Reactivity of Nodular Cells in Vitro: A Guide to the Pharmacological Treatment of Dupuytren's Contracture

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Introduction

Since the time of Dupuytren attempts have been made to use drugs to either alleviate the symptoms or stop the progression of Dupuytren's contracture. In Dupuytren's *leçons orales* (1832) one reads: "M. Dupuytren in treating several cases of contraction of the ring fingers employed one after the other vapourised fumigation, first of an emollient and then of a sedative character, plasters . . . leeches, friction with resolvent ointments and calomel, alkaline, simple sulphurous and saponaceous douches at various temperatures and all without the slightest effect."

Such treatments reflected perhaps a desire to avoid surgical correction of the disease with its associated risks. In the intervening years many drugs of a similar diversity as used by Dupuytren have been employed in an attempt to (a) reduce an existing contracture, (b) inhibit a developing contracture, (c) facilitate resection of tissue during surgery and (d) prevent or delay the recurrence of the disease after surgery. A list of drugs used during the last 100 years of clinical practice for all these kinds of therapy is shown in Table 1. Most of these drugs have passed into history, at least as far Dupuytren's contracture is concerned. Nevertheless an assessment of their place in therapy merits consideration, since such an assessment has not previously been reported and it provides a perspective of the pharmacological approach which has been taken towards the disease.

One major problem in any discussion of the pharmacological treatment of this disease is the lack of objective, multicentre, controlled trials of potentially beneficial drugs. Most studies have included limited numbers of patients of varying ages, different sexes, and at various stages of the disease. In addition some of the subjects used in these studies have had previously unsuccessful treatments, which may complicate interpretation of any later results. Consequently, the variability in the intensity of the disease between individuals, the differences in the rate of progression of the disease and possible periods of quiescence all contribute to great difficulties in assessing whether a drug does or does not have a beneficial effect. Thus, it is not surprising that the usefulness of drug treatment in Dupuytren's contracture is so controversial.

Table 1. Drugs used to treat Dupuytren's contracture

Thiosinamin (Rhodallin)
Thiosinamin-sodium salicylate
Thiosinamin-ethyl iodide
Iodine ointment
Thyroid extract
Copper sulphate solution
Pepsin
Parathyroid extract
5% salicylic acid ointment
Humanol (human sterilised fat)
Vitamin E/tocopherols
Hydrocortisone
Trypsin/α chymotrypsin/hyaluronidase
Potassium para-aminobenzoate (PABA)
Dimethlysulphoxide (DMSO)
Procarbazine (Natulan)
Trypsin/chymotrypsin/hyaluronidase
6-Methyl predisolone
Aprotinin (Trasylol)
α-Mercaptopropionylglcine (Thiopronin)
Allopurinol

A century ago there were many theories concerning the aetiology of the disease, the majority of which are no longer tenable. In contrast, the histology of the palmar nodules and cords was precisely known. Fibroblast proliferation in the palmar nodules and alterations in the appearance of the collagen fibres of the aponeurosis led to this disease being classified as belonging to the fibromatoses. This had an influence in deciding possible treatments, since a treatment applied to any of the allied conditions, such as Peyronie's disease, was thought appropriate to try in Dupuytren's contracture. It is true to say that no drug has ever been specifically produced for Dupuytren's contracture; rather, their use has been extrapolated from experience with other diseases.

One of the early aetiological factors were thought to be a hormonal imbalance which was responsible for the fibromatoses. So, to correct this imbalance thyroid extract was given (Gilbert 1913; Leopold-Levi 1913, cited by Wainwright 1926). The results were said to be encouraging but it was not widely used. In a similar way the contracture was compared with muscles in tetany and this was believed to be due to hypocalcaemia and so this led to the introduction of parathyroid extract. The results were not encouraging (Leriche and Jung 1930, cited by Powers 1934).

