

# Treatment of Intra-abdominal and Abdominal Wall Desmoid Tumors With Drugs That Affect the Metabolism of Cyclic 3', 5'-Adenosine Monophosphate

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A female patient with Gardner's syndrome was treated with  $\Delta^1$ -testolactone (200 mg daily) because of growth of a large desmoid tumor in the pelvis and lower abdomen and a tumor in a scar from a previous laparotomy. There was also pain and swelling of the left leg. An immediate effect of the drug therapy was complete relief of pain followed shortly thereafter by disappearance of the edema of the leg. After two months, the numerous sebaceous cysts were less prominent. The gross measurements of the diameter of the pelvic and lower abdominal tumor clearly demonstrated tumor shrinkage following therapy. Small polyps scattered over the rectal mucosa and numerous osteomata were not demonstrably affected. After one year of treatment with  $\Delta^1$ -testolactone, a laparotomy for partial small bowel obstruction was necessary. Obstruction was caused by the involvement of small bowel mesentery and the bowel itself in a contracted residuum of dense fibrous tissue. Substitution of theophylline and chlorothiazide for the testolactone in January 1974 was followed by further diminution of the measurable abdominal and pelvic desmoids. All of these compounds synergize the action of 3', 5'-adenosine monophosphate and at least the latter two may function by inhibiting the action of 3', 5'-adenosine monophosphate diesterase.

THE TREATMENT of patients with Gardner's syndrome is unsatisfactory in many respects. Polyposis of the colon has usually been considered sufficient indication for subtotal or total colectomy to prevent development of carcinoma. On the other hand, polyps of the duodenum usually have been kept under observation or excised locally, and polyps of the small intestine have been similarly managed except when malignancy developed. Various palliative operations have been carried out for desmoid tumors in the abdominal cavity, retroperitoneal area or abdominal

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wall but these lesions are often inoperable, amenable to only partial excision or capable of removal only with great risk of complication and mortality.<sup>13-15,23,25</sup> Furthermore, local recurrence is common and outright fibrosarcoma development from tumors whose early growth patterns and histologic characteristics have appeared benign has been reported.<sup>5,8-10,17,23,25,33,36-38,44,45,47,50</sup> The biologic problems of desmoid tumor control are related to such non-neoplastic lesions as retroperitoneal fibrosis,<sup>25</sup> juvenile fibromatosis,<sup>26</sup> congenital generalized fibromatosis<sup>4,43</sup> and other poorly characterized pathologic conditions.<sup>3,26,12</sup>

This report concerns the chemical treatment of intra-abdominal and abdominal wall desmoid tumors with  $\Delta^1$ -testolactone for one year and then attainment of further improvement over a six-month period when the patient was taking theophylline (Choledyl (R<sub>x</sub>)) and chlorothiazide (Diuril (R<sub>x</sub>)). These compounds are inhibitors of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE). There is an extensive literature concerning the *in vitro* effects of cAMP on tumor cells.<sup>7,16,20-22,24,30,39,40,42,51</sup> Growth of tumors can also be inhibited *in vivo*.<sup>11</sup>

## Case Report

C.G.H. No. 382891. A 23-year-old woman entered Colorado General Hospital April 11, 1971 with a diagnosis of familial Gardner's syndrome. She was known to have had colon polyps for nine years since the time of the first examination of the colon. Admission was prompted by radiographically demonstrated rapid growth of polyps in the transverse colon. Other stigmata of Gardner's syndrome included a presumed desmoid tumor underlying and involving an old appendectomy scar in the right

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Date	Transverse cm	Vertical cm	Protrusion beyond anterior iliac spine	Silhouette to approximate scale
Jan. 1973	15.0	7.0		
March 1973	12.0	7.0	4.5	
June 1973	9.5	6.5	4.0	
Sept. 1973	9.0	10.5	3.5	
Jan. 1974	7.5	14.0	1.5	
June 1974	6.5	6.5	1.0	

