit, (the start of the maintence program) to weigh before breakfast and dressing the next morning. This establishes a base weight. They are further told when at the base weight or below, they need take no medication for that day. Any morning that the weight is above this level, they are to take the dosage as directed for one day and are to repeat this weighing process every morning. The purpose of having the patient weigh in the morning is so that throughout the days they exceed base weight, they can take the entire scheduled dosage including morning, noon and evening medication. Day by day control of glandular physiology will insure the attainment of stability. Gradually patients will need less and less medication. They are generally advised that the initial supply of maintenance material (normally a four weeks supply when taken daily) will last them six to eight weeks. The second visit under maintenance, the supply should last four to six months. It is our opinion that the person who has maintained his weight for six months, is in a stabilized condition and will remain that way without any dietary restrictions until or unless intercurrent glandular strains occur, such as pregnancy or the climacteric at which time there should be a new evaluation.

Experience with this method of handling weight reduction has been far more satisfactory than dietary control. The patient's feeling of well being, his freedom to eat ad libitum, actual loss of weight with adiposity disappearing from areas in which it was excessive, lack of wrinkling and haggard appearance, will attest to patient's acceptance of this therapy.

Absence of ill effects and the satisfaction of correcting a condition so common in the general population in such

manner that preventive measures are included against diabetes, arteriosclerosis, atherosclerosis, hypertension, cardiovascular renal diseases, hepatic insufficiency, electrolyte imbalance, should imbue the physician with satisfaction, enthusiasm, and mental awareness that he is providing benefit far transcending his monetary returns.

Opportunities to treat and to see patients who are medical rarities present themselves in this field. Many people who suffer interesting conditions, are not aware of unusual aspects of their problem, but oftentimes are obese people who enter our care simply for the purpose of losing weight.

People who desire to lose weight have the intelligence to recognize dangers inherent in obesity and they desire to correct their problem. To hand them a diet list and an amphetamine tablet is not fair, nor is it in keeping with premedical and, medical education, internships, residencies, and training that the patient has the right to expect of any licensed physician. The clinician should not attempt to correct obesity if he has not made a study of it, for that would be analogous to a third year medical student attempting to remove surgically a basophilic tumor of the pituitary gland. Obesity management requires concentrated study and thorough understanding of the endocrine gland system as well as possible results to the body of added work load due to obesity. Successful rectification of obesity encompasses all physiology and when it is properly executed is of the greatest gratification to both patient and doctor.

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Gamma Globulin

The first chapter of this book discusses the requisite of living protoplasm for protein. It also traces digestion and fate, thus indicating the proper dietary protein supply. Protein concentrates and/or hydrolysates are recommended in the absence of sufficient integrity of the digestive tract.

In this chapter it will be emphasized that albumin is an indispensable constituent of circulating blood and that attenuation is concurrent with disease processes. It occupies a unique status in that increases of the globulin component are in inverse proportion to a decrease of albumin. This globulin gain can be due to abnormal gamma components, such as the rheumatoid factor. Such dysproteinemias are capable of acting as antigens in the allergy phenomena.

It is quite feasible that desensitizing or inactivating this dysproteinemia is accomplished by using gamma globulin therapeutically. It is also possible the albumin level is guarded by furnishing gamma globulin from exogenous sources. This alleviates the demand for endogenous creation, which may be faulty, fabricating distorted gamma globulin molecules.

In this chapter it will be reflected upon that the endocrine system can be both regulatory in the protein field and, conversely, affected by protein level, therefore a further facet of therapy is implied.

In general proteins are fundamental for every vital function. All enzymes and glandular emanations are proteins.

The pituitary tropic secretions are either a union of fat with protein i.e., lipoprotein, or a blend of sugar with protein i.e., glycoprotein. Thyroxine is a combination of the amino acid tyrosine with iodine. Insulin is a compound of 27 amino acids. Exocrine creation from the pancreas, protease, amylase and lipase are all formed from the basic protein molecules. The corticoid dominance over the liver to perform gluconeogenesis, as well as its hematopoietic influence on lymphoid tissue connects adrenal hormones with protein metabolism. Gonad products are generally considered to be protein anabolic.

Hormones are to a great degree motivating to protein synthesis, action, and degradation. Many endocrine functional aberrations directly mutate anabolism, catabolism and intermediary physiology. These protein products under discussion were derived originally from food intake.

