DRUG-INDUCED LOCALIZED SYSTEMIC SCLEROSES

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I am happy to be asked, as an emeritus member, to return to this meeting of the Clinical and Climatological Association in order to go right on talking about the subject I first brought to your attention in 1966, namely, localized systemic inflammatory scleroses (1). Ormond, in 1948 (2), had shone a light on one of them, retroperitoneal fibrosis, and others gradually appeared out of the back rooms and corners of the body to form a "Falstaff's army" of diagnostic odds and ends and remnants, each with its own nickname and unusual character. I was telling you at that time how a two line mention in the New England Journal of Medicine in 1964 (3) of two cases of retroperitoneal fibrosis associated with our use of methysergide for migraine headache had stimulated a flood of correspondence and a collection of cases which led us, eventually, to conclude that this drug was probably, in part, responsible for the development of several of these fibroses in the retroperitoneal, the pleuro-pulmonary and the endocardial spaces (4).

This unique finding of a drug producing localized fibroses has stimulated increased knowledge about these conditions and their etiology since that time. My goal today is to tell you about some of these developments. Incidentally, I am all in favor of "Letters to the Editor" that bring such observations, whether regarding dangers or benefits, to the attention of the professional public, as long as they are labeled as *observations*, not *proofs*. Single anecdotes need aggregation to make a true story, but if not recorded they sink without a trace into the oeean of ignorance.

Table 1 shows the areas in the body in which these entities are now know to take place idiopathically. There are nineteen of these listed (5) and I have recently learned of three or four more which possibly should be added: the lacrimal and salivary glands (6), the lateral carotid triangle (7) and, possibly, the posterior pituitary (8).

Drugs are now known, with varying degrees of reasonable assurance, to be related to development of these fibroses in thirteen of these locations of the "idiopathic" group. They are listed in Table 2.

Table 3 presents a list of 23 localized fibroses of which we may count 14 with varying degrees of certainty (represented by the number of pluses from one to three) which are at times related to the use of certain drugs, 11 with positive *familial occurrence*, 22 which have occurred, at one time

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TABLE I

Localized Systemic Inflammatory Fibroses-Locations

Retroperitoneal Space	Neck
Peritoneal Cavity	Orbit
Mediastinum	Eye
Pericardium	Hand and Foot
Pleural Cavity	Penis
Lung	Testicle
Heart Wall and Lining	Skin
Major Arteries	Knuckles
Biliary Tree	Ear
Pelvis	

TABLE II

Fibroses Related to Drug Therapy-Locations

Retroperitoneal Space	Peritoneal Cavity
Pleuro-pulmonary Space	Mesentery
Pericardial Space	Eye
Endocardium	Orbit (?)
Great Vessels	Penis
Pelvic Space	Skin
Lungs	

or another, in patients suffering from one or more of the other localized fibroses we are talking about, and 13 which have occurred as one feature of generalized disorders of collagen. In the case of endomyocardial fibrosis, reported chiefly from Africa, there may be tribal influences at work, such as diets high in serotonin-containing foods, and it is well recognized that keloids are more common in Blacks, thus implicating possible racial trends (5).

The pathology of these conditions, whether "idiopathic" or drug-induced, although ranging widely in acuteness and/or chronicity, follows certain similar lines for all of them. Table 4 shows this order of events.

Table 5 shows the tissues affected in the chosen locations. Fat, fascial planes and areolar tissues, serosal surfaces, outer vessel walls, cartilage, heart valves and chordae tendineae, tendon sheath coverings, tumor surfaces and fascia. A common feature among them is that they are mostly structural tissues with low metabolism and relatively low blood supply and flow.

Table 6 lists a number of diseases in which, from time to time, our family of localized systemic scleroses take a part. I would like to call attention especially to the carcinoid syndrome in which serotonin produced by the carcinoid tumor is delivered into the general circulation and causes endocardial fibrosis and, at times retroperitoneal and other localized scleroses (9, 10).