TABLE 1. Measurements of pelvic tumor. These measurements are approximate and represent the presentation of the tumor anteriorly. As the intra-abdominal tumor mass decreased in size, the abdominal wall mass became evident. This is believed to account for the changed general shape of the tumor and the apparent increase in the vertical dimension after six months. See case report for details. No sketch of the tumor was made in June 1973.  $\Delta^1$ -testololactone was administered in 1973, chlorothiazide and theophylline thereafter.

lower quadrant, multiple sebaceous cysts and osteomata in the ribs, mandibles, calvarium and pelvis. Several subcutaneous desmoid tumors had previously been removed from the abdominal wall. There was a history of frequent migraine headaches and of duodenal ulcer demonstrated radiographically. The patient's mother, maternal grandmother, two uncles and an aunt had Gardner's syndrome. Only one uncle still survived at this time, the affected relatives having died of desmoid tumors and/or complication of the primary disease. Numerous laboratory tests on the patient were all normal except for the results of radiologic examination of bones and colon. On April 14, 1971 subtotal colectomy, splenectomy and partial resection of the diaphragm were carried out. The latter organs were removed because of the presence of a fibrotic mass overlying the upper pole of the spleen and involving the diaphragm. It was initially thought to be a malignancy. Bilateral tubal ligation was performed. The polyps in the colon were benign and the mass involving the spleen and diaphragm was made up of acellular fibrous tissue. The patient's convalescence was complicated by left lower lobe streptococcal pneumonia and serous pleural effusion. The response to antibiotics was satisfactory and the patient experienced uneventful convalescence from that time on.

In January 1973 the patient was hospitalized again for removal of enlarging abdominal wall and pelvic desmoids. For several months she had had pain radiating down the left thigh posteriorly and medially. In addition, the left leg and foot became swollen when she remained upright to carry on her work as a beautician. There was a hard, fixed mass (15 × 7 cm) involving the lower abdominal wall and bony pelvis which was considered inoperable because of its size and fixation to surrounding structures. Previous

descriptions of the desmoid tumor were meager with no recorded measurements. Osteomas in the mandibles, ribs and pelvic bones were again noted. A 2 × 3 cm firm tumor mass had grown in the center of the laparotomy scar. A few mucosal polyps in the remaining rectum were noted. Because the desmoid tumor in the lower abdomen and pelvis was symptomatic and considered inoperable, the patient was started on  $\Delta^1$ -testololactone (Teslac [R<sub>x</sub>]) in a dose of 50 mg four times daily by mouth. The patient provided a clue for this approach when she related that the numerous sebaceous cysts over her body, particularly on her scalp and face, had enlarged when she was taking birth control pills and receiving injections of provera for six months in 1969 and 1970. They regressed somewhat when this medication was stopped.

The patient was re-evaluated in March 1973. She had no further pain in the left thigh. Whereas she had been previously taking Darvon daily, she had taken only two tablets after hospitalization in January. There was no swelling of the foot and leg even though she customarily worked 12 hours a day. The tumor in the laparotomy incision had gradually disappeared, leaving only a thickened area. The transverse diameter of the abdominal and pelvic desmoid, previously 15 cm, was recorded as 12.0 and 13.5 cm by two different observers (Table 1). The vertical measurement in the midline was found to be 7.0 and 7.5 (previously 7.0). Twelve mucosal polyps in the rectum were fulgurated. The patient was discharged back to her home in Wyoming with instruction to continue the  $\Delta^1$ -testololactone, 200 mg daily.

