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THE TOCOPHEROLS (VITAMIN E) IN THE TREATMENT OF PRIMARY FIBROSITIS

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William Balfour, an Edinburgh practitioner, first described the occurrence of fibrous thickenings in chronic muscular rheumatism in 1816. On this subject he wrote a book, in which he described numerous nodular tumors and fibrous thickenings which were painful on pressure and which caused referred pain. The term fibrositis was coined by Gowers almost 100 years later (1904). Stockman [23] described the pathology of fibrositis in the same year, although he failed to differentiate between the pathology of primary and secondary fibrositis in this description. Llewellyn and Jones wrote a book on fibrositis in 1915. Stockman [24] wrote several excellent chapters on fibrositis, panniculitis, and Dupuytren's contracture in his book "Rheumatism and Arthritis" which was published in 1920. In England, Telling stressed the clinical importance of fibrositis in general practice in 1935, and Slocumb brought its attention to the American physician in 1936.

Kelchner's definition of fibrositis, which was taken from Stockman [24], is all-embracing. He states, "Fibrositis is a rheumatoid disorder characterized by a non-suppurative inflammatory reaction in the white fibrous connective tissue, anywhere in the body, with a swelling and proliferation of the fibrous tissue in response to chilling, toxic influence, trauma, or fatigue. Acutely tender fibrous bands and nodules frequently form in the muscles, tendons, ligaments, fasciae, periosteum, joint capsules, and nerve sheaths, and press on arterioles and nerve filaments, causing muscle spasm and secondary pressure effects." Fibrositis is no more one disease than is anaemia or arthritis. The primary type is of unknown etiology. The secondary type is part of the picture of some general infection—such as rheumatic fever, influenza, gonorrhoea, syphilis, atrophic arthritis—or a systemic disease,—such as hypertrophic arthritis, gout, plumbism, or alcoholism. The primary type may be classified according to the type of tissue, muscle, or group of muscles involved. The most frequent muscles involved are the sternocleidomastoid, the trapezius, the intercostal, the latissimus dorsi, the serratus anterior, the serratus posterior inferior and superior, the splenius capitis and cervicis, the sacrospinalis and semispinalis capitis, semispinalis dorsi and cervicis, and the small deep muscles of the back; the deltoid, and the muscles of the scapula,—such as the teres major, the rhomboidei, the suprapsinatus and infraspinatus. Occasionally the muscles of the anterior abdomen (external and internal oblique, transversus abdominis, and rectus abdominis) are involved. The capsule and surrounding ligaments of various joints may be involved, at

which time the condition is spoken of as periarticular fibrositis. The bursae may be involved. The sheath of the sciatic nerve is often involved, and the condition is spoken of as perineural fibrositis. Tendons, fasciae, and aponeuroses may be involved. In the author's experience, the fascia lata, the inguinal ligament, and the palmar fascia of the hand have been frequently involved. Primary fibrositis may affect the subcutaneous fibro-areolar and adipose tissues.

Primary fibrositis is uncommon in young people. It usually manifests itself for the first time during the latter part of the fourth decade of life, and reaches its peak incidence in the fifth decade. Although most textbooks state that the disease occurs more frequently in males than in females, in the author's experience it has been equally divided between the sexes. The affected individual has the usual physical appearance of "good health". The disease may be acute or chronic. Acute attacks, not unlike that of gout, are the rule. However, these attacks usually last for a period of weeks, rather than days, which is characteristic of gout. Patients complain of severe pain and tenderness, which may be localized or generalized. The localized area may consist of a small tender nodule, the size of a pea, or may involve one muscle or group of muscles. These localized areas are not only tender, but are usually undurated and under spasm. The generalized condition is usually associated with generalized stiffness. Drafts and cold, damp weather definitely aggravate the condition or initiate an attack. Warm weather or the application of local heat brings relief. A slight degree of exercise usually limbers up these patients, and an excessive amount of exercise stiffens them again. Temporary deformities may occur during an acute attack. Thus an attack of fibrositis involving one of the sternocleidomastoid muscles may cause traction of the head to the affected side. Involvement of one group of the back muscles may cause a temporary lateral curvature of the spine. Fibrositis is usually characterized by the absence of an increased sedimentation rate, leukocytosis, or fever.