TABLE III

Scleroses and Likelihood of Association with Drugs

Name of Disease	Due to Drugs	Familial Occurrence	Related to Other Localized Scleroses	Related to Generalized Disorders of Collagen
Major "Visceral" Scleroses				
Retroperitoneal Fibrosis	+++	++	+++	++
Endocardial Fibrosis	+++	0	+++	+++
Mediastinal Fibrosis	++	+	+++	0
Pleuropulmonary Fibrosis	++	0	+++	++
Pulmonary Fibrosis	+	0	+	+++
Pericardial Fibrosis	+	0	++	+++
Endomyocardial Fibrosis	0	+	0	0
Endovascular Fibrosis	++	0	++	0
Perivascular Fibrosis	+++	0	+++	0
Sclerosing Cholangitis	0	+	+++	+
Carcinoid Syndrome	0	0	++	++
Intraperitoneal Fibrosis	++	0	++	+
Retractile Mesenteritis	+	0	+	0
Cirrhosis	0	+	+	0
Epilepsy	0	0	+	0
Minor "Superficial" Scleroses				
Oculo-muco-cutaneous Sclerosis	+++	0	+	0
Dupuytren's Contracture	0 (?)	+++	+++	++
Riedel's Struma	0	+	+++	+
Pseudotumor of the Orbit	+	+	+++	+
Peyronie's Disease	++	+	++	0
Balanitis Xerotica Obliterans	0	0	+	+
Keloids	+	+++	++	+
Garrod's Knuckle Pads	? 0	0	++	? 0
Testicular Fibrosis	0	+	+	0

Suggestive = +.
Suspicious = ++.
Certain = +++.

TABLE IV

Pathological Changes (in order of their appearance)

1. Lymphocytic infiltration of fat, fascia, serosa or areolar tissues
2. Plasma cell infiltration (occasionally polymorphs and eosinophiles)
3. In some patients inflammatory involvement around or in walls of arterioles and venules
4. Occasionally necrosis
5. Fibrosis, resorbable in early stages, later non-resorbable

Figure 1 shows the chemical formulae for serotonin and methysergide. Methysergide, which is now known to produce these same fibrotic conditions in susceptible people, has a chemical structure very similar to that of serotonin. Thus, it is fascinating to find that the details of the pathology

TABLE V

Tissues Involved in Pathologic Process

Fascial Planes
Areolar Tissue
Fat
Serosal Surfaces
Vessel Walls
Cartilage
Heart Valves and Chordae Tendineae
Tendon Sheath Tissues
Tumor surfaces and Fascia
? Lymphatics

TABLE VI

Occurrence of Sclerosis as a Feature of Other Diseases

Rheumatoid Arthritis
Rheumatoid Spondylitis
Wegener's Granulomatosis
The Carcinoid Syndrome
Desmoplastic Tumors
Lymphosarcoma, Lymphoma, Hodgkin's Disease
Ulcerative Colitis and Crohn's Disease
Cirrhosis of the Liver
Epilepsy

of the heart valves in both carcinoid heart disease and the valvular lesions produced by methysergide show the same unusual feature, namely, a plaque of collagen deposited on the surface of an otherwise healthy valve, quite a different lesion from the destructive fibrosis of the valve itself seen in rheumatic heart disease. This unusual collagenous plaque on the valve surface has been seen in all the valves of the six patients examined by us whose lesions were related to methysergide therapy (Figure 2).

Desmoplastic tumors and members of the lymphomatous group of diseases may present as mediastinal, retroperitoneal or biliary tree fibroses (5, 11). Multiple biopsies may be needed to avoid missing the underlying tumor. Selective aortography of the lumber vessels may also help to identify these pre-operatively (12). Ultrasound and body CAT scan (as shown in Figure 3) may be very useful in localizing, diagnosing and following up these fibrotic conditions and the tumors sometimes associated with them (13, 14). Caval venography, as shown in Fig. 4, through the femoral vein, may also be very useful in showing where fibrotic lesions are in the retroperitoneum, and in revealing large collaterals that could interfere with surgery in the pelvis (15, 16).

