HYPOGONADISM

By ROBERT B. GREENBLATT, M. D., and D. MARION SILVER, M. D.

There is a type of anterior pituitarism that is manifested in the young adolescent male and female by obesity, hypothyroidism and hypogonadism. The hypogonadism in the male is evidenced by hypogenitalism, with or without cryptorchidism, while in the female there is frequently a delayed menarche. It is true that in many instances these manifestations are but a question of delayed puberty. However, many of these, if untreated, persist into adulthood.

In recent years the tremendous wave of enthusiasm for the glandular therapy of undescended testes has waned considerably. The number of successes has been matched by an equal number of failures. The reason for failure may be due to insufficient dosage of gonadotropins, complete testicular atrophy, obstruction in the canal and the treatment of those boys who have cryptorchidism without endocrine imbalance. It is also true that many of the successful cases treated may have undergone spontaneous descent before puberty.

The purpose of this communication is to record the treatment as well as some of the unusual features in several patients with hypogonadism.

Case 1: A tall, obese white boy, 12 years of age (a private patient of D. M. S.) weighing 201 pounds with marked girdle obesity, tapering of the terminal phalanges of the hands, a high pitched voice, hypogenitalism and bilateral cryptorchidism. His basal metabolic rate was minus 34 and glucose tolerance was within normal range. The sella
turcica appeared normal by roentgenography. He received several courses of chorionic gonadotropins from several physicians without causing descent of the testes. On examination, penis and scrotum were small, no pubic or axillary hairs were present and the testes were not in the scrotum nor could they be palpated in the inguinal canals. The patient, however, volunteered the information that at times he has been able to feel small balls (testes) descend into the scrotum for short periods of time and then disappear into the abdomen again. In June 1938, on the suggestion of the senior author, he was given increasing doses of thyroid medication up to six grains per day, one anterior pituitary lobe tablet (Armour) and two whole pituitary lobe tablets (Armour) t. i. d. and 400 rat units of chorionic gonadotropin (Antophyisin-Winthrop) per day for five days. In fourteen days, small testes could be palpated in the inguinal canals at the scrotal junction. Testosterone propionate (Perandren-Ciba) was then administered in 5 mg. doses twice per week. Five weeks after onset of treatment the scrotum was well developed, the penis enlarged, the testes were fuller and were well down in the scrotum, the pitch of his voice was lower, pubic hairs were present, the patient's weight was reduced to 186 pounds. On subsequent examination progressive improvement was noted and the testes never again retracted into the inguinal canals.

Case 2: An obese white boy, aged 12 (a private patient of D. M. S.) with hypogenitalism and bilateral cryptorchidism. On examination no testes could be felt in the inguinal canals. On the suggestion of the senior author, a course of injections of 5 mg. of testosterone propionate (Perandren-Ciba) biweekly was administered for six weeks, followed by a course of Gonadotropic Factor—(Armour) 1 cc. biweekly until 10 cc. were given. He was given thyroid gr. 1 t. i. d. Fig. 1 is a photograph taken at the onset of therapy. Fig. 2 is a photograph taken immediately after the cessation of the first course of gonadotropin medication (11th week of therapy). Note the development of the scrotum and the descent of the testes. Fig. 3 was taken after a second course of therapy — testosterone propionate followed by gonadotropic factor (24th week).

It is felt that a course of testosterone propionate prior to a course of gonadotropins enhances the chances for success in cryptorchidism of so-called Frohlich's syndrome.

Case 3: A young female, aged 14, markedly obese, tall, with tapering phalanges of the hands, weight 200 pounds, scanty menses at very irregular intervals. Basal metabolic rate was minus 41, glucose tolerance was normal, urine negative, blood studies negative. High protein, low carbohydrate, low fat diet was administered with increasing doses of thyroid until 5 gr. per day were tolerated. Anterior pituitary extract (Pheloban-Winthrop) was administered at weekly intervals. Therapy was continued for several months. Menstrual cycle immediately regulated itself, the patient's weight was gradually reduced to 160 pounds, her general contour became definitely feminine. The results were maintained after cessation of therapy.