Stockman [24] has described the pathology of fibrositis at various stages: "Histologically they all consist of inflamed white fibrous tissue, the more recent ones being much less dense and containing more serofibrinous exudation than the older ones. The walls of the small blood vessels are much thickened, and the nerve filaments show interstitial inflammation". He showed one section of a small soft swelling, of about three weeks' duration, on the periosteum of the sternum. This section showed newly formed proliferating fibrous tissue, marked oedema, and many fibroblasts and blood vessels with many new capillaries. No leukocytic reaction was present. In another section, through a comparatively recent but older area of inflammation of the perimysium of the gluteus medius, new fibrous tissue was shown in a serofibrinous matrix. The fibroblasts were not numerous, and no leukocytes were present. All the coats of the small blood vessels showed very distinct thickening. Another section through an old, dense nodule from the heel showed closely packed fibrous tissue

with disappearance of the interspaces. Stockman also showed another section of chronic inflammation of the areolar tissue of the panniculus adiposus. Many fibroblasts were shown in the hypertrophied inflamed connective tissue. Interstitial neuritis was shown in the nerve twigs, and all walls of the blood vessels were thickened by increase in the connective tissue. Increased fat deposit was present in areas in which the

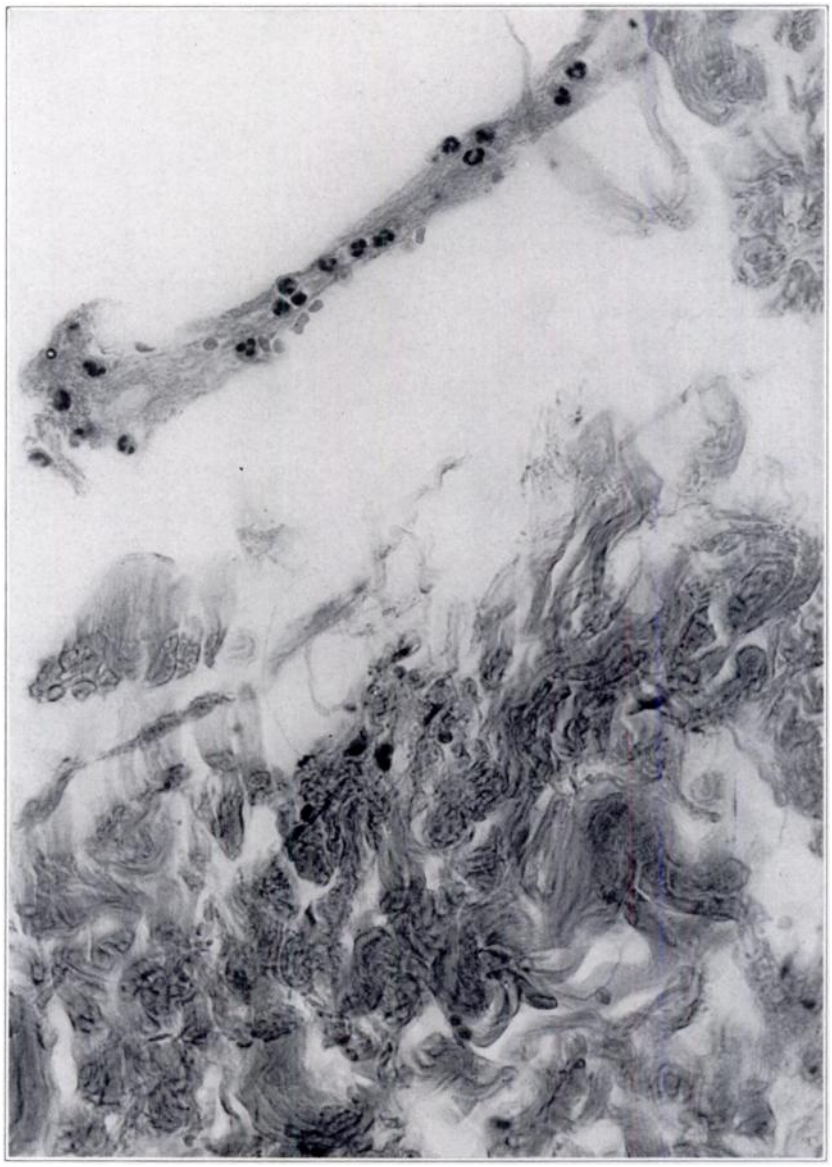

FIG. 1

Case 1. Photomicrograph (×400) showing polymorphonuclear infiltration, fibroblastic proliferation, and oedema.