The increased incidence of ulcerative colitis and Crohn's Disease with certain of these fibroses is of interest, especially retractile mesenteritis,

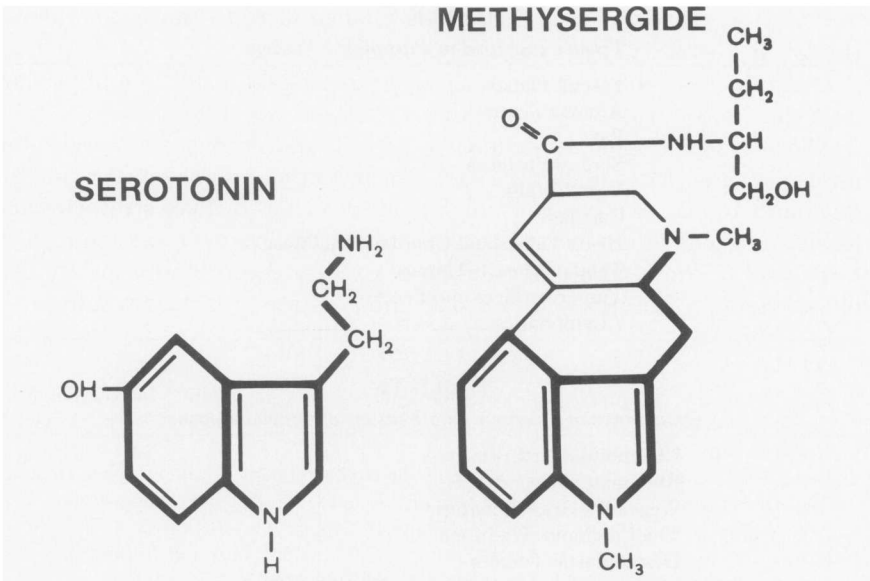

FIG. 1. Chemical formulae for serotonin and methysergide.

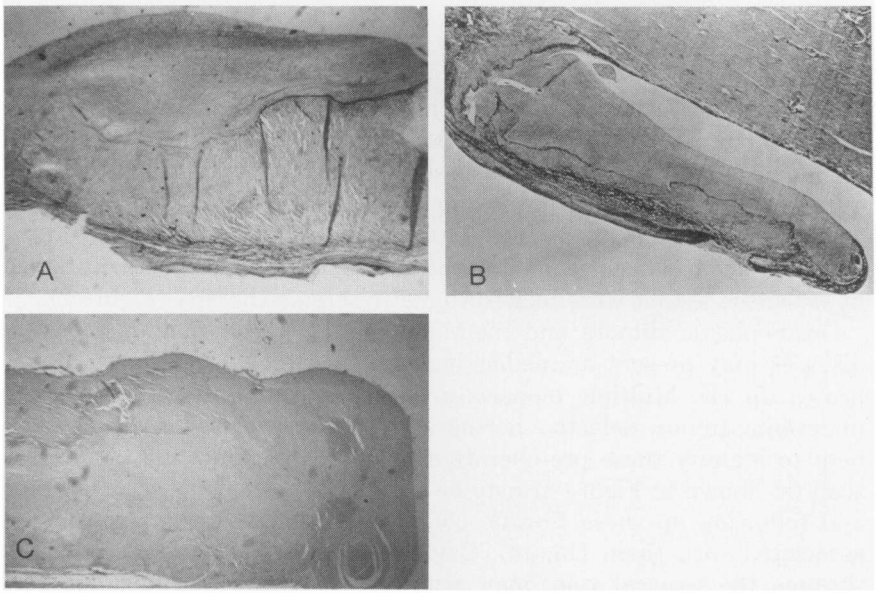

FIG. 2. Methysergide-induced fibrosis of mitral valve (A). (Pathological material was supplied by the late Dr. Donald S. Munroe of Vancouver.) (B) mitral valve from the carcinoid syndrome (Courtesy of Drs. Roberts and Sjoerdsma of National Institutes of Health.) (C) A mitral valve from a patient with rheumatic heart disease. The "methysergide" valve and the "carcinoid" valve both show a plaque of collagenous material superimposed on a normal valve, whereas the rheumatic valve is itself replaced by fibrosis and calcium.

