

Original Articles

Dupuytren's Disease

Its Association With Abnormal Liver Function in Alcoholism and Epilepsy

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Dupuytren's disease (DD) was found in 25% of 60 men with alcoholism, and in 55% of patients with long-standing epilepsy who were receiving anticonvulsant therapy. Abnormal liver enzyme values were common in both groups (despite rare hyperbilirubinemia in alcoholics and abnormally low bilirubin in epileptics). Among alcoholics, those with DD had more elevated γ -glutamyl transpeptidase levels (81% vs 50%) and evidence of chronic liver disease. Among epileptics, those with

DD had more elevated alkaline phosphatase levels (78% vs 45%) and leucine aminopeptidase values (25% vs 4%). Among male epileptics, 71% had abnormal serum glutamic pyruvic transaminase and associated high creatine phosphokinase levels; these changes may suggest muscular involvement in DD. Patients with epilepsy on a regimen of anticonvulsant drugs should be checked for subtle evidences of abnormal hepatic function, as should all persons with DD.

with alcoholism is confirmed by finding a higher incidence of DD in patients with liver disease due to alcoholism (44.4%), than in those with nonalcoholic liver disease (18.8%).^{1,4} Wolfe et al⁵ also reported an incidence of DD of 66% in liver disease due to alcoholism. Other studies^{1,6} point to the fact that 33% to 50% of epileptics present evidence of DD (females, about 25%). Winslow and Suk (unpublished data), in a study of 1,934 epileptics, found an overall incidence of DD of approximately 20% with a slight difference between males and females (53%:47%). Hueston¹ suggests that the inheritance of a tendency to produce DD is in some way associated with the inheritance of an increased tendency to epileptic manifestations. Others,^{6,7} noticing widespread occurrence of Ledderhose disease, of knuckle pads, or of induratio penis plastica among epileptics, suggested some pathogenic connection between epilepsy or protracted phenobarbital treatment and these affections.

Dupuytren's disease (DD) is characterized by a degeneration of elastic fibers and thickening and hyalinization of the collagen fiber bundles in the palm, increasing with age. There is a sex difference in incidence (2:1, male:female) and more severe deformity in men. It appears to be confined to the white race and is often found in association with alcoholic liver disease, epilepsy, pulmonary tuberculosis, and chronic invalidism, but without relation to occupation.

The earliest observable change is a thickening in the palm, fixed to the palmar fascia, either localized as a nodule or extending as a plaque or

band to the fingers. Grosser signs of fascial retraction have been preceded by the less obvious palmar nodule, and the acceptance of this palmar nodule as the earliest sign is considered to give a true index of the incidence of DD (1% to 2% of the population¹).

In addition, there appears to be what may be termed a Dupuytren's diathesis. The freedom of oriental races from DD is an example of ethnic selectivity.² Racial or ethnic and hereditary factors (a positive family history in up to 40%) may interact to produce a varying strength of diathesis in different patients.³ The nodule, the band, or the contracture itself is often associated with other, so-called fibromatous affections (plantar changes or Ledderhose disease, induratio penis plastica, knuckle pads, and fibrosis mammae virilis), and should be regarded as a reparative hyperplastic growth of connective tissue as a reaction to regressive processes.

There is no doubt that DD accompanies other diseases. Association

One interesting fact deserves special attention. At the beginning of this century in the time when the association between DD and alcoholism was well known and documented, a study by Féré and Francillon (1902)⁸ mentions only one case of DD among epileptics. This finding is in favor of the possibility that the affection of the hand is a relatively new symptom in epilepsy. Féré and Francillon's statement dates, of course, from the time before phenobarbital therapy was introduced for epilepsy. The sug-

Received for publication Feb 8, 1971; accepted Sept 5.

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gestion that prolonged use of this drug could have contributed to the symptoms of DD is also supported by Lund's observations (1941)⁶ that, in 38 epileptics to whom phenobarbital (instead of bromide) was given for two years, only five showed the earliest changes of the palmar aponeurosis, whereas from the occurrence in epileptics treated with phenobarbital for many years, he would have expected 18 cases. This led Lund to suggest that constant treatment with phenobarbital over a period of years may contribute to the pathogenesis of DD among epileptics.

Like hydralazine, phenobarbital alone or in combination with diphenylhydantoin is able to produce the biologic alterations that are seen in systemic lupus erythematosus, rheumatoid arthritis, or scleroderma. And "phenobarbital rheumatism,"^{9,10} resembling shoulder-hand syndrome (which often accompanies DD¹¹), has been described in a patient who also developed palmar aponeurosis. A biopsy of the aponeurosis showed a fibrous structure, similar to that found in DD. Upon cessation of the phenobarbital therapy, the patient was cured and the palmar changes disappeared.