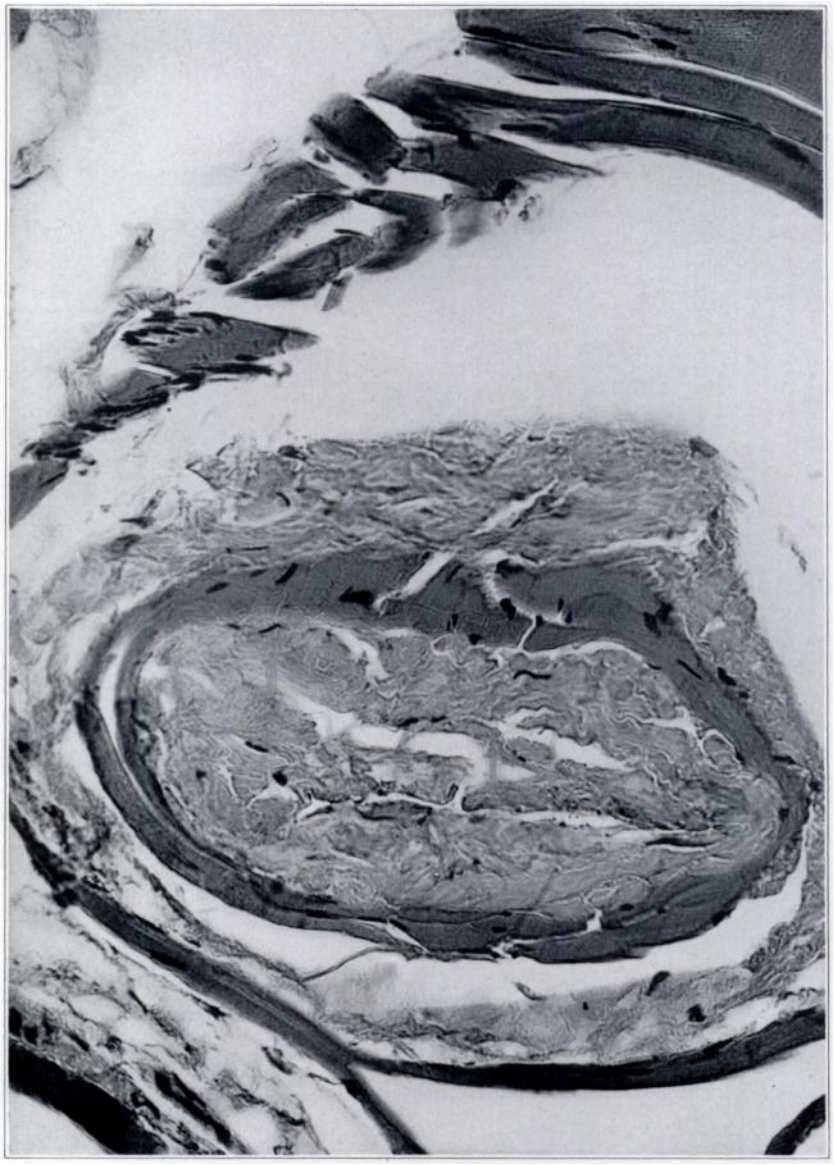

FIG. 2-A

Case 2. Photomicrograph (×400) showing a small area of hyaline degeneration of muscle with loss of cross striations and disappearance of nuclei.

inflammation occurred in patches. These patches were felt as small rounded fibrofatty tumors which were very painful on pressure, thus differentiating them from ordinary lipomata. He described the typical flexion deformities of the fingers occurring in Dupuytren's contracture as being due to the gradual contraction of this pathological fibrous tissue.