Protein digestion will be reviewed on the basis that it connotes therapeutic approach. Proteins are acted upon at the stomach level by pepsin. They are hydrolyzed into short polypeptide chains termed proteosis and peptones. Cells of the gastric mucosa supply pepsinogen, a stable material in alkaline solution but an active enzyme when pH drops below 6. Peptic activity is optimal at pH2. This acidity is maintained by gastric hydrochloric acid. Pepsin thus liberated acts upon its own precursor pepsinogen to accelerate formation of more pepsin. One other product is secreted in the stomach, known as rennin, which acts chiefly upon milk.

Pancreatic proteolytic enzymes trypsin, chymotrypsin, and carboxypetidases, in conjunction with enzymes of the succus entericus, are the major actors in the small intestine. Here the proteosis and peptones are hydrolyzed into amino acids.

Amino acids are not absorbed from the stomach but are taken from the small intestine very rapidly. This process is completed by the time the contents reach the iliocecal valve.

Following absorption, the amino acids may travel through several pathways depending upon needs of the body. One direction is synthesis of purines and pyrimidines, porphyrin, creatine, proteins including plasma proteins, structural tissue protein, enzymes, hormones and other vital protein supply. Another route allows amino acids to become deaminated. They can be oxidized to form carbon dioxide and water or processed into fat or glucose and glycogen. At this point we are primarily concerned with the protein converted into plasma proteins.

Due to the ease and lack of surgical trauma associated with withdrawal of blood it has become a popular tissue for study of protein coalitions. There is little doubt, especially since using isotopically label compounds, that 90 to 95 per cent of plasma proteins are composed in the liver.

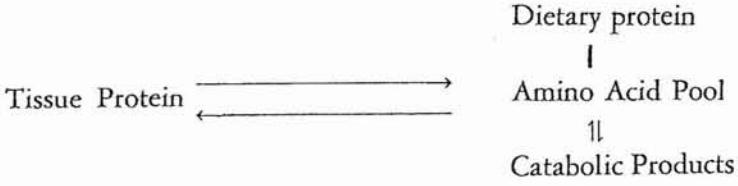
The unilateral inverse relationship between globulin and albumin gives rise to suspicion that formation of blood protein is under influence of an extremely rigid central regulating mechanism. Colloid size as a function of state of colloid osmotic or oncotic pressure has been suggested in this connection.

The normal level of plasma protein is guarded more than that of tissue protein. The former (plasma) is maintained by the latter (tissue) during protein deficiency in the ratio of 1 to 30. Whipple (1940) found that plasma protein administration maintained depleted recipients in positive nitrogen balance when all other therapeutic nutritive methods failed.

Plasma proteins are last to suffer in dietary deficiency

since all tissues and organs (notably the liver) are drawn upon first in correcting the negative nitrogen balance in the body.

Plasma albumin is primarily diminished but the contraction of the total plasma volume in protein deficiency tends to mask this reduction. The serum protein level is, therefore, no index of the nutritional status, since tissue repletion in severe malnutrition continues for months after the plasma proteins have been completely restored.
Thus:



The separate components of plasma protein can be fractionated in the laboratory and their specific identity as well as function determined. It will facilitate understanding to consider separately the various members.

Albumin is manufactured entirely by the liver and is of utmost essentiality in maintaining fluid volume and electrolyte balance. This is a molecule of very small size. It is the available source for intracellular cytoplasm supply. Albumin is a precursor of other plasma and intracellular protein especially globulin. Plasma proteins particularly albumin form tissue protein or are formed from them, depending upon the metabolic state of the organism.

"A study of internal diseases and comparison between 234 patients with absolute albumin values below 3.0 Gm per cent and 545 patients with serum albumin over 3.0 Gm per cent show that immediate mortality of the first group

is six times higher than that of the second. The absolute quantities of albumin especially in subacute and chronic diseases is prognostically much more reliable than that of total protein."

Prognosis in the individual case grows worse with the sinking of albumin and its persisting at a low level.

Along with other data albumin values determined by means of electrophoresis are also important for expert evidence and for planning of therapy, especially transfusions of albumin and plasma as well as treatment with liver extract.

The albumin fraction is not a homogenous group but can be separated into further divisions as for example a pre-alpha group.

From the clinical standpoint it is significant that diminution of plasma and serum protein in circulating blood i.e., hypoproteinemia, is always and in every case due to decrease of the finely dispersed albumin fraction. This is found especially in nephrotic syndrome, chronic liver disease, chronic gastro-intestinal disease, debilitating infections and neoplastic processes, chronic dermatosis, purulent processes and deficient nutrition.