In a previous study¹² one of us (J.P.) has pointed to the fact that among accompanying diseases in patients with DD, there was frequent occurrence of stomach and duodenal ulcers, cholecystitis, hepatitis in history, diabetes, and liver cirrhosis. The frequent coincidence of DD with these diseases attracted our attention to what extent the hepatic lesion was accompanied by enzymatic changes. Not having found any outstanding changes in the levels of serum transaminases, we measured the activity of excretory enzymes, leucine aminopeptidase (LAP), γ -glutamyl transpeptidase (GGTP), and alkaline phosphatase, and found statistically highly significant elevation of LAP and GGTP with occasional changes in alkaline phosphatase also.¹² This suggested that DD has been often ac-

companied by a latent liver injury, shown by the disturbance of some liver enzymes.

We have assessed the frequency of DD in persons with alcoholism and persons with severe epilepsy who have been treated for many years with phenobarbital and other drugs. We attempted to determine whether there is a common liver injury in both groups, whether there is a demonstrable difference of liver injury in patients with and without DD and, finally, how often the patients with DD manifested their liver injury by a changed enzyme pattern in serum.

Materials and Methods

Two groups of patients were studied. The first consisted of 60 men, aged 26 to 75 (52 white, 8 Negro), with chronic alcoholism who were admitted consecutively with acute alcoholic intoxication to the Monroe County Psychiatric Hospital Unit. These patients were examined for evidence of DD and liver disease and fasting blood samples were collected on the day following admission. The second group consisted of 65 patients, aged 23 to 75 (30 women, 35 men; 59 white, 1 Negro) chosen unselectively from among those with epilepsy at the Craig Colony in Sonyea, NY, in whom epilepsy had been present for 7 to 71 years (more than 20 years in all but two). All had been treated for many years with phenobarbital, very often in combination with diphenylhydantoin, and some in addition with mephenytoin or primidone. These patients were examined and fasting blood samples taken as in the first group.

Ten determinations were made on serum from the blood samples, by the methods and with the limits of normal values as follows: alkaline phosphatase (Bessey et al¹³), up to 85 milliunits (mU)/ml; amylase (Caraway¹⁴), 60 to 160 units; total bilirubin (Malloy and Evelyn¹⁵), 0.3 to 1.1 mg/100 ml; creatine phosphokinase (CPK) (Rosalki¹⁶), 20 to 50 mU/ml; glutamic oxaloacetic transaminase (SGOT) (Karmen¹⁷ and Henry et al¹⁸), up to 50 mU/ml; glutamic pyruvic transaminase (SGPT) (Wroblewski and LaDue,¹⁹ and Henry et al¹⁸), up to 50 units; γ -glutamyl transpeptidase (GGTP) (Szasz²⁰), 3 to 20 units; lactic dehydrogenase (LDH) (Wroblewski and LaDue,²¹ and Henry et al¹⁸), up to 20 mU/ml; leucine aminopeptidase (LAP)

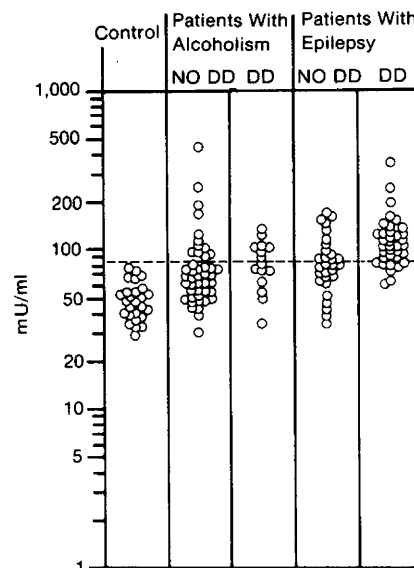


Fig 1.—Results of serum alkaline phosphatase determinations in milliunits (m-U) per milliliter. Control represents 27 hospitalized patients without known liver disease; no DD, no Dupuytren's disease; DD, Dupuytren's disease; and dashed line, upper limit of normal values.