The patient was re-evaluated in June 1973. The desmoid was irregularly contracted. The transverse diameter was 9.5 cm and the vertical diameter was 6.5 cm. In contrast to the previous fixed status, the mass was now movable in all directions. About one month previously there had been a 24-hour episode of pain and tenderness in the tumor after which it became softer. Frequent nausea, occasional vomiting and increased frequency of loose stools occurred, possibly as side effects of the  $\Delta^1$ -testololactone. There was a definite increase in acne but the sebaceous cysts and osteomas appeared unchanged. Extensive laboratory measurements including 17 hydroxysteroids, 11 oxysteroids, aldosterone and blood cortisol were all normal. Three minute polyps were visualized in the remaining rectal mucosa.

There were short hospitalizations in September 1973 and January 1974 for the purpose of evaluating the status of the tumor, rectal polyps, osteomas and sebaceous cysts. The large desmoid was smaller as shown in Table 1. The tumor in the wound had completely disappeared. There were 13 tiny polyps in the rectal mucosa in September 1973; five were found in January 1974 and four in June 1974. The osteomas had not changed. Acne on the face had healed remarkably. The numerous sebaceous cysts were the same except that three lesions had ruptured spontaneously several months previously and had not reformed. At the January 1974 admission the patient complained of attacks of abdominal pain and diarrhea. Radiologic examination of the gastrointestinal tract showed a partially obstructed and grossly dilated loop of mid-jejunum. On January 18 1974 a laparotomy was carried out to relieve this lesion. The observations during the operation were somewhat at a variance from the interpretations and measurements made from physical examination. In the first place, there were numerous patches of desmoid tumor formation throughout the abdomen, particularly in the large bowel mesentery. The measurements shown in Table 1 for January 1973 were probably of a pelvic desmoid tumor which had contracted to a small irregular mass no more than 2-3 cm in diameter in the mesentery of the terminal ileum. The bowel was adherent to and caught in this contracted remnant with conformation like the bows of a Christmas package ribbon.

The tumor measurements of September 1973, January 1974 and June 1974 were of a flattened mass of desmoid tumor in the abdominal wall and extending out from the incision to the extent indicated by the measurements. It could have been resected in January, but there would have been a large abdominal wall defect and the decision was made to rely on chemical control of this tumor along with the numerous other intra-abdominal tumors.  $\Delta^1$ -testololactone was discontinued because of menorrhagia and concomitant anemia. Theophylline (Choledyl [R<sub>x</sub>], 400 mg daily) and

chlorothiazide (Diuril (R<sub>x</sub>), 500 mg daily) were substituted for  $\Delta^1$ -testololactone. This desmoid tumor continued to shrink as shown in Table 1. Acne cleared completely. The osteomata and sebaceous cysts remained unchanged.

### Discussion

Biopsies taken from normal and tumorous regions in this patient have been used to establish tissue cultures in which response to various drug administrations is under study. The fortuitous recognition of a significant feature in a female Gardner's syndrome patient's history involving the adverse effects of birth control medication has led to what appears to be a method of control of her desmoid tumors. The patient noted the growth of sebaceous cysts while on these drugs. Long after this episode and presumably stimulated by laparotomy and subtotal colectomy, previous quiescent desmoid tumors in the pelvis enlarged over the course of about one year to a point where they were considered inoperable or at the very least requiring very extensive operation. The probability of growth of new tumors following operation also served to contraindicate further surgery since a hard tumor mass was noted in the most recent laparotomy incision. The situation was charged with emotional apprehension stemming from long and fatal illnesses of the patient's mother and a maternal uncle from desmoid tumors. The former died of inanition after multiple small bowel resections necessitated by necrosis of the bowel as a retroperitoneal desmoid occluded arterial blood supply to the intestine. The uncle died of respiratory failure and pulmonary infection secondary to encroachment of an enormous desmoid tumor in the upper abdomen. The patient and her husband, as well as their doctors, were willing to pursue any alternative therapeutic lead, however slight its chance of success.