Case 4: A white female, aged 18, weight 150 pounds, height 5 feet, 3 inches, with girdle and trochanteric obesity, had very scanty menses occurring at irregular and lengthy intervals. Her basal metabolic rate was minus 35. She was depressed, had nervous and dizzy spells, flushes and headaches. Examination revealed an infantile
uterus and infantile breast development. Vaginal pH was 4.5 and smear reaction showed mild estrogen deficiency. Her physician had been administering thyroid, estrogen and chorionic gonadotropin without success. She was recently placed on increasing doses of thyroid
medication and small doses of estrogen during the first half of the cycle followed by a course of anterior pituitary extract (Polyansyn-Armour) 2 cc. per day for five days, during the second half of the cycle. The patient has responded well to therapy.

Case 5: A white female in her early twenties with girdle obesity and abdominal bloating, complained of continual headaches, fatigue and general let-down feeling. She had a very irregular cycle and menses were scanty, lasting but one-half to one day. Thyroid medication improved the patient temporarily but the improvement was not maintained upon additional therapy. Individual courses of various gonadotropins were followed occasionally but not consistently, by improvement. When the patient was placed on monthly courses of combined anterior pituitary extract and chorionic gonadotropin, abdominal bloating was reduced, the menstrual cycle became regulated and lasted five to eight days. Marked improvement in the general well-being of the patient and gradual disappearance of the headaches were noted.

Conclusions

Hypogonadism in the male and female will frequently respond to gonadotropin medication. In the hypogonad male with cryptorchidism, a short course of testosterone propionate followed by a potent gonadotropin will frequently yield successful response which otherwise might be attended by failure or marked delay in results. In the female with stigmata of hypogonadism, anterior pituitary extracts are preferable to chorionic gonadotropins and occasionally their action may be enhanced if a precursory course of estrogens are administered. The use of combined anterior pituitary extracts and chorionic gonadotropins may yield results in certain resistant cases where individual gonadotropins are not successful.

Patients with hypopituitarism usually have a low basal metabolic rate. Thyroid medication is invaluable as an adjunct to therapy.

(Grateful acknowledgment is made to Armour Laboratories for the supplies of gonadotropins (Gonadotropic Factor and Polyansyn), to Winthrop Chemical Company for the extract of the anterior pituitary (Preloban), and to Ciba Pharmaceutical Products, Inc., for the testosterone propionate (perandren).)

LEGEND

Case 2: Hypogonadism. Descent of testes and development of scrotum and penis followed a course of Gonadotropic Factor (Armour) after priming with small doses of testosterone propionate (Perandren-Ciba). Fig. 1 taken at onset of the therapy; Fig. 2 after cessation of first course of treatment (11th week); Fig. 3 after second course of treatment (24th week).

CORONARY DISEASE

By W. J. CRANSTON, M. D.

Several years ago I wrote a paper on coronary disease because I thought there was an increasing mortality from this syndrome and that the profession should become more coronary disease minded. It has been interesting to observe the trend of medical papers on this subject since that time. From every section of the country clinicians were presenting papers similar to mine, until there was a perfect deluge of essays on coronary disease. During the past two or three years, there have appeared papers by competent clinicians warning against too much pessimism in our prognosis, and within the past year there came to my desk an excellent article by Dr. Ernstene warning us against attributing
all pain in the precordium to coronary artery disease. This is quite
wholesome. It first becomes necessary for us to become aroused about a
certain menace, but the medical profession has always been conservative,
therefore it becomes necessary for the more conservative and cautious
members of the profession to apply the brakes, for fear we lose our
perspective and allow certain syndromes to assume undue prominence
in our thinking.

Coronary disease though, is so important a syndrome, I feel con­
strained again to raise my voice, no longer as "one crying in the wilder­
ness," but as a minor chord in a mighty symphony.

In his analysis of 4000 necropsies done at the Massachusetts General
Hospital between 1896 and 1919, of which 1906 showed cardio-vascular
disease, Cabot showed myocardial infarct occurred three times in the
first thousand, two times in the second thousand, six times in the third
thousand, and eight times in the fourth thousand.

Levy, Bruenn and Kurlz made a statistical study of the autopsy and
clinical records of 762 cases of coronary artery disease observed at the
Presbyterian Hospital from 1910 to 1931 and found that coronary
disease showed a slight but steady increase during this 21-year period,
the greatest increase being between the ages of 25 and 44. In 2,877
consecutive autopsies, lesions of the coronary artery were found in
25.9 per cent. In spite of these striking figures, they say, "The increase
in the incidence of affections of the coronary arteries is not to be
regarded as a matter of concern. Rather should it be a source of
satisfaction that, due largely to effective control of infectious disease,
men may survive to an age when disorders incident to senescence lead
to the termination of life."