(Szasz²²), 8 to 22 units; lipase (Cherry and Crandall²³), up to 1.0 units. The discrete sample analyzer (Beckman) was set for the kinetic determinations of these biological compounds²⁴ (with modifications by Radi-vojevic, unpublished data). In addition to usual standards, 27 "control" sera obtained from a hospitalized population (aged 26-73, mean 47 years; 13 women, 14 men) without known liver disease were also included; these showed no significant deviation from the limits of normal values stated previously.

For statistical analysis of the results, nonparametric techniques were used (X^2 and Wilcoxon test), inasmuch as the data from enzyme determinations were far from normally distributed even with logarithmic transformation (Figs 1 to 5).

Results

Among the 60 patients with acute and chronic alcoholism, 16 (25%) had DD. Of these, 12 had clinical hepatomegaly, 9 had erythema palmare, and 8 had spider angiomas.

Among the 44 alcoholics without DD, 22 had hepatomegaly and 8 had erythema palmare; none had spider angiomas. Hyperbilirubinemia was

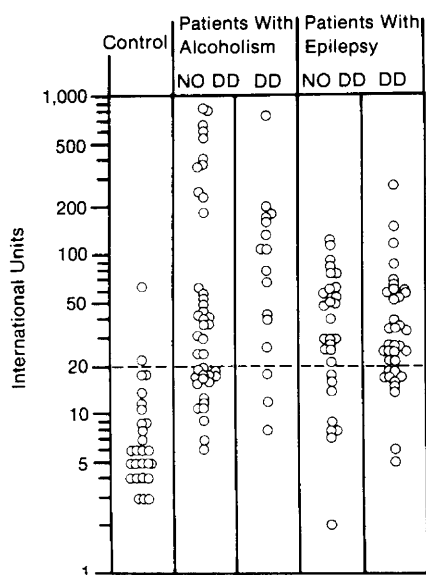


Fig 2.—Results of serum γ -glutamyl transpeptidase determinations. For abbreviations see Fig 1 legend. Dashed line signifies upper limit of normal values.

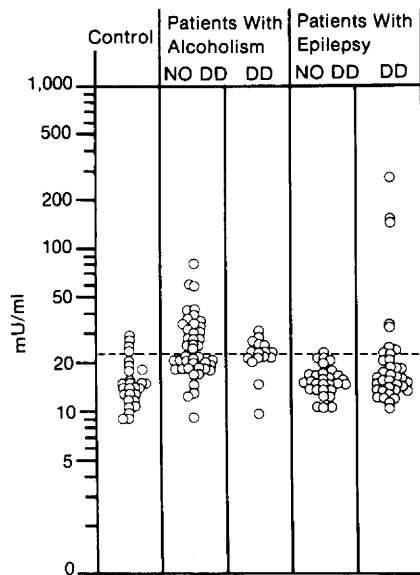


Fig 3.—Results of serum leucine aminopeptidase determinations. For abbreviations see Fig 1 legend. Dashed line signifies upper limit of normal values.

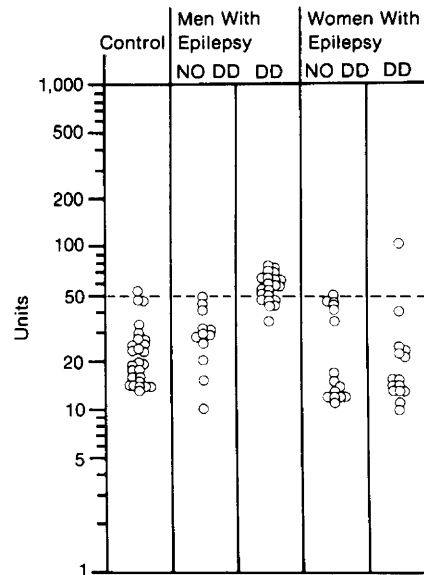


Fig 4.—Results of serum glutamic-pyruvic transaminase determinations. For abbreviations see Fig 1 legend. Dashed line signifies upper limit of normal values.

rare in both groups (2 with DD, 4 without DD). There were no Negroes among the alcoholic patients with DD and eight among those without DD. With two exceptions (one Puerto Rican and one third-or-more generation American), all alcoholic patients with DD were first or second generation Americans from central Europe.

As a group, the alcoholic patients with DD were older (range 40-65 years, mean 55.4 years) than those without DD (range 26-75, mean 46.3 years). Inasmuch as the appearance of DD is age- and race-related and the likelihood of liver disease probably increases with age in this population, comparisons were made between the 16 patients with DD and the 28 patients without DD who were white and 40 years old or older. Of the latter, 17 had hepatomegaly, 7 had erythema palmare, and 3 had hyperbilirubinemia. Erythema palmare was significantly more common among the alcoholic patients with DD than among those of the same race and age with DD ($X^2 = 4.33, P < .05, 1$ degree of freedom [df]).