A more systematic approach to treatment began when fibrolysin was introduced. This drug and its derivatives were used in Dupuytren's contracture after its reported success in the treatment of scleroderma and scar remodelling. It was said to exert its effect by softening and improving the elasticity of sclerodermatous and scar tissues. In addition to these in vivo effects the drug was found in in vitro experiments to convert collagen into gelatin. The combination of its use in one of the allied conditions and its effect on collagen

in vitro led to its application in Dupuytren's contracture. It was tried over many years and by many workers; its last reported use being in 1946 by Noix, who used the drug electroiontophorectically but its effectiveness in all these studies is perhaps best summarised in the conclusion of Black in as early as 1915: "Thiosinamin has been tried but the results cannot on the whole be regarded as encouraging". Nevertheless, this was an example of a drug in which both the in vivo and in vitro findings were applied to the treatment of Dupuytren's contracture. Such a combination of in vivo and in vitro approach in drug evaluation was very rare in the treatment of this condition in those days.

In contrast to the mere softening of collagen with thiosinamin the degradation of collagen was the objective in the use of pepsin (Hesse 1931) and later in the use of trypsin, α chymotrypsin and hyaluronidase (Bassot 1969; Hueston 1971). The effects of this mixture of enzymes were pronounced and clearly did effect an improvement in the condition but the treatment has not found widespread usage.

With the introduction of steroids the therapeutic objective was to induce a restraining effect on the formation of fibrous tissue. Several groups of investigators hoped that it would have the success seen in the treatment of other fibromatoses such as Peyronie's disease (Bodner et al. 1954; Desanctis and Furey 1967; Furey 1957; Rothfeld and Murray 1967) and keloids (Conway and Stark 1951; Ketchum et al. 1974; Kill 1977; Vallis 1967). Despite initial optimism the results for hydrocortisone (Zachariae and Zachariae 1955) and later more powerful derivatives such as 6-methyl prednisolone were disappointing (Kaufhold 1962). The drugs appeared to have little effect on an existing contracture (Baxter et al. 1952) and certainly did not cause a regression of the disease (Ritchey 1952). The most significant successes were when steroid was used postoperatively when it reduced oedema and facilitated mobility and rehabilitation of the hand (Bernstein 1954).

The subsequent introduction of dimethylsulphoxide (DMSO), which was said to dissolve pathologically formed collagen but leave normal collagen intact (Rosenbaum et al. 1965; Vuopala and Kaipainen 1971), and paraaminobenzoate (PABA) proved to be of questionable effectiveness. This was surprising since both agents had previously had some degree of success in treating Peyronie's disease and scleroderma (Zarafonetis 1964; Zarafonetis and Horrax 1959).

Perhaps the most investigated drug to treat Dupuytren's contracture is vitamin E. Its reported successful use in Peyronie's disease (Burford and Burford 1957; Scardino and Scott 1949) and other fibromatoses was followed by trials in Dupuytren's contracture. The results of high dose (300 mg per day) long-term therapy were extremely variable. Conclusions as to the effectiveness of the drug ranged from a good success rate (Steinberg 1946, 1951; Thomson 1949) to total ineffectiveness (King 1949; Langston and Badre 1949; Oldfield 1954; Parsons 1948; Richards 1952). The lack of its use today perhaps indicates that time has proved it to be ineffective.

Chance findings are very common in most types of therapy in which a drug given for one disease was unexpectedly found to be beneficial for another

disease. This was the case for procarbazine which Aron (1968), on giving it to a patient with Hodgkin's disease, also noted that it not only cured the lymphoma but also the patient's Dupuytren's contracture. This led to clinical trials in both Dupuytren's and Peyronie's diseases but the incidence of side effects and questionable effectiveness precluded its widespread use (Morgan and Pryor 1978; Oosterlinck and Renders 1975). However, it did establish that an antiproliferative agent had an effect on the cells present in the nodule and thereby reduced the rate of contracture.

This anti-proliferative approach was followed by drugs designed to inhibit the formation of collagen, namely the lathyrogens. An example of this class of drugs is mercaptopropionylglycine (Bray and Galeazzi 1980; Cimmino et al. 1982). These agents are the first of their type to be used clinically to treat the condition. Their promise is yet to be fully determined but on theoretical grounds they may well have a beneficial effect on the disease and prevent its progression to a fixed contractured state (Fuller 1981).