On the other hand, A. R. Barnes of the Mayo clinic says "Coronary
sclerosis accounts for a large proportion of deaths from heart disease.
This might not be so depressing if death from coronary sclerosis came
after a long life, but too often the condition claims its victim when he is
in his prime and when elsewhere in his body, there is no evidence of
serious deterioration."

Since we are constantly on the look out for coronary disease, it is
more frequently recognized than formerly. With the electrocardiogram
as an aid more precise diagnosis is made possible. With the frontiers
of our knowledge being constantly pushed forward we are acquiring
a certain wisdom about coronary disease which enables us to take a more
hopeful view. Deadly as is coronary occlusion, we need not issue a
death warrant to the patient, as we were inclined to do a decade ago.
We know there have been many cases of infarcts in the myocardium
from which the patient has recovered and lived a long useful life.
Autopsy findings have shown this to us many times. With intelligent
treatment and perfect team work between patient and doctor, lives can
be saved for many years of usefulness.

A brief summary of the coronary circulation to refresh your mem­
ory might not be amiss. From the right and left side of the aorta,
within the area occupied by the cusps of the semilunar valve, the right
and left coronary arteries are given off. The right coronary passes
between the right auricle and ventricle, circling around to the posterior
surface, where it turns abruptly downward to terminate near the apex.
It gives off branches to the right ventricle, and small branches to the
right auricle, and from the descending posterior branch to the
left ventricle. In like manner, the left coronary, usually larger than the right, leaves the left side of the aorta and immediately divides. The descending branch passes between the left auricle and pulmonary artery to the sulcus, in which it descends to the apex. It gives off large branches to the septum ventricularium and left ventricle and smaller branches to the right ventricle. The other branch, the circumflex, passes around to the posterior surface, and turns sharply downward. It gives off large branches to the left ventricle and smaller ones to the left auricle. Spalteholtz states that both coronaries anastomose by small branches, mostly within the muscle, but some superficially. While more recent studies tend to disprove this, Levine says the coronary arteries anastomose more freely than was formerly thought. The veins follow the course of the arteries, more or less, and empty into the right auricle at the coronary sinus. The Thebesian veins open directly into the right auricle.

The coronary arteries are subject to the same deteriorating processes that affect other arteries. They may be a part of a general arteriosclerosis, or they alone may be affected. We see men with cerebral arteriosclerosis and soft radials, and others with marked systemic arteriosclerosis and perfectly clear minds. The degree of arteriosclerosis is not necessarily the same in the systemic, cerebral and coronary arteries. Coronary arteriosclerosis is the most frequent pathological finding in necropsies done on patients dying of coronary disease. Levine says he has consistently found coronary sclerosis in all patients dying of coronary disease who have come to autopsy.

There is a growing tendency to place emphasis on heredity. This requires careful study. If the shape and size of and course run by the coronaries predisposes to coronary disease, then heredity may well play an important part in this syndrome, because we can inherit circulatory characteristics just as we can the shape of the hands or the length of the long bones. However, it will be necessary to show that the size, shape and course of the coronaries contributes to this syndrome before heredity can be accepted.

Sex plays an important role. It occurs about four times as frequently in males as in females. Herrell and Cusie have shown that tobacco produces a vasoconstriction in certain susceptible individuals. Males heretofore have been the smokers. Now that women have taken to smoking, it will be interesting to observe whether this ratio will be obtained during the next few decades.

Age is important. The majority of the cases occur in the fourth, fifth and sixth decades. However, more cases are being reported in the younger age group than formerly.

Syphilis is but rarely responsible.

Diabetes is a frequent factor, though just why is not clear. Theories have been advanced, but none proved.

Stress and strain of modern life, making individual and family adjustments more difficult, may have an important bearing, but that too is difficult to evaluate. Tension stimulates the adrenals, and more adrenalin is thrown into the blood stream, increasing the pulse rate and raising the blood pressure. This is thought to favor arteriosclerosis and, if proved, would have to be included in the etiology.

Just what happens, and why, we do not know. In angina pectoris, the frequent forerunner of occlusion, there is probably always arterio-
sclerosis. Some patients die in an attack of angina and when studied at the autopsy table, nothing pathological is found except sclerosis, and this may not be severe. What then caused death? Levine reports a case of angina pectoris in which death occurred suddenly while an electrocardiogram was being run. At autopsy, only coronary sclerosis was found, but the electrocardiogram showed a typical ventricular fibrillation. It is probably ventricular fibrillation that is the cause of sudden death in many cases of angina pectoris and coronary occlusion. Leary, in a recent study, showed there was a rupture of a sub-endothelial atheromatous "abscess" which apparently caused the occlusion by thrombosis.