Among the 65 patients with ep-

ilepsy of long standing, 36 (55%) were found to have DD. None of the epileptics had hepatomegaly, history of hepatitis, alcoholic liver disease, gall bladder disease, or diabetes. However, it is of interest that erythema palmare was present in 15 of the 36 patients with DD, but none of the 29 patients without DD. Total bilirubin level was low (0.11-0.24 mg/100 ml) in 38% of epileptic patients, without correlation with presence or absence of DD or erythema palmare.

Age was a factor in the appearance of DD: the mean age of epileptics with DD was 51 years, compared to 40 years for those without DD. There was no significant relation to sex (15 women, 21 men with DD; 15 women, 14 men without DD). The one Negro in the group, a man, had DD.

Noteworthy changes which appeared among enzyme activities measured, in both groups of patients, may be considered in three categories: (1) the hepatic "excretory" enzymes, alkaline phosphatase, GGTP, and LAP; (2) hepatocellular enzymes, SGOT, and SGPT; and (3) an enzyme derived primarily from muscle, CPK.

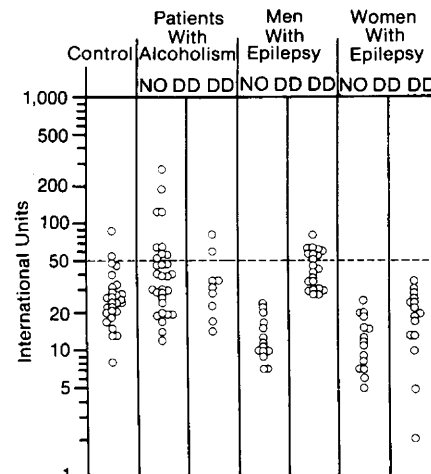


Fig 5.—Results of serum creatine phosphokinase determinations. For abbreviations see Fig 1 legend. Dashed line signifies upper limit of normal values.

Excretory Enzymes.—Alkaline phosphatase, the most commonly measured hepatic excretory enzyme, was elevated in 25% of the patients with alcoholism, with no significant difference between those with and without DD (Fig 1). Among the 36 patients with epilepsy who had DD, 28 (78%) had an elevated alkaline

phosphatase activity, while elevation occurred in only 13 of 29 (45%) of those without DD (Fig 1); this difference was significant ($X^2 = 7.48$, $P < .01$, 1 df). However, when age was taken into consideration, the differences were no longer significant; among white patients 40 years old or older, alkaline phosphatase activity was elevated in 25 of 30 with DD and 7 of 11 patients without DD. That is, the normal values for alkaline phosphatase were primarily among the larger group of younger patients: 12 of 18 such patients without DD had normal values, as did 3 of 5 with DD under age 40. There was no significant difference by sex among the epileptics.

The overall incidence of elevated alkaline phosphatase among the epileptics, none of whom had significant clinical evidence for hepatic disease other than occasional erythema palmaris, was significantly higher (63%) than among the patients with alcoholism (33%) ($X^2 = 11.65$, $P < .001$, 1 df). This difference was preserved when patients 40 years old or older were compared: 78% of epileptics vs 33% of alcoholics had abnormal alkaline phosphatase values. Similarly, comparison of male epileptics with male alcoholics did not significantly change the results: 54% of the former vs 32% of the latter had abnormal values ($X^2 = 4.73$, $P < .05$, 1 df).

Data on GGTP among alcoholics (Fig 2) revealed a greater frequency of abnormality than did alkaline phosphatase, and in addition, the alcoholic patients with DD had a significantly greater incidence of elevated values than those without DD (13 of 16 abnormal among those with DD, 17 of 34 abnormal among white patients without DD; $X^2 = 4.43$, $P < .05$, 1 df, among those of comparable age, 13 of 27 without DD age 40+ were abnormal, $X^2 = 4.51$, $P < .05$, 1 df). Among epileptics, 72% had elevated GGTP, with no significant difference between those with and without DD.

Leucine aminopeptidase showed the least number of abnormalities

among the excretory enzymes (Fig 3). Among the epileptic patients with DD, 25% had elevated LAP, some to striking levels, whereas only 1 of 29 without DD had a minimally elevated level. There was no relation between age and abnormality of LAP.