The globulin fraction of serum protein is formed in the liver and the reticuloendothelial system, (lymph nodes, bone marrow, spleen, monocytes, and plasma cells). This protein forms the transport system for minerals, enzymes and hormones. The gamma globulin section contains body resistance, antibodies, cold agglutinins, antihyaluronidases, antistreptolysins, and cryoglobulins.

Elevation of gamma globulin plays a predominant role in disease and is usually an indication of the patients' response. Initially this reaction involves a greater or lesser

ascent of globulin and a corresponding fall of albumin. This can be considered a displacement of the coarsely dispersed phases, or a shift to the left of the blood protein picture. The opposite situation, a shift to the right, is not seen. Among adults at least, no disease states have been observed except rare gamma deficiency states, in which albumin is either absolutely or relatively increased. The globulin increment may be a distorted perverted molecule, called a dysproteinemia. The rheumatoid factor—an ill-defined entity but common and pathognomonic for rheumatoid arthritis has been found among the components of dysproteinemia. Marked rise in gamma globulin is the underlying basis for pathogenesis of pathognomonic lesions in collagen diseases. They are characterized by systemic involvement of the vascular connective tissue in rheumatic fever, rheumatoid arthritis, lupus erythematosus, scleroderma, dermatomyositis, serum sickness, polyarthritis and possibly arteriosclerosis, all dysgammaglobulinemias. The striking elevation in abnormal gamma globulin is due to plasma cell proliferation in the diseased connective tissue and bone marrow, rather than to tissue injury.

The electrophoretic pattern of these conditions is characterized by an expansion of gamma globulin components. Very frequently this is accompanied by reduction of the albumin fraction, in fact, there are those who believe that the decrease is consistently present. It is compatible with physiological principles that gamma increment is at the expense of the albumin element. When the body is invaded by deleterious influences or under undue stress, gamma globulin is inflated by the assessment of albumin.

Theoretically this amplification in gamma globulin should be beneficial since the fraction is credited with containing body immunity, defense materials and other factors generally of a protective order. It then becomes a question as to why these diseases (or symptoms) are apparent and gamma globulin characteristically heightens commensurate with severity of the illness. Determination of gamma globulin by electrophoresis is quite gross, however so molecules of this size and electric field activity are not differentiated from each other. Apparently the gamma globulin is a heterogenous material and may be distorted with components that are not of necessity helpful to normal functions. Rise in this area does not need to imply excellent resistance and immunity but on the contrary may indicate protein molecules of an ineffective or deleterious nature.

Decline in albumin on the other hand does indicate that the blood stream will find it necessary to gain replenishment. Where this supply of albumin will come from is of great importance. If it is taken from the joint areas, the synovial surfaces will become inflamed, fluid may accumulate, even normal motion may traumatize the tissue, thus arthritis is the clinical picture. Should depletion take place in the gastric mucosa, sinus mucous membranes, colon mucous membranes, or skeletal musculature there would be respectively, gastric or duodenal ulcerations, sinusitis, colitis, or myositis. Essentiality of albumin is beyond question not only in above relationship but also in the field of fluid balance, pH and blood pressure. It is so indispensable the body is provided with means of extracting protoplasmic albumin to resupply a depleted blood stream. Thus when greater quantities of albumin are used in synthesis of raised gamma globulin much damage is potential, or incurred.

With the collagen diseases in mind there are two possible theories as to mechanisms involved, 1. Body and joint

allergy to the abnormal protein molecule. 2. Depletion of albumin of body peripheral tissue and its aftermath of inflammation.

Those disease states characterized by an increase in gamma globulin, either by electrophoresis, or ultracentrifuge, or otherwise, gain their globulin distention at the cost of the albumin component. This can be either intra or extra cellular. Among such conditions are the collagen diseases. When the albumin level is low the blood stream seeks replenishment and may find it from joint areas, (A) joint surface; (B) cartilage; (C) synovial sheath and fluid; (D) capsular membrane; (E) surrounding fascia and muscle. This leaves an area sensitive to cold, heat, trauma, toxin and noxious influences.