Abel and Siebert [1] described three stages in the pathology of primary

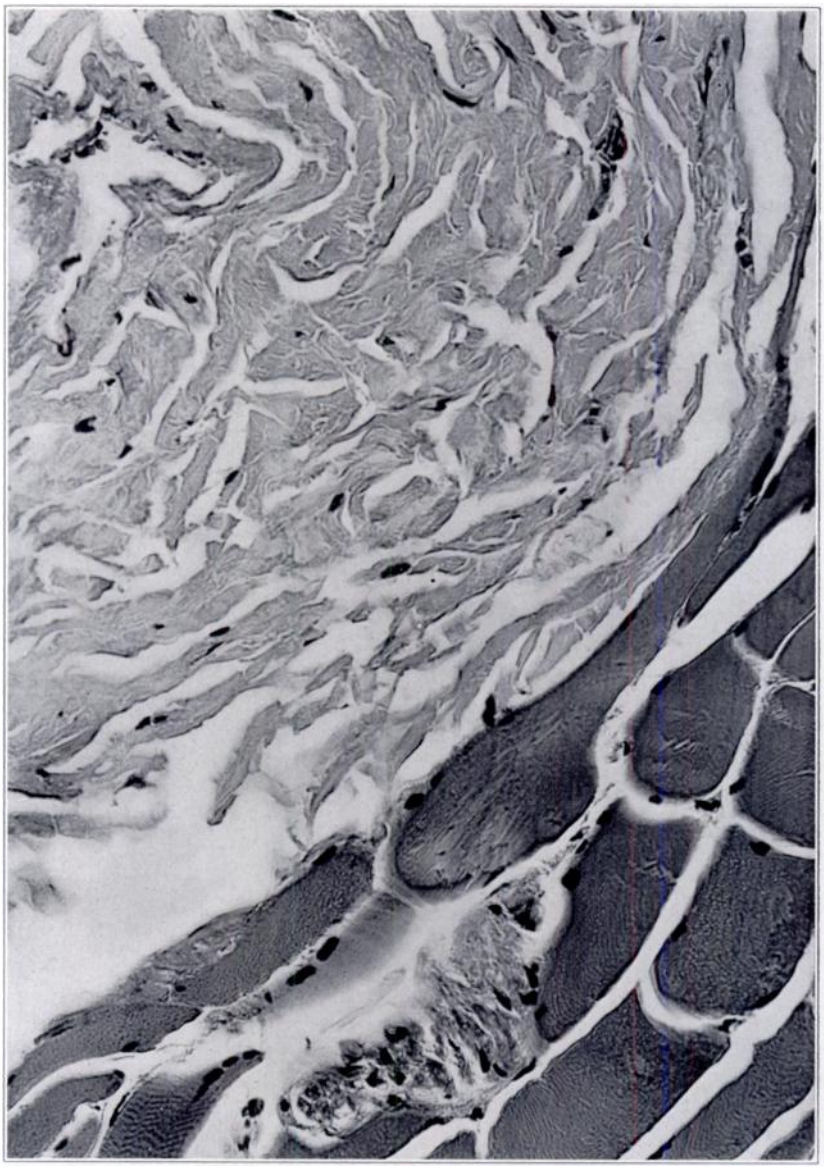

FIG. 2-B

Case 2. Photomicrograph (×400) showing large area of hyaline degeneration of muscle with loss of cross striations, disappearance of nuclei, and fibroblastic activity.

fibrositis,—acute, subacute, and chronic stages. The acute and subacute stages show hemorrhages, hyperaemia, serofibrinous exudate between the muscle bundles, newly formed fibroblasts, mild degenerative changes in muscle, swelling, loss of cross striation, and a few lymphocytes. The chronic stage shows fibrosis of muscle fascia and intramuscular septa, with separation of the muscle bundles, marked degeneration of the muscles

as evidenced by complete loss of cross striation, and hyalinization. There is also lobulation of perimuscular and subcutaneous fat.

CASE 1. A white female, aged fifty-seven, complained of attacks of generalized muscle stiffness and soreness of fourteen years' duration. These attacks lasted from one to thirty days. Her present attack consisted of soreness and stiffness of the back of the neck of several days' duration. A specimen for biopsy was taken from the trapezius