A second consideration was a scattered and long history of laboratory and experimental investigations of the etiology of desmoid tumors indicating some endocrine abnormality and trauma as the outstanding etiologic features.<sup>6,23,27-29,32,34-36</sup> Administration of testosterone has been recorded in two cases without success (Reference 4 in Hunt *et al.*, 23 and 5). It has been shown that a high percentage of the cases with desmoid tumor occur in adult females and that the growth of tumors is sometimes stimulated by pregnancy and parturition, although the condition can occur in males, in children and usually without a demonstrable familial incidence. Assays of estrogen and gonadotropins have been carried out, but the results have been inconclusive, perhaps because of the relatively primitive methods of assay available at that time.<sup>36</sup> Experimental production of fibrous tumors of the abdominal organs, the anterior abdominal wall and thorax in guinea pigs with estrogen preparations has been studied in detail by Lipschütz and co-workers<sup>6,27-29</sup> and others.<sup>32,34,35</sup> In one study, inhibition of development of such tumors by progesterone and some closely related

compounds that interfere with the effect of estrogens was reported.<sup>28</sup> Other rodents, however, were not susceptible.

The selection of a drug for trial in this case was an extension of laboratory and clinical trials of  $\Delta^1$ -testololactone in conjunction with 5-fluorouracil for advanced malignancy. The combination of  $\Delta^1$ -testololactone and 5-fluorouracil proved partially effective in carcinoma of the pancreas,<sup>48</sup> and the combination is known to induce remission in about 50% of patients with disseminated carcinoma of the breast.<sup>19</sup>  $\Delta^1$ -testololactone by itself causes remission in 10-20% of patients with breast carcinoma.<sup>18,41</sup> Especially attractive features of this drug are lack of toxicity and absence of endocrine effects. The mechanism by which this drug affects cancer of the breast and how it potentiates the effect of 5-fluorouracil in carcinoma of the pancreas are not known. Various enzymes are affected<sup>1</sup> and the suggestion has been made that interference with normal steroid metabolism by microsomal enzymes of the smooth endoplasmic reticulum occurs.<sup>48</sup> Synergism with estrogen in inhibiting tumor growth of a transplantable lactating mammary adenocarcinoma in Fischer rats has been reported.<sup>1</sup> It is of some interest that one of the possibilities examined by Lipschütz and Grismali<sup>28</sup> many years ago in a study of natural and synthetic steroid inhibitors of estrogen-induced fibroma was that unsaturation in the A ring of steroids was a requisite for inhibition. These investigators were also impressed by the presence of substitution on the 17 carbon which would, of course, not be fulfilled by  $\Delta^1$ -testololactone although the similarity to progesterone is otherwise close.

More recent experiments have shown striking effects of dibutyryl 3',5'-cyclic adenosine monophosphate and testosterone in promoting differentiation of transformed cultured Chinese hamster ovarian cells to mature fibroblasts. In addition,  $\Delta^1$ -testololactone was tested with dibutyryl 3',5'-cyclic AMP and found to be even more effective than testosterone.<sup>21,22,39,40</sup> The chemical mechanism of this effect on differentiation has not been further elucidated but a phenomenon of fundamental importance seems to have been uncovered. In parallel studies, reverse transformation of cultured sarcoma cells on exposure to 3',5'-cyclic AMP was shown by Johnson, Friedman and Pastan.<sup>24</sup>

Recently, data have appeared concerning the effect of a wide variety of drugs of different classes on cAMP phosphodiesterase activity of rat brain and cat heart.<sup>52</sup> This survey revealed two facts believed important to understanding of the effect of  $\Delta^1$ -testololactone on certain cells in which "reverse transformation" can be demonstrated.<sup>39</sup> In the first place,  $\Delta^1$ -testololactone by itself has some inhibitory effect on cAMP phosphodiesterase. Even more important is the finding that estradiol is a potent inhibitor of this enzyme. This seems particularly pertinent in view of observations from this laboratory showing that in mouse hepatoma  $\Delta^1$ -testololactone impairs metabolism of es-

tradiol and causes accumulation of this administered compound in tumor cells.<sup>2</sup>

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