Embolic probably never occurs, or, if it does, only rarely.

The fact that the occlusion occurs most frequently within the first inch of the descending branch of the left coronary is significant of something, but just what is not clear. It is probable the answer to this will be forthcoming before long, and with it, much light will be thrown on this perplexing problem.

An occlusion can occur in one of the main coronary arteries or in one of their larger or smaller branches. The symptoms will depend largely on the location of the occlusion. If a main artery is occluded, the damage may be so great the heart cannot survive. If one of the minor branches is occluded, the chances of recovery are greater. When the blood supply to the area is abruptly cut off, the muscle begins to undergo softening. If this softening progresses toward the pericardium, there develops an aseptic area of pericarditis. If it is on the anterior wall of the heart, we hear a friction rub on listening with the stethoscope over this area. If it is on the posterior surface of the heart, no friction is heard. If the softening points toward the endocardium, a mural thrombus develops over this area in the heart cavity. Softening progresses rapidly and at the same time, collateral circulation is being established. If softening outstrips the collateral circulation and undue strain is put on the heart, an aneurysm of the heart wall occurs, which may rupture with sudden death. If repair takes place promptly, the muscle fibres are replaced by scar tissue and a firm, but much less elastic heart wall is formed.

If we will recall the plan of the nerve mechanism of the heart, we will readily understand why the occlusion with infarct will cause an alteration of the rate and rhythm of the heart. The pace maker is located in the sino-auricular node in the right auricle. From here impulses pass through both auricles to reach the auricular-ventricular node, thence down the main bundle of His through the right and left bundle branches into the Purkinje fibres.

An infarct cutting through this conducting system anywhere will interfere with the normal flow of nerve impulse and interfere with the rhythmic contraction of the heart muscle.

While coronary occlusion may occur suddenly with no premonitory signs or symptoms, it is generally preceded by mild to severe angina over a period of weeks or months. The anginal symptoms may be so mild as to attract no attention until they are brought out by a searching personal history. On the other hand, they may be so severe and frequent as to be incapacitating. The distribution of the pain is interesting.

MacKenzie in his book, Disease of the Heart, explains it as follows:
If a sensory nerve be stimulated anywhere in its course from the brain to the periphery, the resultant sensation will be referred to the peripheral distribution of the nerve in the body wall. A constant stream of energy is pouring from the viscera to the cord by the afferent nerves and stimulating the efferent nerves that run to muscles, blood vessels, skin, etc. If a morbid process in a viscus gives rise to an increased stimulation of the efferent nerves, this increased stimulation affects the neighboring centers. If it affects the sensory nerve from the skin to the brain, it will be referred by the brain to the peripheral distribution of the sensory nerve. This disturbance in the cord may continue for some time. So that stimulation from other neighborhood areas may cause pain referred to the original sensory nerve distribution. Thus, taking food in a case of gall stone colic may cause pain over the hyperalgesic skin area.

In angina pectoris the pain is sometimes referred to remote areas. The reason for this is found in the evolution of the nervous system. In the lower forms of life, the spinal nerves are distributed segmentally around each half of the body. As the arms bud out from the body, they drag with them away from the body portions of the cervical and upper dorsal nerves, so that parts of the first and second dorsal nerves are distributed to the ulnar border of the forearm and inner surface of the upper arm. A stimulus arising in the heart would be referred to the arm or forearm.

One of my patients, an elderly widow of a doctor, complained bitterly of pain in her wrists for weeks before she had an occlusion. Following three months rest in bed after the occlusion, she was completely relieved of the anginal pains.

The anginal pain may come on very insidiously and arouse no anxiety in the patient. It is generally thought to be due to ischemia of the heart muscle, and there is considerable experimental evidence to support this theory. There are five cardinal symptoms that should be sought in taking the history: (1) shortness of breath; (2) paroxysmal dyspnoea; (3) severe pain under the sternum radiating into one or both arms; (4) angina of effort; (5) indefinite pain.