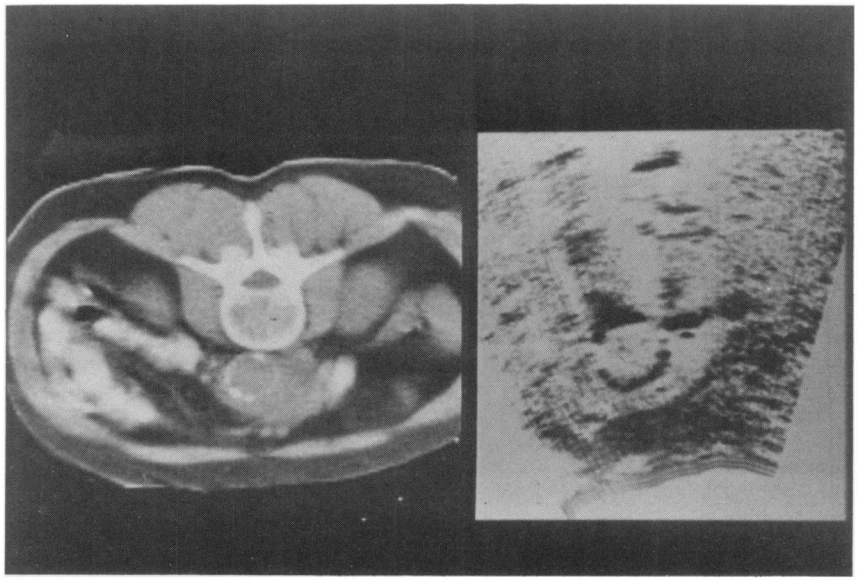

FIG. 3. Ultrasound and CT scan of patient with retroperitoneal fibrosis. Thick plaque of fibrotic material is observed stretching over the aorta.

sclerosing cholangitis and retroperitoneal fibrosis (17–19). Dupuytren's Contracture is a talisman to warn of other underlying fibrotic conditions, such as cirrhosis of the liver and epilepsy (20), especially in those patients taking anti-convulsant therapy.

Table 7 shows the drugs which have definitely been associated with the development of these fibroses and several that have a suggestive but as yet unproved relation are labeled with a question mark. In any case, they should not be used in anyone who has had one of these fibroses for fear of reactivation of the process. This is particularly true of ergot derivatives, of which LSD is one, and of hydralazine which is well known to create a lupus-like syndrome (21–25).

Perhaps the most important message I have to bring to you is that there is growing evidence that beta-blocking agents, such as practolol, propranolol and metoprolol, have now been suggestively associated with the development of several of these localized systemic scleroses, especially in the peritoneal cavity in the form of fibrous peritonitis; in the eye as a severe sclerosing inflammation of the conjunctiva, sclera and cornea (oculo-muco-cutaneous disease) with the consequent withdrawal of practolol from the British market; and in the shaft of the penis as Peyronie's Disease (or penile strabismus as the French so quaintly put it) (5), (26–40). These conditions are elusive and often escape the attention of the patient for quite a while, and even of the doctor. They must be rare