Among all patients studied, in addition to the GGTP being the most frequently abnormal test, there was a close correlation of abnormal alkaline phosphatase and LAP values, with abnormal GGTP values. Among 59 patients with an abnormal alkaline phosphatase activity in whom GGTP was done, 47 (80%) had an abnormal GGTP value. Similarly, among 41 patients with an abnormal LAP level, 35 (85%) also had an abnormal GGTP value. There was less correlation between abnormal LAP and alkaline phosphatase values. 20 of 41 patients with abnormal LAP also had abnormal alkaline phosphatase. Analysis by age did not change these relationships.

Hepatocellular Enzymes (SGOT and SGPT).—In many of the alcoholic patients both of these enzymes were elevated: overall, 52% of SGOT and 32% of SGPT values were abnormal; in 24% of patients both values were abnormal. There was no correlation with age or with presence or absence of DD.

Among patients with epilepsy, no SGOT values were abnormal. A peculiar pattern appeared for SGPT (Fig 4): all male epileptics with DD had high-normal to clearly abnormal SGPT levels, whereas one man without DD and two women (one with, one without DD) had abnormal SGPT levels. The differences in men with and without DD were highly significant ($P < .01$ by Wilcoxon test). There was no relation to age.

Creatine Phosphokinase.—Among alcoholic patients, 28% of those tested showed elevated CPK levels with no significant difference between those with and without DD (Fig 5). For patients with epilepsy, an unusual pattern similar to that seen with SGPT again appeared: all men with DD had

high-normal or abnormal CPK values (43% abnormal), whereas no men without DD and no women, with or without DD, had elevated values (Fig 5). There was a close correlation for abnormal CPK and SGPT levels: eight of nine patients with abnormal CPK also had abnormal SGPT values. There was no relation between age and abnormality of CPK.

Other enzymatic measurements showed occasional abnormalities. Among alcoholic patients, lipase was elevated in four of 15 of the group with DD (1.6, 1.8, 2.6, and 35 units, respectively, the very high value occurring in a patient with a bilirubin level of 12 mg/100 ml), and in eight of 39 of the group without DD (1.1 to 1.7 units). Amylase was normal in all patients with DD, elevated in five of the 44 patients without DD (166 to 201 units)—in four instances occurring in patients with elevated lipase. Lactic dehydrogenase level was elevated in two of 15 patients with DD (206 and 360 units) and in eight of 44 without DD (201 to 390 units). With none of these determinations were there statistically significant differences between those with DD and those without DD. In epileptic patients all lipase and LDH determinations were normal. Amylase was minimally elevated in two patients (162 and 183 units), one with and one without DD.

Comment

These results demonstrate (1) high frequencies of occurrence of DD among unselected patients with alcoholism and with epilepsy on a regimen of prolonged anticonvulsant therapy; (2) high frequencies of abnormalities of hepatic excretory enzymes in both patient groups despite rare evidence of gross impairment of liver function; (3) associations of the presence of DD with clinical evidence of liver disease and with certain enzymatic abnormalities; and (4) an association of age with DD but only to a limited degree with the enzymatic abnormalities. Among the patients with alcoholism, there was a significant as-

sociation of DD with elevated GGTP; among patients with epilepsy, there was a significant association of DD with elevated alkaline phosphatase, LAP, and (among men only) SGPT and CPK. Of these, correction for age eliminated the statistical significance of only one: DD with alkaline phosphatase in epileptics.

Thus, epileptics taking phenobarbital may well not have normal hepatic function despite frequently low serum bilirubin levels.²⁵

What is the common link between ethanol and phenobarbital, supposing that these drugs were mostly responsible for the frequent evidence for hepatic dysfunction shown here both in alcoholics and in epileptics? Ethanol plays several distinct roles in the animal or human organism. Most widely appreciated is its effect on the central nervous system and its hepatotoxic effect leading to hepatic steatosis, liver cell damage, and, in some patients, eventually to cirrhosis. Of more relevance here is the fact that ethanol acts as a drug similar to phenobarbital or diphenylhydantoin. The long-term administration in the rat and in man of ethanol or one of these drugs produces similar changes: hypertrophy and vesiculation of smooth surfaced endoplasmic reticulum in hepatocytes.²⁶⁻²⁸ At the same time hepatic lipids and the activities of drug-metabolizing enzymes (aniline hydroxylase and nitroreductase) are increased. Ethanol administered for 12 days to human volunteers was found to result in a doubling of hepatic pentobarbital hydroxylase.²⁹ Further increase of microsomal cytochrome P₄₅₀, with possible implications for porphyric metabolism, increase of cholesterol biosynthesis, inhibition of the metabolism of other drugs and oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent, aerobic microsomal enzymes, follow.