The first symptom may be embarrassed breathing when any heavy exercise is taken, as walking uphill. This may last for weeks or months before other symptoms develop. Or, the angina may appear as paroxysmal dyspnoea following some violent effort and lasting for several hours. In some cases, it is initiated by severe pain under the sternum radiating to the arms, forearms, face or neck, or maybe limited to the arms. The first attack may come as pain associated with muscular or mental effort, great excitement, or nervous strain. Sometime the only symptom is a vague indefinite pain or distress referred to the sternum or arm.

A severe attack may come without warning. The patient has a sudden violent tearing, stretching or squeezing sensation referred to the sternum. He becomes terrified fearing his end has come. He becomes immobile, fearing even to breathe. After a few minutes, the violence of the storm has spent itself and he makes a few cautious muscular efforts. One attack of this character fills him with dread of future attacks. The attacks may vary in intensity and frequency, and are generally associated with muscular effort.

After a variable period of time, an occlusion of one of the coro-
naries is inevitable. This always comes violently. Exercise is not always associated with the attack as is generally the case with angina. The attack may come while the patient is asleep. Pain is not invariably present, but when it is, it is severe. Shock is always present. The face takes on an ashen hue, the pulse is small, rapid, feeble and, in some cases, irregular and unequal. Great beads of perspiration drench him. He suspects death is at hand, as, indeed, frequently it is. There may be nausea or vomiting arousing the suspicion of acute indigestion. This picture lasts from a few hours to three or four days, unless the patient succumbs, which may happen at any time, due to fibrillation of the ventricles or other complications. The temperature is likely to be normal the first ten or twelve hours, and then rises one to three degrees per rectum, although the mouth temperature may remain normal. The leucocyte count rises with the temperature, and may be as high as 10,000 to 20,000. As a rule the blood-pressure drops within the first ten or twelve hours. Since there generally is a hypertension, this drop is striking, the systolic pressure sometimes dropping to ninety. Curiously enough, the pressure does not always drop. As recovery takes place the pressure goes back up, but not as high as before the occlusion.

It is not possible to predict the outcome of any given case because unpredictable accidents may occur at any moment. Auricular fibrillation frequently accompanies the attack. Should the ventricles fibrillate, death is instantaneous. This is probably the most frequent cause of sudden death in coronary disease. Should a thrombus get loose from the right side of the heart it may block the valve, or pass into the lung, producing a pulmonary infarct. Should a thrombus leave the left chamber it may lodge in the brain, causing hemiplegia; in an artery to a limb, causing dry gangrene, or in the kidney, causing a renal infarct, etc. Should the infarct in the myocardium cut across the bundle of His there would be complete heart block, with the danger of standstill of the heart long enough to cause sudden death. Should the myocardium become greatly weakened, the heart wall may rupture.

Should these hazards be successfully passed, and repair take place in the damaged myocardium by anastomosis of the collateral vessels, a firm cicatrix will form. There will be a certain degree of crippling as a result, but a fairly efficient organ will remain capable of reasonable work within a circumscribed field, for a variable number of years.

Bearing in mind the pathology, the treatment suggests itself.

Rest must be absolute. Immediately after the attack the patient should not be disturbed, even to remove the clothes, unless they interfere with treatment or his comfort. No visitors; no noise so far as it can be controlled. The bed pan and urinal should be used. No effort to produce a bowel movement under three or four days. Morphine 15 mg. (1/4 gr.) or dilaudid 3 mg. (1/20 gr.) or Pantopon .02 gm. (1/3 gr.) should be given at once and repeated every half hour until the pain is controlled. In case of persistent fibrillation, digitalis may be given during the first three days, but not after that for fear of dislodging a thrombus. In case the blood pressure drops alarmingly, 0.5 cc. to 1.0 cc. of adrenalin (1-1000) should be given. This drug may also be used every two to four hours in case of complete heartblock with periods of unconsciousness. Paroxysmal ventricular tachycardia
may arise. This can be controlled with quinidine 0.3 gram t. i. d. or even larger doses. Levine uses quinidine routinely for the first two weeks unless there is definite contra-indication. Any impairment to the conduction system, as bundle branch block, partial or complete, or auricular-ventricular block, would contra-indicate its use, since quinidine can further impair the conduction system.

The diet should be light and of small bulk for the first few days. After the shock of the first week has passed, the diet may be increased and the bowels moved by enemata. Rest in bed should continue for six to eight weeks, and exercise then should be very gradually permitted. First sitting up in bed a few days, then in a chair three or four times a day, then walking about the room, then out of doors until a walk of several miles a day can be taken without fatigue.