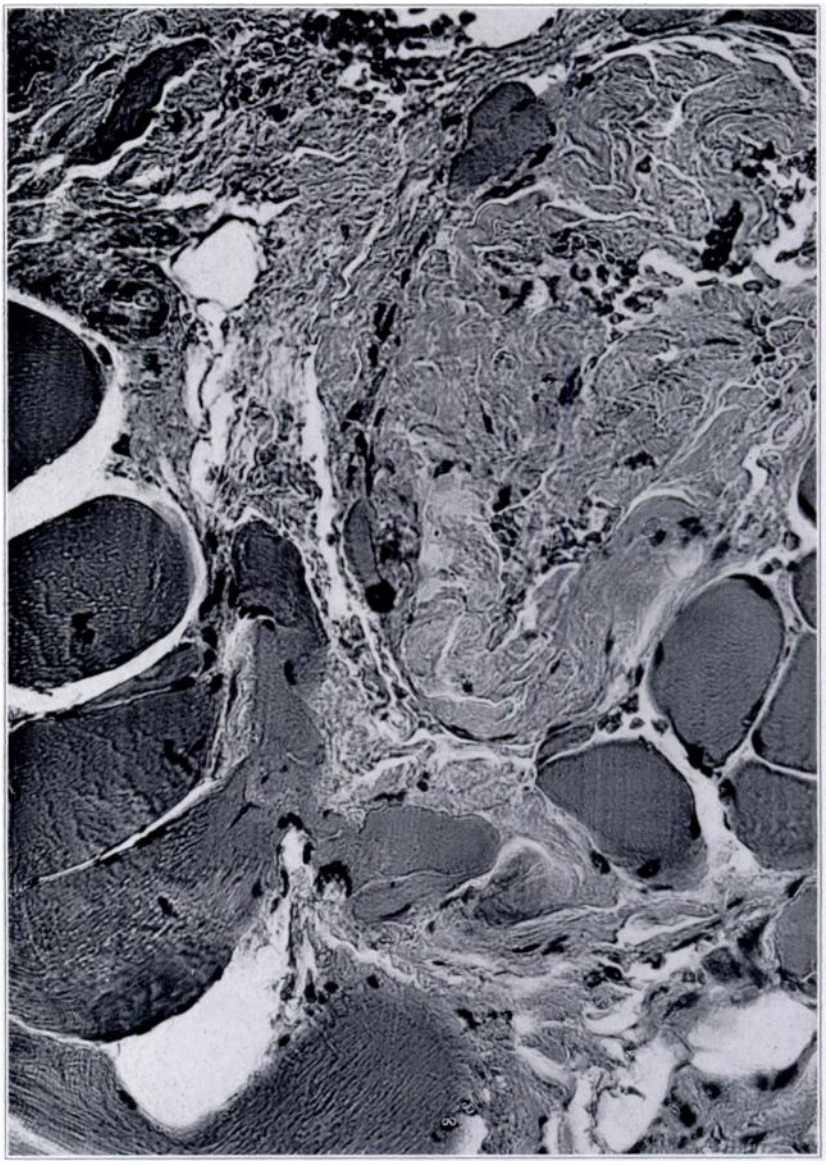

FIG. 3

Case 3. Photomicrograph (×400) showing hyalinization with loss of cross striations, disappearance of nuclei, and fibroblastic activity.

muscle. The acute stage of fibrositis is represented by Figure 1. Section from this tissue showed polymorphonuclear infiltration, fibroblastic proliferation, and oedema. This patient had been diagnosed as a psychoneurotic by several physicians. Compare this with normal muscle (Fig. 6).

CASE 2. A white female, aged twenty-two, complained of severe pain in the entire back, of thirty-two months' duration. The onset was acute, after the patient had sus-

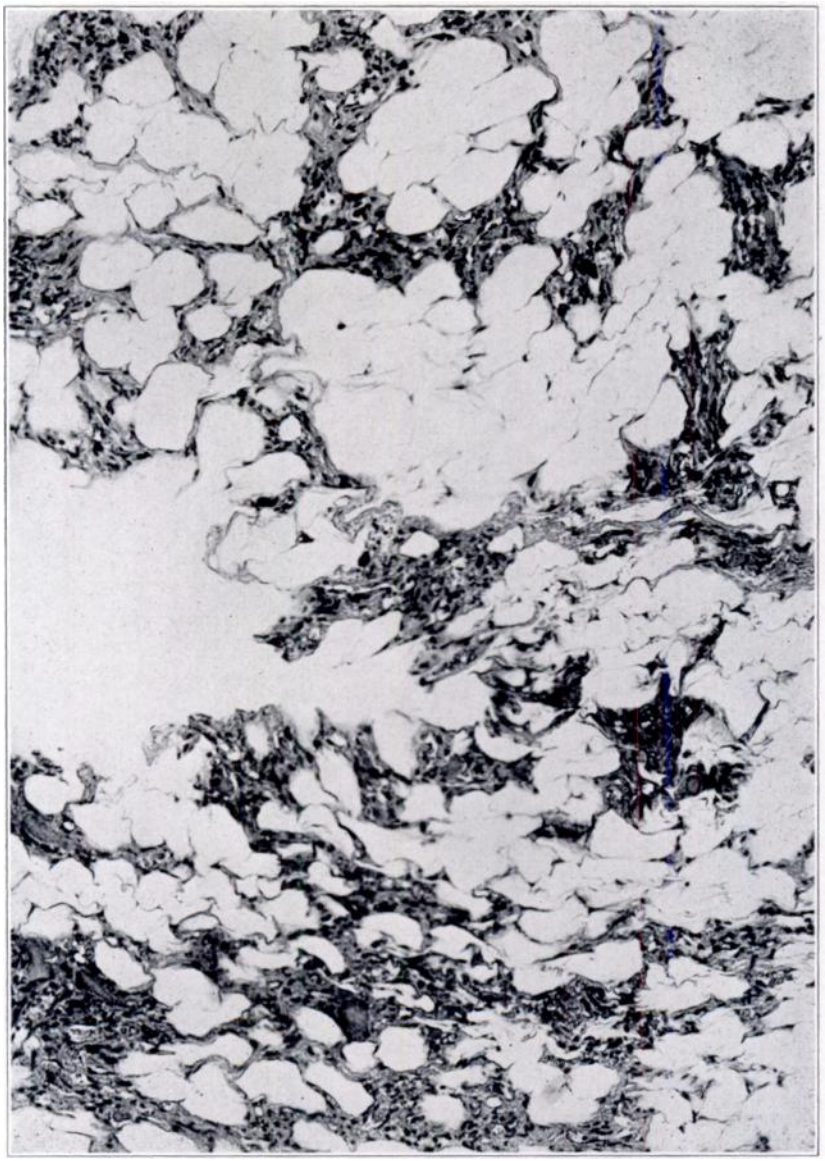

FIG. 4

Case 4. Photomicrograph (×400) of a nodule showing fibroblastic activity with increased local fat deposit.