The last drug which has been used is allopurinol (Murrell et al. 1987). Again its effectiveness in Dupuytren's contracture was found by accident and its exact mode of action in improving the condition of the disease awaits elucidation. It is at present unclear how the prevention of free radical generation decreases the contracture of the disease. This topic is dealt with in much greater details elsewhere in these proceedings.

In summary, the pharmacological treatment of Dupuytren's contracture over the last 100 years has been controversial and often empirical. Many treatments are clearly ineffective, some of the more promising ones are potentially toxic and perhaps the overall position is best summarised in the statement of Wesson (1943): "Whenever a variety of treatments are recommended for any disease we know that none is specific and that the symptoms are merely being treated while waiting for Nature to bring about a cessation of advancement if not regression." Unfortunately in Dupuytren's disease regression does not occur!

The Background to the Current Study

From the list of drugs given in Table 1 it is clear that there is a lack of basic knowledge as to the nature of the factors which induce the cellular proliferation in the palmar aponeurosis and to the nature of contractility in these cells which eventually produce the fixed contracture. The nodular cell generally considered to be responsible for the process of contraction is the myofibroblast (Gokel and Hubner 1977; Tomasek et al. 1987). It would be logical to attempt to antagonise the contractility of this cell type since if contraction was inhibited the deformity would be reduced and recurrence after surgical intervention could be minimised. None of the drugs in Table 1 have the property of modifying the contractile activity of the cell. This is surprising since in 1959 Luck suggested that: "The ideal form of therapy would be a method that could be employed with the first appearance of the nodules that

would cause a prompt evolution of the nodules without the nodule undergoing contracture."

The question is of course what is the best procedure to use in order to find this "method" which in our terms would be a drug to inhibit myofibroblast contractility. Consequently, a study of myofibroblasts is needed in which the cells can be studied by a reproducible method and the experimental conditions can be varied so as to detect drugs which can modify myofibroblast contractility. Perhaps the most obvious way would be to culture the cells and then assess their contractility. Although the cells have been cultured (Vande Berg and Rudolph 1985) the assessment of contractility using conventional culture techniques is complex (Badalamente et al. 1988) and easier alternatives are not very precise. For example one study measured the wrinkles formed on a silicone sheet placed beneath the culture. In addition the normal cell to cell contacts and cell to stroma contacts may be different from those found in the in vivo state.

In contrast to the complexities of the tissue culture approach the pharmacological procedure would be either (a) to utilise an in vivo model or (b) to select an isolated tissue containing myofibroblasts and use it in a classical organ bath technique. However, Dupuytren's disease has never been reported in any animal species (Davis 1965) and the work of Gabbiani et al. (1973) seemed to suggest that strips of Dupuytren's nodules when used in organ bath studies did not respond as did strips of tissues containing myofibroblasts such as granulation tissue. Thus the position appeared to be that there is no animal model and isolated strips of Dupuytren's nodular tissue did not respond.

However, it was noticed that Gabbiani et al. (1973) used an unusual auxotonic transducer (Kapanci et al. 1974) which studies in our laboratory had found to be unsuitable for in vitro work on myofibroblasts (Illingworth and Naylor 1981). If an isometric transducer was substituted for the auxotonic type then strips of Dupuytren's nodules were found to contract in vitro.

To further enhance the sensitivity and reproducibility of the method several other changes were incorporated and found to provide a stable and sensitive system. The physiological solution used in the original method was Tyrode and this was replaced by Krebs-Henseleit solution which is more generally used for the study of human tissues. The technique of superfusion (Gaddum 1953) was used in addition to the conventional immersion bath arrangements since superfusion has the major advantages of continuously washing the tissue and so provides a very stable baseline on which to accurately assess any contractile effect. In addition the tissue was connected to the transducer with braided stainless steel wire and the anchorage point in the tissue was a barbless bronze fish hook so as to avoid any loss of a response due to the compliance of the cotton thread that is normally employed. These simple changes provided a sensitive and reproducible in vitro preparation.