Coramine in 1.0 cc. doses t. i. d. for months after convalescence has been established and appears to be beneficial.

Aminophyllin or some similar drug is generally given. I have used it for years, but cannot say whether or not it is helpful.

Tobacco should be omitted.

An electrocardiogram taken during the angina pectoris may give definite information as to the impending occlusion. Occasionally, it fails to show anything. One electrocardiogram though, is not conclusive, and, if we get a normal reading, this should be repeated several times before dismissing a case as having normal coronaries. Even after an occlusion, one electrocardiogram may show no damage, but if repeated, would show the typical Pardee curve. For months after recovery, electrocardiograms should be run, which would give definite information as to the permanent damage that had been done.

*GENERAL PRINCIPLES IN ALLERGY*

By HARRY T. HARPER, Jr., M. D., Department of Medicine, University of Georgia School of Medicine.

**Incidence.** It is thought by most men that the incidence of allergical disorders is about 10 per cent. In other words, one out of ten persons will suffer with some manifestation of allergy at some time during his life.

**Etiology.** It is generally conceded that sensitivity to foreign protein is responsible for the signs and symptoms of allergical disorders. The foreign protein may be ingested as in the case of foods, inhaled as in the case of epidermal products, and inhaled as in the case of pollens. The foods most often at fault are milk, wheat, and eggs. House dust and feathers are the inhalants usually producing symptoms and bermuda grass and ragweed form the pollens usually responsible for hay fever in this section of the country. In each case the reaction is the same but it takes place in a different system or “shock organ” as it may be called.

*This paper was delivered at the staff meeting of the Wilhenford Hospital, November 1940.*
The bronchi and bronchioles in the case of asthma, the nasal mucosa in the case of hay fever, the skin in the case of eczema, the gastrointestinal mucosa in gastrointestinal allergy, the cerebral vessels in the case of migraine, the skin in the case of urticaria and angioneurotic edema, are the organs at fault. Sensitivity to bacteria or their products may also occur and must always be thought of when allergy is first observed late in life. Histamine is now thought to play an important role in allergy. It is well known that the intradermal injection of histamine will produce a wheal and flare quite like that seen in typical allergic skin reactions. Sir Thomas Lewis thinks that histamine or the "H" substance is very definitely important in the production of allergical symptoms and that an excess of circulating histamine is present in such cases.

**Relation of Allergy to the Specialties.** Allergy is very closely interwoven with all the medical and surgical specialties. A large proportion of the cases seen by the rhinologist have their beginning in an allergic response to contact with allergens to which the patient is sensitive. Rhinitis and conjunctivities are not infrequently allergic. More than one normal appendix has been removed through no fault of the surgeon because of gastrointestinal allergy usually producing spasm or colic of the smooth muscle of the bowel. In atypical cases and cases which present a history of other forms of allergy this should be kept in mind. Epilepsy is very occasionally due to allergic involvement of the cortex of the brain with localized edema and a resultant seizure. The dermatologic forms of allergy are obvious—urticaria, eczema, angioneurotic edema, contact dermatitis, erythema multiforme. Allergy is most closely of all linked up with internal medicine with its asthma, bronchitis, cardiospasm, pylorospasm, spasm of the gut, physical allergy, perhaps spasm of the coronary vessels, spasm of the cerebral and dural vessels, etc. Incidentally, pruritus ani is thought to be due to food sensitivity in many cases especially sensitivity to chocolate.

**Diagnosis.** The history is most important. In most cases other members of the family will have suffered some form of allergy. This is quite constant. And usually, the patient will have suffered some other form of allergy himself. A careful history will nearly always give leads as to what the patient is sensitive to, especially in the way of certain foods, dusts, and physical allergy. Occasionally the history is much more reliable in this particular than are the skin tests, and if the two do not corroborate each other it is better to rely upon the history.

The examination gives obvious findings in the case of bronchial asthma, the increased expiratory phase with the presence of musical, asthmatic rales, etc. In the case of nasal allergy, the mucosa is nearly always pale, boggy, glistening, and wet. In infectious rhinitis the mucosa is red and a purulent exudate is obvious. Eczema is characterized by involvement of the flexor surfaces, the absence of vesiculation, and the presence of lichenification.