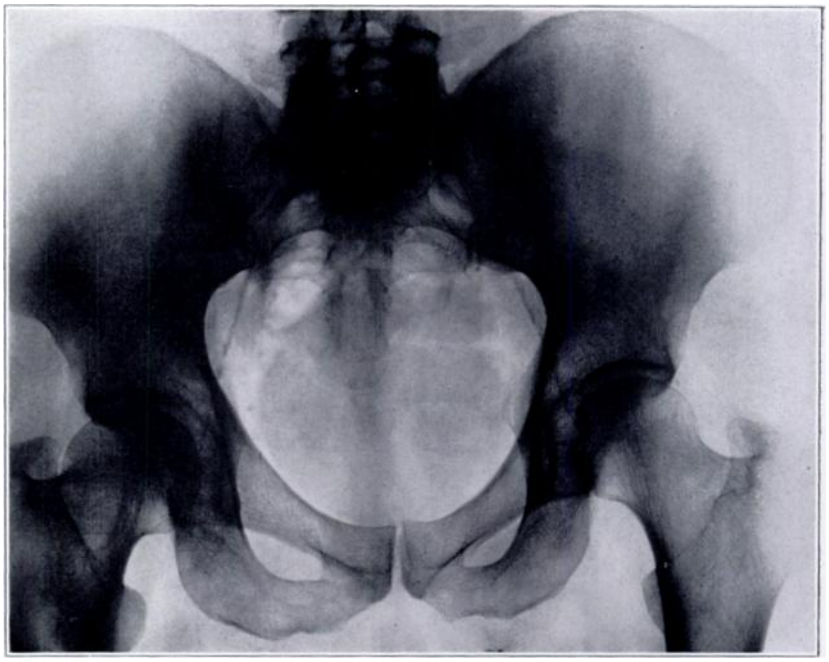

FIG. 5

Case 5. Roentgenogram of the pelvis showing calcification of the sacrotuberous ligament.

tained a blow on the back. Marked tenderness was present over all the soft tissues of the back. Roentgenograms of the vertebrae and pelvis were negative. Sedimentation rate was 0.30 millimeters per hour (Wintrobe and Landsberg method); uric acid, 1.9 milligrams per 100 cubic centimeters; and serum phosphatase, 1.22 Bodansky units. Biopsy sections from the trapezius muscle showed one small area (Fig. 2-A) and one large area (Fig. 2-B) of hyaline degeneration of muscle, with loss of cross striations and disappearance of nuclei.

CASE 3. A white female, aged fifty-four, complained of attacks of lumbago over the previous two years. These attacks lasted from two to seven weeks. The present attack was in its second week. Examination revealed marked tenderness, induration, and spasm of the muscles of the lower back. Sedimentation rate was 0.42 millimeters per hour (Wintrobe and Landsberg method); uric acid, 1.5 milligrams per 100 cubic centimeters; and serum phosphatase, 3.3 Bodansky units. Roentgenograms of the pelvis and spine were negative. Biopsy sections from the latissimus dorsi showed hyalinization with loss of cross striations, disappearance of nuclei, and definite fibroblastic activity (Fig. 3).

CASE 4. A white female, aged fifty-five, complained of tender nodules on the right forearm and right leg of three week's duration. These nodules were very painful and tender. Biopsy of one of these nodules (Fig. 4) showed marked fibroblastic activity with increased local fat deposit. This picture is not unlike that described by Stockman [24] as occurring in panniculitis.

CASE 5. A white male, aged fifty-four, complained of backache of five months' duration. He stated that his backache was caused by lifting a heavy weight. He had pain also in the soft-tissue structures of the palms of his hands of three weeks' duration. Pain was produced by either flexion or extension at the hips. Sedimentation rate was

0.48 millimeters per hour (Wintrobe and Landsberg method). Roentgenograms of the pelvis (Fig. 5) showed calcification of the sacrotuberous ligament. This represents one of the end stages of fibrositis when the ligaments are affected.