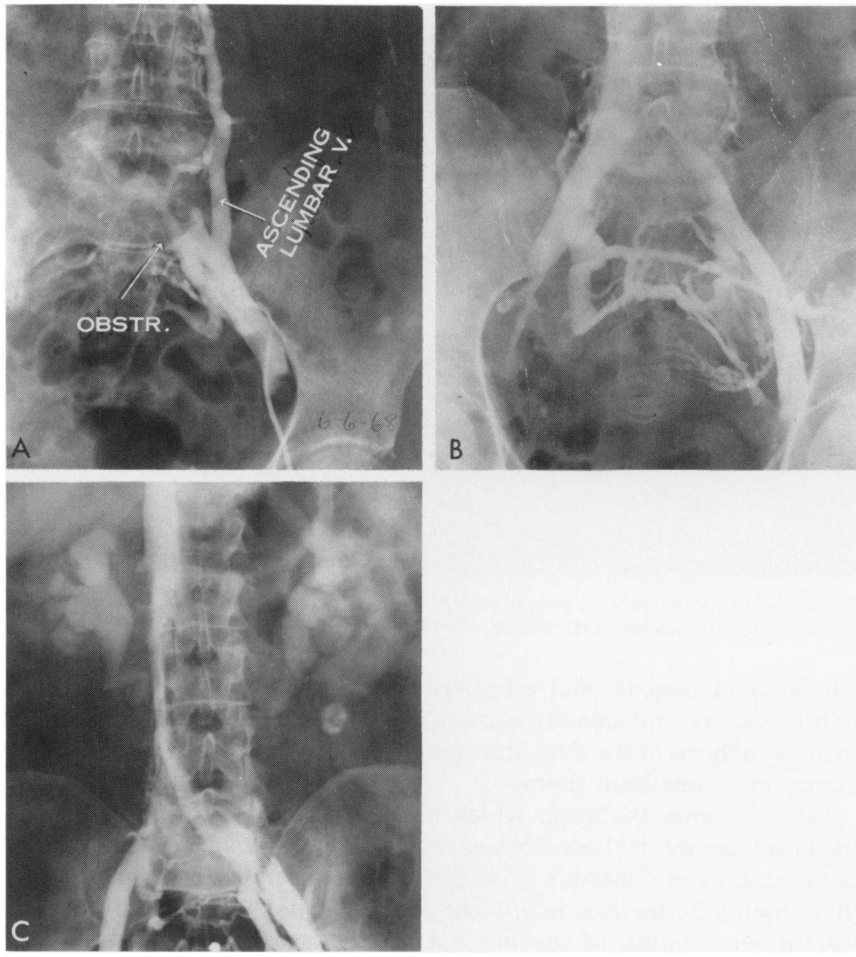

FIG. 4. Venacavography via the femoral vein demonstrates in (A) a block of the iliac vein above the ascending lumbar vein which is much enlarged; in (B) a block in the left iliac vein below the lumbar veins causing gross enlargement of collateral veins crossing the pelvis to the right iliac vein; in (C) a large meniscus of fibrosis partially obliterating the lower vena cava (and greatly dilated renal pelves).

among the millions who now take beta-blockers. But, of 146 patients who presented to Pryor and Kahn for Peyronie's Disease, 19 had been taking beta-blockers for over six months, whereas no one in a similar group presenting to them for bladder-neck surgery had taken them at all (41).

This leads me to conclude with some theories. Table 8 suggests some theories that have been proposed (42–47) some of which are undoubtedly

applicable to some cases, such as retroperitoneal hemorrhage, urinary extravasation, infection, and 16 reported cases of retroperitoneal fibrosis developing around the site of abdominal aneurysms. The lists on the right suggests immune mechanisms. In selecting an hypothesis for an explanation that could include most of the elements which appear on the right side of the table, I vote for the "Non-pulsatile flow theory" (Table 9).

TABLE VII

Drugs Involved in Fibroses

Methysergide	Practolol
? Ergotamine	? Propranolol
? Dihydro-ergotamine	? Metoprolol
?? LSD	? Analgesics
? Hydralazine	? Anticonvulsants
? Methyldopa	

TABLE VIII

Theories Regarding Etiology of These Fibroses

Trauma	Vasculitis
Hemorrhage	Autoimmune Reaction
Urinary extravasation	Haptene-drug Reaction
Aneurysm	Vasoconstriction
Infection	Serotonin-like Effect
Fat Necrosis	Alpha-1-Antitrypsin Deficiency
Talc	Non-pulsatile Flow Theory
Radiation Therapy	
Desmoplastic Tumors	
Postoperative Reaction	

TABLE IX

Non-Pulsatile Flow Theory

1. Lesions occur in tissues with relatively low blood supply.
2. Constriction effect of ergot-like drugs (methysergide, LSD, ergotamine) cuts down already small blood supply.
3. Beta-blockers a) reduce inotropic force of heart thus decreasing peripheral pulsatile blood flow and b) decrease vasodilatation.
4. Resulting ischemia leads to tissue damage.
5. Products of tissue damage produce auto-immune inflammatory reaction leading to fibrosis.
6. If stimulus is removed, early collagen formation regresses. After collagen fibers develop fascicular bindings, they do not regress.