We rely on many laboratory aids in diagnosing allergical conditions. The blood smear often presents an eosinophilia which may be striking and may first call attention to an allergical state. The nasal smear in rhinitis is very helpful, an increase in the number of eosinophiles present indicating nasal allergy, a vast predominance of polymor-
phonuclear neutrophiles indicating an infectious process. Of course, a mixture of the two can occur. Nasal cultures are helpful. We usually have an autogenous vaccine made if pathogenic organisms are present and then test the patient to his own bacteria by injecting a small amount of this intradermally. If after 24-48 hours the patient reacts positively to this we consider him sensitive to these bacteria and administer the vaccine therapeutically. Skin tests are used routinely in detecting the allergens at fault. First we test the patient with the allergens by the scratch method as a safety measure, thus preventing any undue reaction which might result if the patient is unusually sensitive to an allergen. Deaths have been reported from the hasty use of intradermal allergens in cases of unusual sensitivity. We usually use around 30-40 of the commoner foods, 12-15 inhalants, and 8-12 pollens prevalent in this locality. If we do not get good sharp reactions apparently accounting for the trouble we then use intradermal tests using those to which the patient did not react by the scratch method. This prevents catastrophes. If we still cannot account for allergy which we think is due to food sensitivity, we may next try leukopenic indices. This is a method introduced by Vaughn for detecting food allergy. After doing a white count on a patient in the morning, we give him a portion of a single food substance and then take white counts at 20, 40, and 60 minutes after he takes the food. Normally, the number of white cells may slightly increase but certainly should not drop more than 1000 within an hour. If a drop of more than 1000 occurs we call this a positive leukopenic index and think that this indicates sensitivity to the food used. If we are still unable to identify the foods at fault, we may resort to a trial diet, placing the patient on a diet of a few foods that we know he is not sensitive to, such as lamb, rice and pears. After he becomes symptom free on this diet we add one article of food at a time to the diet waiting a few days after each addition to see if it produces symptoms. A food diary is sometimes helpful if kept over a period of time and the relationship to symptoms and attacks carefully analyzed.

From experience we have found that it is always worthwhile to have the sinuses X-rayed in either perennial rhinitis or bronchial asthma, since occasionally a symptomless involvement of the sinuses, the presence of polyps or cysts, will serve as an etiological factor in these cases.

**Treatment.** Treatment of asthma consists of the treatment of the acute attack and of efforts to prevent attacks or cure the condition. Adrenalin is a specific for most forms of allergy but unfortunately its action is short-lived. Adrenalin in oil acts for from 6-12 hours and gives very good results. It should not be given to patients who are sensitive to peanuts since it is dissolved in peanut oil. There is now available an epinephrine in gelatine which is satisfactory except that it must be refrigerated and then warmed for using, to promote fluidity. Ephedrine or some of the newer synthetic substances such as propadrine or racephedrine or benzylephedrine may give happy results if taken at regular intervals of three or four hours. These may be combined with a small amount of phenobarbital and with aminophyllin or theophyllin which is helpful in some cases. Potassium iodide is useful because of its expectorant and thinning action and because it is eliminated through the respiratory epithelium. A small amount of apomorphine sometimes helps considerably if cough is a troublesome feature.
In cases of "Status Asthmaticus" aminophyllin is particularly helpful if the patient has become refractory to adrenalin. Seven and one-half grains in 20 c. c. of diluent may be given slowly intravenously as often as every four to eight hours if needed. Large doses of the barbiturates, paraldehyde, and even ether and oil by rectum may be necessary to quiet the patient. Morphine should be avoided if possible because of its depressant action on the respiratory center. Glucose, intravenously, in a concentration of 20 per cent is sometimes of help. Oxygen by tent or nasal catheter often helps and, if available, helium with oxygen is of considerable help because of its ready diffusibility.

Based on the idea that histamine is an etiological factor in allergy, in the past few years there has been developed a product called Histaminase which is an enzyme derived from the intestinal mucosa and the kidney of the hog which is supposed to neutralize or detoxify an excess of histamine in the system. We have obtained fairly good results with this especially in the urticarias, eczemas, and angioneurotic edema. It is given by mouth in tablet form. Incidentally it must not be given to patients who are sensitive to pork.