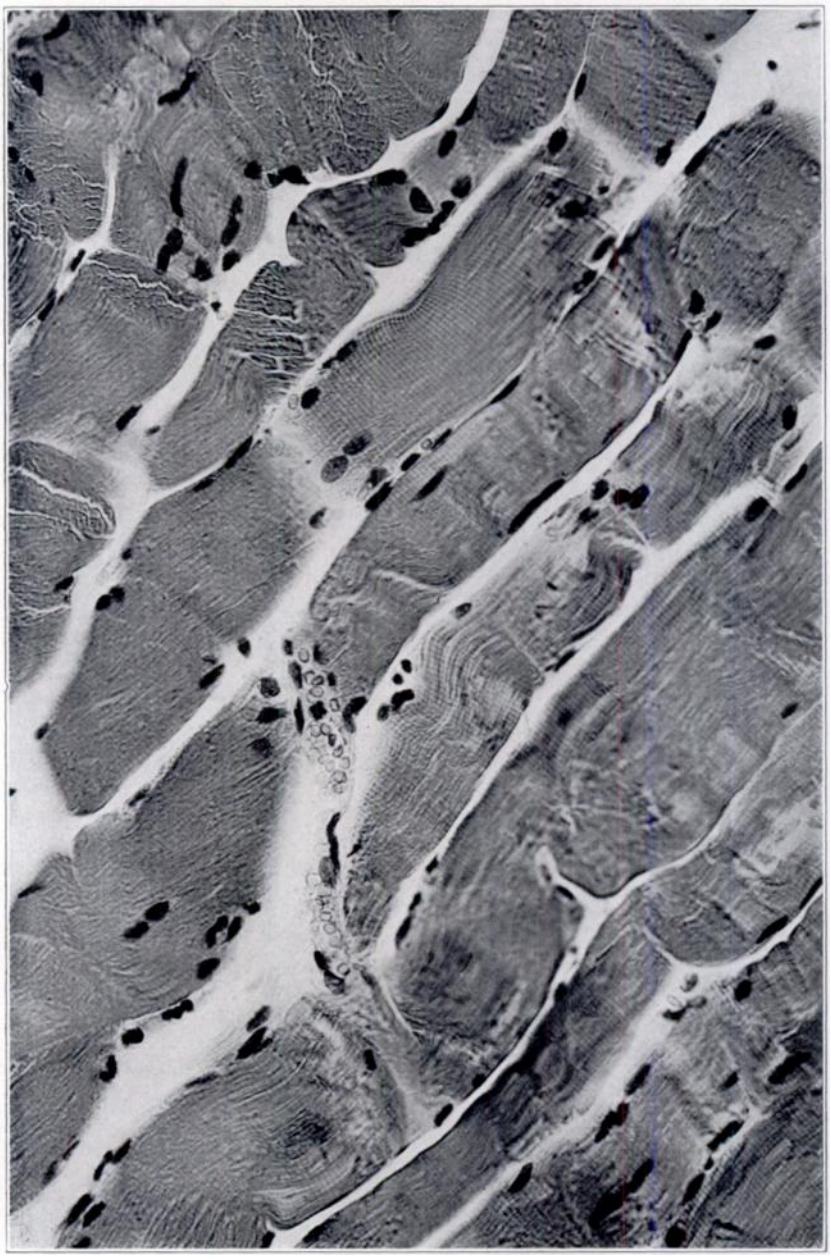

FIG. 6

Photomicrograph (×400) of normal muscle showing normal cross striations and arrangement of nuclei. Compare this with the pathological changes in the above cases.

The pathology of primary fibrositis and that of nutritional muscular dystrophy occurring in young rats, as described by Pappenheimer, are strikingly similar. The early stages of nutritional muscular dystrophy show marked interstitial oedema, in part fibrinous. Marked inflammatory reaction with polymorphonuclears is present. The oedema soon disappears and the polymorphonuclears are replaced by mononuclear histiocytes. This is followed by calcification of the necrotic fibers. Nutritional muscular dystrophy was first described by Goettsch and Pappenheimer in rabbits and guinea pigs in 1931. Evans [3] and his coworkers described degeneration of cross-striated musculature in rats whose diet was low in vitamin E. Knowlton and his coworkers described similar changes in skeletal muscle, resulting from diets deficient in vitamin E. Morgulis and Spencer in 1936, and Morgulis and his coworkers [17] in 1938, reported that at least two factors, both present in whole wheat germ were required to cure nutritional muscular dystrophy in rats: a water-soluble factor present in defatted wheat germ, and a fat-soluble factor present in the unsaponifiable matter of wheat-germ oil. Mackenzie and his coworkers [14] in 1940 were able to show that nutritional muscular dystrophy in the rabbit could be prevented and cured by alpha tocopherol in the absence of the water-soluble factor. They were able to refute the previous report of Morgulis and his coworkers [16, 17] that rabbits fed Pappenheimer's diet "13", deficient in vitamin E, required two factors for the structural integrity of their skeletal muscles. The water-soluble factor was not required. The antidystrophy requirement of the rabbit for prevention and cure of nutritional muscular dystrophy was found to be 0.6 to 1.0 milligrams per kilogram of body weight for alpha tocopherol. Another interesting observation of Mackenzie and McCollum was the establishment of simple criteria for the development and improvement of nutritional muscular dystrophy. It was found that a great increase in urinary creatine invariably attended the deficiency, and preceded gross symptoms by at least two weeks. A marked reduction in urinary creatine occurred within twenty-four to forty-eight hours after starting the administration of vitamin E.