To contract the tissue a range of agonists were tested some of which other authors had shown to produce myofibroblast contraction in tissues such as croton oil induced granulation tissue (Gabbiani et al. 1972; Garcia-Valdecasas et al. 1981; Majno et al. 1971). These included angiotensin, noradrenaline,

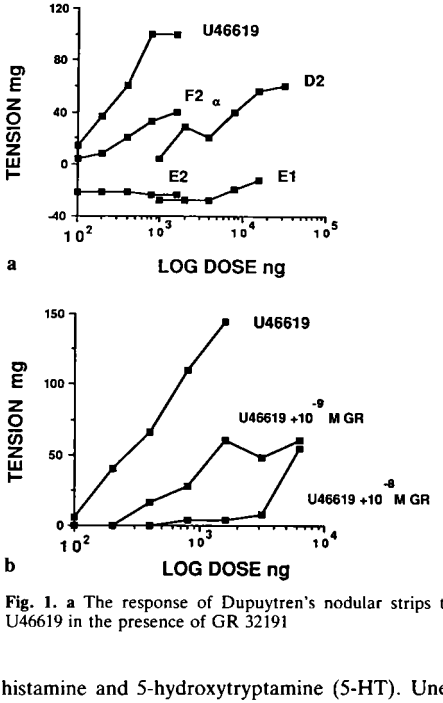

Fig. 1. **a** The response of Dupuytren's nodular strips to prostanoids. **b** The response to U46619 in the presence of GR 32191

histamine and 5-hydroxytryptamine (5-HT). Unexpectedly, when used in our studies with Dupuytren's nodules all these agonists proved ineffective. When prostaglandins, namely PGE_1, PGF_1, PGD_2, PGE_2 and $PGF_{2\alpha}$, were used they produced a range of effects (Fig. 1a). PGD_2, PGE_2 and $PGF_{2\alpha}$ were contractile whereas PGE_1 and PGF_1 were relaxatory. A stable form of the prostaglandin endoperoxide U46619, which acts on thromboxane receptors, was also found to be contractile. Indeed it proved to be the most potent contractile agonist of the group. The H_1 antagonist mepyramine also exerts a contractile response in these preparations. All the contractile responses were slow in onset and prolonged even in the superfusion experiments. In contrast to these effects on nodular tissues all studies on samples of cords were unresponsive to the prostanoids. It should be stressed that all the responses were fully reversible and this allowed antagonism studies to be carried out. Using the immersion baths the responses to U46619 were capable of being selectively antagonised by a specific, selective thromboxane antagonist GR32191 in a concentration-dependent manner. Over the concentration range of U46619 used, 10^{-7} *M* GR32191 completely abolished the responses whereas 10^{-8} and 10^{-9} *M* exerted a concentration-dependent antagonism (Fig. 1b). The

Table 2. Human tissues used in vitro

Induced
Dupuytren's nodules
Dupuytren's cords
Tissue expander capsule
Tissue implant capsule
Hypertrophic scar
Keloids
Granulation tissue
Structural
Postauricular skin
Breast skin (reduction)
Placenta
Whartons jelly
Endocervical canal

response to mepyramine is unaffected by GR32191 which indicates that mepyramine does not act on thromboxane receptors (Coleman et al. 1989).

We have therefore shown that certain prostanoids are potent contractile agents on human myofibroblasts found in the palmar nodules of Dupuytren's contracture, and evidence obtained with the thromboxane receptor blocking drug GR32191 suggests that thromboxane receptors are involved. Although it is not clear whether prostanoids are involved in the aetiology of the disease further studies using agents such as GR32191 may provide the answer. Certainly the in vitro studies of Dupuytren's nodules showed that stable and sensitive preparations can be obtained from nodular tissue which give reproducible responses to prostanoids. It is clear that agonist-antagonist studies can be performed with such a tissue and potential anticontractile agents can be assessed.