It is clear that both ethanol and phenobarbital greatly interfere with organelles and their enzyme functions in hepatocytes. It was demon-

strated in Kühn's and Richter's recent experiments³⁰ in rats with artificial cholestasis, which had been treated with phenobarbital or cycloheximide, that there was an increase in the excretory enzymes, alkaline phosphatase and LAP, and the hepatocellular enzyme SGPT, in addition to the rise of bilirubin and cholesterol levels. The frequently low plasma bilirubin levels in epileptics is usually explained by the persistent induction of glucuronyl transferase or by increased secretion of bilirubin from the hepatic cell. How bilirubin is excreted from the hepatic cell is unknown; it appears to utilize a pathway different from that of bile salt secretion. In any event the elevation of the excretory or bile enzymes, alkaline phosphatase, GGTP, and LAP, in serum are probably more the reflection of their increased synthesis in the liver cell than a sign of an impaired excretion; the concept of cholestasis thus resembles the pathologic anabolic reaction as it was described by Popper.³¹

Richens and Rowe³² have also recently reported elevated alkaline phosphatase values in 29% of epileptics receiving long-term anticonvulsant therapy. They separated the alkaline phosphatase into its "liver" and "bone" isoenzymes, and found frequent increases in both: of 160 patients studied, 28 had elevated alkaline phosphatase confined to the liver isoenzyme, 18 had elevated bone isoenzyme. In the present study, although isoenzyme separation was not attempted, the high degree of correlation (85% among epileptic patients) of elevated alkaline phosphatase with elevated GGTP, another hepatic excretory enzyme, strongly suggests that most of the alkaline phosphatase elevation was of hepatic origin.

We have been surprised by our observation of the increased serum CPK levels in 25% of epileptic men with DD and no instances of elevated CPK in epileptics without DD. In our set of epileptics with DD presenting elevated CPK, with one exception, there

were either bilateral III-IV degrees of DD (according to the classification of Moorhead,³³ i.e., advanced changes) or even combination of Ledderhose disease with DD. This group included the most typical clinical cases of DD of our whole study. It is also interesting that all of these patients showed at the same time the elevation of the hepatocellular enzyme SGPT (with one exception whose SGPT was at the upper limit of normal). The elevation of CPK in alcoholics (with or without DD) has been better known since Nygren's description³⁴ of a "muscular syndrome" in alcoholics and since the observation³⁵ that even in alcoholics without the muscular syndrome there are always minor signs of abnormalities in the muscle biopsy specimens.

In spite of the fact that the primary lesion in DD is in fibrofatty tissue, there are some suggestions of the participation of muscles in this disease. The earlier theory of Krogius,³⁶ that the new tissue arises from residues of embryonic muscle in the palm, has been revived by Stein et al³⁷ who, on the basis of "bundles of spindle cells which take tinctorial shadings suggestive of muscle," proposed muscle involvement in DD. MacCallum and Hueston³⁸ thought that a conversion of striated muscle fibers to Dupuytren's tissue can in some specimens be demonstrated where the nodules at operation had been adherent and merging with formed skeletal muscle masses (palmaris brevis, etc). There is no doubt that there are continuous functional and anatomic changes going on in the inactive striated muscle group in proximity to Dupuytren's contractures. A difference in the peripheral vasomotor function between the hand with DD and the normal hand probably contributes to the state of peripheral muscles of the hand in question.⁵ The most specific and sensitive enzyme for all muscle disease is CPK which appears also to reflect a sex-related difference, somewhat lower average values of enzyme being ob-

served in women than in men. It must be emphasized, however, that the variations of CPK activity merely reflect underlying disturbances in muscle metabolism, the biochemical etiology in many muscular diseases or dystrophies being as yet undefined.

What is the nature of the relation between DD and hepatic dysfunction?

For ultimate clarification, histologic and histochemical studies of liver and other tissues beyond the scope of this investigation would be necessary. At this time we may only speculate that DD is one of several manifestations of a reparative hyperplastic growth in certain people with a fibromatous hereditary tendency.

Thus, Noel Fiessinger's aphorism "Ne devient pas cirrhotique qui veut" (he does not become cirrhotic who wishes), might also be paraphrased, "He does not manifest DD who wishes."

Susan Hanson, MD, and Philip M. Winslow, MD, made their patients available for these studies. Blood samples were collected by Marilyn Gordon.

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