Two previous communications [21, 22] have called attention to the value of vitamin E in the treatment of primary fibrositis. Sydenstricker has called attention to the fact that the fat-soluble vitamins A, B, E, and K seem to be requisite for the maintenance and repair of certain specialized tissues. It has been the writer's contention that vitamin E is necessary for the prevention of the particular type of abnormal connective-tissue changes which occur in primary fibrositis and for the cure of this condition. John and Günther, Evans and his coworkers [3], and Smith [20] have shown that more than a single chemical substance can function as vitamin E. The list of substances include hydroquinone itself, various ethers of durohydroquinone, chromanes, coumaranes, coumarines, coumarones, and alpha, beta, and gamma tocopherols. Over forty of these compounds show vitamin-E activity. This is nothing new in the field of biological

chemistry, as similar conditions exist in the case of vitamin D, vitamin K, and the estrogenic hormones.

This report concerns itself with various chemical combinations, physical forms, and routes of administration of the tocopherols in the treatment of primary fibrositis. Wheat-germ oil which contains alpha, beta, and gamma tocopherols was first employed by the writer in the treatment of primary fibrositis. It had several drawbacks: It was unpalatable; and it caused gastric disturbances and skin rashes. The assay of total tocopherols varies with different batches of wheat-germ oil. The tocopherol content of a molecular distillate of vegetable oils contains a fixed quantity of the tocopherols. Twenty cases of primary fibrositis were treated with this preparation. These patients were given 120 to 240 milligrams of total tocopherols daily. Marked improvement was noted in all cases. Forty more cases of primary fibrositis have been treated with this molecular distillate. These patients received 300 milligrams of total tocopherols the first week and then 150 milligrams of total tocopherols daily. Most of these patients manifested improvement in a period of one week of such treatment, and all except five were completely relieved of their fibrositic symptoms. These five patients were relieved from pain, but not completely from generalized stiffness.

Hickman and his coworkers have found that 95 per cent. of the tocopherols administered by mouth are excreted in the faeces of healthy individuals. Therefore, it was decided to try the parenteral route. Nine patients with primary fibrositis were given 334 milligrams of mixed tocopherols (alpha, beta, and gamma tocopherols) intramuscularly at weekly intervals. All had severe local reactions, consisting of swelling, pain, and increased local heat at the site of injection. Two had systemic reactions, consisting of fever, nausea, and vomiting. All these patients were observed for a period of three weeks, at which time this mode of administration of the molecular distillate had to be stopped. All noted marked relief in their fibrositic symptoms, and one patient showed complete disappearance of the fibrositic nodules (Fig. 4).

Each of twelve patients with primary fibrositis was given 200 milligrams of synthetic alpha tocopherol in corn oil intramuscularly at weekly intervals. These patients were observed over a period of two to four months. All noted marked relief in their fibrositic symptoms.

The inunction route was tried in four cases; 0.30 cubic centimeters of 40 per cent. solution of the molecular distillate containing alpha, beta, and gamma tocopherols was rubbed into the skin daily. These patients were observed over a period of two months. They objected to the bad odor of the drug; the results were poor.

Two salts of the tocopherols were tried in twenty-two cases of various muscle disorders. Twelve patients received 0.065 of a gram of alpha tocopherol succinate capsules by mouth three times daily. These patients were observed for a period of two to four months. Nine cases of primary fibrositis were completely relieved. No relief was obtained in one

case of secondary fibrositis and two cases of psychosomatic rheumatism. Ten cases of fibrositis received 0.065 of a gram of gamma tocopherol palmitate three times daily by mouth. These cases were observed over a period of two to four months. Complete relief was obtained in six cases of primary fibrositis. One patient with secondary fibrositis noted mild relief, but this patient noted marked relief with the oral molecular distillate. One patient with secondary fibrositis noted moderate relief. No relief was obtained in one patient with combined sclerosis complicating pernicious anaemia, and in one case of osteitis deformans. Sixty cases of primary fibrositis have been successfully treated by the oral administration of a molecular distillate of the tocopherols. Twenty-one cases of primary fibrositis were treated successfully by the intramuscular injection of alpha tocopherol or the molecular distillate. Alpha tocopherol succinate and gamma tocopherol palmitate were successfully used in the treatment of fifteen cases of primary fibrositis.

These clinical experiments indicate that either the oral or parenteral routes are equally efficacious. The striking similarity between the pathological changes of primary fibrositis and nutritional muscular dystrophy is no mere accident. This fact, plus the marked clinical improvement obtained in both conditions by giving the tocopherols, indicate that primary fibrositis is a metabolic disorder concerned with the deprivation of vitamin E. This paper concerns itself only with the antidystrophy biological factor of vitamin E. The recommended dosage at the present time is 300 milligrams of mixed tocopherols daily for the first week, and 150 milligrams by mouth daily for the next two weeks. A maintenance dose of 100 milligrams daily may be continued indefinitely. The calculated maintenance requirement of 1 milligram of the tocopherols per kilo of body weight should suffice for the average individual.

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