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DISCUSSION

DR. THORN (Boston): I think we all owe a great debt of gratitude to Jack Graham bringing all these aspects to our attention and I have had about 200 patients that I can comment on. During the 40's and 50's when we implanted pellets of desoxycorticosterone every subcutaneous implant had a nice capsule of fibrous tissue around the pellet which gave the patient a year of continuous therapy. In that instance the fibrosis was a helpful thing because the capsule delayed the absorption of the DOCA pellet. In contrast a cortisone pellet came right up through the skin and never produced any fibrous tissue. I was interested in the close chemical relationship between methysergide and the steroid

nucleous effect as to whether this might or might not be a factor. The other area in addisonian patients were the calcified ears and contracted tendons. So we had two very interesting examples of a specific reaction to an identifiable chemical compound which increased fibrotic reaction.

DR. GRAHAM: Thank you George, very much. There is some work on the direct effect of serotonin on tissues in animals in which it is shown that the use of steroids may influence whether you get the fibrosis or not.

DR. BEAN (Iowa City): Jack, that was a fascinating study. I think to set the record straight you ought to recall that William Osler using the alias of Egerton Yorick Davis in the early 1880's discussed Peyronie's syndrome as "strabismus of the penis." Now the French may have been ahead of that but I doubt it.

DR. GRAHAM: Well, they cling to it, let us say. Actually, some of these fibroses were described a long way back. Retroperitoneal fibrosis is well described by people like Albarran a hundred years or so ago. They have gradually been put together as time has gone by.

DR. CHALMERS (New York): That's a superb example of how there's no end of fundamental discoveries that can be made by clinical observation. I wondered why you had a question mark by the drug relationship of Dupuytrens. Isn't it associated with the drug alcohol along with cirrhosis of the liver? I had one objection to your pathophysiologic rationale in that it seems to me that people with Dupuytrens and people with cirthosis have warm hands rather than cool. Maybe it's a redistribution of the circulation in the hands, rather than decrease in circulation to the hand.

DR. GRAHAM: Thank you Tom. I try to bend over backwards in being careful about casual associations between drugs and diseases in an etiological sense. In that first slide a large table showing plusses, I used 1 plus for "suggestive," 2 plusses for "suspicious" and 3 plusses for "certain" relationships. I think that the most certain relationship one can establish between a drug and a condition it supposedly might have been causing is that the disorder not only comes when the drug is used but also that it regresses when the drug is withdrawn and comes back when that drug or a similar drug is used again. It would be hard to make all of the correlations I talked about fit those postulates. Consequently, in others I've placed a question mark or less plusses by them to indicate that they are definite examples of these associations but one cannot say with certainty that the relation is one of cause and effect. However, they're so suspicious, as the original retroperitoneal fibroses from Sansert were, that in the course of time one was able to establish more firmly the associations. The nonpulsatile blood flow theory in already deprived areas is only a theory and hypotheses. I have not made careful studies of these deprived areas like tendon sheaths, areolar tissues and so forth to know that they have such compromise to their blood flow. But in general it seems to me they look that way grossly and that a small blood flow, now affected by vaso-constricting or anti-dilatory medication, may suffer more, and their tissues may suffer more, when the force with which the blood is driven through them is diminished so as to seriously compromise the effective circulation. In regard to the way people with cirrhosis and some other conditions that you mentioned, have warm hands I should point out that the blood supply in the body can be cold in one place and warm in another, especially in headache subjects. I know there are cold hands and warm heads during migraine. It could be that the circulation in the tendon sheaths and areolar tissues of the cirrhotic's hands is decreased despite the "palmar flush" of the superficial tissues.