Unfortunately there is a problem with such studies in that large numbers of specimens are required to determine the effect of an agonist and antagonist. Tissues are simply not available in the quantities required to carry out methodical studies and so other types of tissues were investigated (Table 2).

Human tissues from keloids, hypertrophic scars and granulation tissues were investigated as was tissue formed around tissue expanders when they were removed prior to the insertion of an implant. These we classify as "induced" tissues and the presence of myofibroblasts has been documented in all of them. The most suitable tissue was found to be the tissue expander capsule as it had a range of sensitivity comparable to Dupuytren's nodules – for example it is insensitive to 5-HT but responsive to U46619.

Again this tissue is in limited supply so other tissues in which myofibroblasts occur as structural elements were investigated in the in vitro superfusion system. Post-auricular skin was used as a control for the keloids and not unexpectedly was insensitive to all the agents used. The skin from breast reduction procedures, placentae, Wharton's jelly and endocervical canal tissue were found to have limitations due to their content of smooth muscle which masked the much weaker contractile abilities of the myofibroblasts. As an

Table 3. Rat tissues used in vitro

Structural
Testicular capsule
Ovarian capsule
Placenta
Lung
Uterus
Splenic capsule
Adrenal capsule
Induced
Wound granulation tissue[a]
Implant capsular tissue
Croton oil granuloma pouch
Tissue expander capsule[b]
Oestrogen stimulated immature uterus

[a] Also from minipig.
[b] Also from pig.

alternative, animal tissues (Table 3) were investigated to see if there were any which could provide a spectrum of sensitivities similar to that of Dupuytren's nodules. For the induced myofibroblasts wound granulation was suitable especially that of the minipig. The capsules which formed around both the perspex cylinder and tissue expander in the rat were insensitive. This contrasted with the reactivity of the tissue expander capsule in the pig. Oestrogen stimulated immature rat uterus was insensitive. The croton oil induced granuloma tissue widely used as a model for myofibroblast studies was certainly sensitive but its abnormally high responsiveness to 5-HT suggest that it is atypical of other tissues containing myofibroblasts. For the structural sources of myofibroblast containing tissues testicular capsule proved useful but the others, due to the complications of smooth muscle being present, were found to be of limited usefulness. It is clear that the ideal alternative tissue to Dupuytren's nodule, either human or animal, for investigating the activity of anticontractile drugs is still to be found.

Future Possibilities

A recent series of experiments has been carried out using Dupuytren's nodules to determine if the endogenous contractile mediator(s) can be characterised in a simple in vitro system.

If a strip of nodular tissue is left in an immersion bath for a prolonged period of time (>1 h) without changing the bath fluid several events occur (Fig. 2). There is an initial decrease in tension as the tissue relaxes and if the tissue is not retensioned but left alone this is followed by a "plateau" period in which the tension remains constant. At some time after the plateau period is reached, ranging from 25–45 min, the tension slowly and steadily increases until the tissue is washed. After washing the tension slowly falls towards the baseline but

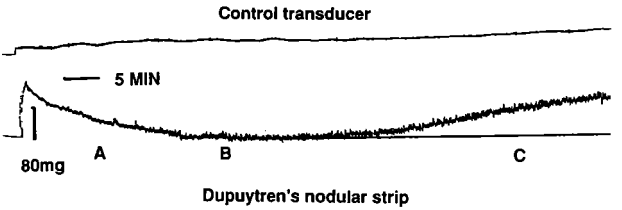

Fig. 2. The tension recorded in a strip of a Dupuytren's nodule. *A* The period of relaxation; *B* the period of maintenance of a constant tension, and *C* the period of a gradual increase in tension

never actually achieves it. Consequently it remains in a partially contracted state. This suggests that a substance(s) is released by the nodular tissue into the bathing fluid which exerts a powerful contractile effect upon itself. An analysis of the bath fluid is underway to determine the nature of this contractile substance.

Perhaps this simple experiment indicates another possible avenue of in vitro research to pursue in developing specific anticontractile agents for modulating the activities of myofibroblasts in Dupuytren's contracture.

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