In reference to therapeutic approach any effort to preserve albumin will be a step in the right direction. It has been my experience to find that although a patient was given protein hydrolysates, for supply, and/or lipotropics and vitamins to stimulate liver physiology the symptom complex (rheumatoid arthritis) still persisted in some instances. On this basis further search was made for an albumin sparer. The possibility that albumin was low in order to assist the gamma globulin growth implied some substance that would provide accretion of globulin without decimating the albumin. Thus supplying gamma globulin from an exogenous source might be advantageous. Immune gamma globulin (human) reasonably might serve. It is not known to have any contraindications and upon many repeated administrations has not evidenced any tendency to produce adverse reactions.

Dosage would have to be empirical or by trial and error since there are no reports in the literature re: The use of

gamma globulin in collagen diseases and those with high gamma globulin levels. Our starting dose was one-half c.c. intramuscularly. This produced some response so we increased the volume to one c.c. These injections were given at weekly intervals for six weeks and then extended to one c c. every two weeks. Results have been phenomenal. Every patient on whom we used this treatment reported that he felt better generally. Specifically joint stiffness and limitation of motion were relieved as well as the depressing muscular weakness that usually accompanies rheumatoid arthritis.

The dose used was so small the possibility has occurred, since there is considerable proof of the allergic nature of rheumatoid arthritis, that the victim of this symptom complex may have developed reaction to his own gamma globulin. Were the rise of gamma globulin so characteristic of rheumatoid arthritis due to distorted protein molecules (the antigen), and auto gamma globulin may have antibodies to it, then there would be a likelihood of desensitizing this body by using small doses of exogenous gamma globulin.

A more probable mode of action in using gamma globulin for those conditions characterized by high gamma globulin component would be since the gamma globulin increase is impoverishing albumin, supplying additional exogenous gamma globulin to this patient would remove the necessity of his own manufacture of gamma globulin. This would spare albumin for tissue uses or at least lessen the need of the blood stream to rob cytoplasm of its albumin supply.

This explanation is more acceptable because gamma globulin is applicable in any and all conditions characterized

electrophoretically by a high gamma globulin. The discovery, by Whipple, that the blood must rob 30 grams of protoplasmic albumin for every gram advance in its own level lends further credence to the probability of protecting albumin levels by using injectable gamma globulin.

Use of gamma globulin is not new. In previous applications it has been confined more or less to prevention of polio, infectious hepatitis, measles in exposed pregnant women and possibly as preventative of mumps. It has been considered specific therapy for the relatively few cases of agammaglobulinemia. Our experience indicates injections of gamma globulin are, over and above those mentioned, very useful and effective in infections and as concurrent therapy with antibiotics, for enhancing the protein level of those patients receiving corticoids, in leukopenias, anemias, and generally as support in chronic debility.

The employment of gamma globulin as a therapeutic measure in patients characterized by a high gamma globulin has not been universally tried. In my practice injections of gamma globulin have been given to many cases with this finding. Invariably the patients' clinical symptomatology ameliorated, in some complete recovery ensued. Additionally, laboratory followup on this type of problem has produced evidence that albumin level elevated and that gamma globulin level declined despite exogenous gamma globulin administered to the patient and logically one might expect to find gamma globulin more prominent.

The therapy is to administer intramuscularly one c.c. of immune (human) gamma globulin per week for six consecutive weeks following which the time interval is extended to two weeks i.e., one c.c. intramuscularly of immune globulin every two weeks. This may be continued indefinitely since there are no harmful effects. It has been found that six to ten injections on a two week interval usually suffice.

Administration of this quantity is effective and while various other levels of dosage varying from one-half c.c. to six c.c. have been employed, results have been optimum at the one c.c. dose level. There is no contraindication for injection of gamma globulin except it must be intramuscular rather than intravascular. In repeated doses, as stated by a manufacturer of gamma globulin, there has been no evidence to indicate build up of sensitivity to this substance, i.e., it does not become an antigen. Furthermore, the injections are painless.

Results are excellent response in decreased swelling of joints, stiffness of joints, weakness of the patient, edematous accumulation and this occurs whether or not the patient is using corticoids. Effects are enhanced by concurrent use of a combination of male and female gonad anabolic hormones. The results in patients suffering conditions other than collagen diseases have been as dramatic and satisfactory. Patients suffering from bursitis, neuritis, anemia, herpes zoster, myofascial strains and a variety of skin diseases particularly psoriasis have been equally as corroboratory.

Applying gamma globulin to the surface of open running sores or ulcerations and allowing the droplet to dry, made the tissue form a scab, dry, cease leaking and heal in an exceptionally short period of time.

Its use is indicated in any condition wherein protein aberration is manifest since it is one step more in establishment of protein support.

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