The usual regime consists of elimination of any foods from the diet, if the patient has given positive reactions to these or any other evidence of sensitivity to these is present. Any allergens to which the patient is sensitive should be eliminated from his environment if possible. If he is sensitive to feathers he should not sleep on feather pillows. If sensitive to dust he should use allergen-proof covers on both pillows and mattress. Any animals to which the patient is sensitive should be avoided. If it is impossible for the patient to avoid allergens to which he is sensitive an attempt is made to desensitize the patient to these by having an extract made and giving him increasing doses of the extract. This is the procedure usually carried out in hay fever. Unless the physician does allergy exclusively and has his own private laboratory it is cheaper and he can get better extracts from commercial laboratories or pharmaceutical houses which specialize in this business. He can either send them his prescription for a treatment set or can send them a list of the allergens to which the patient has reacted with the degree of reaction and they can make a very satisfactory extract.

We usually start with 0.1 c. c. of the extract dilution which just produces a very mild reaction when injected intradermally. In most cases this is the 1:100,000 dilution. The dose is usually increased by 0.1 c. c. at three day intervals until the maximum tolerated dose is found which is usually around 0.5 c. c. of a 1:20 dilution. Then, the interval between doses is lengthened until the patient is receiving a dose per month. This is continued the year round. As the next hay fever season approaches the interval is decreased and the amount of allergens decreased to compensate for the added amount of pollen allergen in the air at that time.

The allergical patient asks the doctor many questions. Some of these are as follows:

"How long must I take the shots?" The answer is, that it varies with the individual. Some few patients get results with one course of 18 or 20 injections, which are permanent. The majority of patients require treatment for a period of from three to four years before they obtain
a measure of permanent relief. And a few patients must take the desensitizing treatment indefinitely to maintain relief.

"What results can you promise me?" As a rule, we can promise the patient that 75 per cent of the patients get at least 75 per cent relief. Along this line it is interesting to note our results in allergical cases during the past two and one-half years. During this time we have studied 60 cases thoroughly. Of these 60 cases, 71 per cent have reported good results or satisfactory results, 11 per cent have given questionable results (the results have either been equivocal or the patient or his family physician has not been heard from), and 18 per cent of the patients have reported poor results. The accompanying table breaks these cases down into the subdivisions of allergy and is of interest.

<table>
<thead>
<tr>
<th>Type of Allergy</th>
<th>No. Cases</th>
<th>Good results</th>
<th>Doubtful results</th>
<th>Poor results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma, bronchial</td>
<td>14</td>
<td>85 per cent</td>
<td>7.5 per cent</td>
<td>7.5 per cent</td>
</tr>
<tr>
<td>Seasonal Hay Fever</td>
<td>19</td>
<td>73 per cent</td>
<td>6.0 per cent</td>
<td>21.0 per cent</td>
</tr>
<tr>
<td>Perennial Rhinitis</td>
<td>14</td>
<td>35 per cent</td>
<td>23.0 per cent</td>
<td>42.0 per cent</td>
</tr>
<tr>
<td>Eczema</td>
<td>4</td>
<td>75 per cent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria and Angioneurotic Edema</td>
<td>9</td>
<td>100 per cent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The poor results obtained in perennial rhinitis are interesting. This form of allergy has consistently been the most difficult for us to get results in. Why this is so, we do not know. However, we believe that this is due to a very definite neurogenic factor which seems to be prevalent in these cases. Twenty-eight per cent of these cases presented a very definite neurogenic or psychoneurotic factor while the incidence of the same factor in allergic cases as a whole was only eight per cent.

One case of asthma and one of urticaria responded nicely to massive doses of estrogenic hormone. Both of these cases were in women suffering with the menopause. This factor must always be considered. With the development of the purified male sex hormone, its therapeutic use must be considered in males who might possibly be suffering with the male climacteric as an etiologic factor in their allergy.

If an individual cannot tolerate histaminase because of sensitivity to pork, injections of histamine phosphate can be given in gradually increasing doses in an attempt to sensitize him non-specifically in this manner.

Allergical therapy is expensive. Allergy is not easily treated in the poor. The patient must exhibit patience, he must stick with his doctor and have faith in him. Unfortunately, the patient may begin to feel better after a short period of treatment and may stop coming for his treatment. Sooner or later he will get into trouble again and will think that allergic therapy is the bunk. All these things should be explained to the patient at the start and perseverance must be emphasized. Patience, tact, and careful psychotherapy and guidance on the part of the physician are most important. In the majority of cases, however, the results obtained are satisfactory and from the viewpoint of the patient warrant the time, cost, and trouble which allergic study and therapy entail.
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