DUPUYTREN'S CONTRACTURE: AN AUTO-IMMUNE DISEASE ?

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Dupuytren's contracture is now known to have a genetic basis, and in certain (Caucasian) populations it is a rather common chronic disease (Early 1962, Hueston 1963, Ling 1963). At the age of seventy-five and over, nearly 20 per cent of men and nearly 10 per cent of women were found to be affected in the combined (English) population studied by Early. In an Australian general hospital population—from which chronic bed patients, epileptics, chronic alcoholics and tuberculous patients were excluded—Hueston found that nearly 30 per cent of men and nearly 20 per cent of women over sixty had the disease. Prevalence increases steeply with age, but the mechanism whereby the diathesis, or genetic predisposition, expresses itself in the form of the contracture is unknown. The earlier etiological theories were reviewed by Skoog (1948) and subsequent ones have been described by Hueston (1963).

In this article attention will be directed to the quantitative details of the age-specific and sex-specific prevalence of the disease. It will be shown that the age distribution reflects certain general characteristics exhibited by diseases that are widely believed to have a spontaneous, disturbed-tolerance auto-immune etiology.

DISTURBED-TOLERANCE AUTO-IMMUNITY: THE THEORETICAL BACKGROUND

In discussing the consequences of his clonal selection theory of acquired immunity Burnet (1959) proposed that random somatic mutation in certain cells of the lymphoid system might initiate the growth of "forbidden-clones"; he postulated that such clones escapes the normal control or defence mechanism, and that their auto-antibody products (humoral or cell-bound) reacts immunologically with normal "self" antigenic determinants. The immune reaction is pathogenic and leads to the symptoms and signs of auto-immune disease. Burnet has often insisted that one of the main objectives in immunology is to understand why the immune system is normally tolerant towards the exposed antigenic determinants of "self," and his clonal selection theory gives a possible interpretation of this phenomenon. Burnet envisaged that gene mutations occur at a high rate in presumptive lymphoid stem cells during embryogenesis, and, as a consequence, many different antibodies with a wide range of specificities are synthesised; should any of these antibodies have a reactive relationship with the normal exposed antigenic determinants of "self" tissues, he postulates that a control mechanism eliminates cells synthesising such products and thereby prevents the development of clones. It follows that the antibodies from surviving clones of cells should be capable of reacting with a wide range of foreign ("not-self") antigens, while being tolerant and non-reactive towards "self" antigens.

Burwell's (1963) theory offers a fundamentally different alternative (Burch, Burwell and Rowell 1964; Burch and Burwell 1965), and his approach is in many ways the direct opposite of Burnet's. Thus Burwell argued that the primary and intrinsic function of the lymphoid system is the feed-back regulation of the growth, and the maintenance of size (metrostasis), of target tissues throughout the body; the immune defence function exercised against foreign antigens is regarded as a secondary, although inevitable, concomitant of the primary function. The control of growth and of size depends on the control of mitosis, and, because each distinctive tissue must be separately regulated, it is theoretically essential that a specific, but sub-immune "recognition" relationship, must exist between each target tissue and its

associated controlling element in the lymphoid system. "Recognition" must take place along both the effector and affector pathways of the feed-back control mechanism. A logical argument (based on the auto-immune evidence) shows that this specific relationship is achieved through the identity of polypeptide chains in the controlling and controlled tissues. The molecular basis of "self-recognition" appears to reside, appropriately enough, in the weak but highly specific London/van der Waals "self-recognition" forces that occur between identical molecules. In those tissues that are normally freely infiltrated by small lymphocytes it is proposed that these cells provide the mitogenic (or effector) stimulus; however, where a blood-tissue barrier prevents the free infiltration of lymphocytes to target cells (for example, in the central nervous system, articular cartilage, osteocytes, odontoblasts, the epidermis and Schwann cells) it is proposed that the mitogenic agent is humoral and diffusible—probably an α - or β -globulin, and most likely an α_2 -globulin (Burch 1964*b*; Burch, Burwell and Rowell 1964; Burch and Rowell 1965; Burch and Burwell 1965). Thus on Burwell's theory, a special inductive mechanism must operate during embryogenesis to ensure polypeptide identity between molecular components ("mitotic control proteins") of the lymphoid system and the "tissue coding factors" that identify differentiated target cells (Burch and Burwell 1963, 1965). Nevertheless, subsequent gene "mutation" in lymphoid stem cells could convert the molecular identity relationship between the "mitotic control protein" and the "tissue coding factor"—giving a sub-immune interaction—into a complementary relationship giving a strong, immune-type interaction.

But whatever the true interpretation of acquired tolerance to "self" should prove to be, disturbances such as somatic mutations in cells of the lymphoid system could, in principle, give rise to forbidden-clones of cells that fail to recognise "self," and, instead, react immunologically with normal tissues. It has been shown (Burch 1963*a*, Burch and Rowell 1963, 1965) that the age and sex distributions, and the clinical and observational evidence relating to such diseases as inflammatory polyarthritis, rheumatoid arthritis, chronic discoid and systemic lupus erythematosus, systemic sclerosis and Hashimoto's thyroiditis, are strikingly consistent with Burnet's (1959) concept of forbidden-clones. At the same time Burwell's fundamental approach to the intrinsic role of the lymphoid system is strongly favoured.

It is of interest that several other diseases that are not generally regarded as being auto-immune (various cardiovascular diseases, manic depressive psychosis, schizophrenia and involutional psychosis) have statistical characteristics, and certain clinical and laboratory features, that are similar to those associated with the diseases that are widely regarded as having a spontaneous disturbed-tolerance auto-immune etiology (Burch 1963*b*, 1964*a* to *e*). There is a distinct possibility that some of the phenomena of ageing may also be fundamentally auto-immune in character (Walford 1962; Comfort 1963, 1964; Burch 1963*b*, 1964*a*).

Detailed quantitative analysis of the evidence for probable spontaneous disturbed-tolerance auto-immune diseases in man (Burch 1963*a*, 1964*b*; Burch and Rowell 1963, 1965; Burch, Burwell and Rowell 1964) suggests that their pathogenesis is consistent with the following principles: 1) Such diseases are confined to one or more genetically-specific sub-populations. The genetic predisposition may affect only one locus, as in inflammatory polyarthritis, but quite often more than one. The total population "at risk" with respect to some diseases can, however, be as large as, or nearly as large as, the general population; and in this respect it is tempting to regard such auto-immune disorders as representing one aspect of ageing. 2) The size of the sub-population at risk often shows a sex-differential; inherited alleles on the X-chromosome, whether dominant or recessive, can generally account for such differences. 3) The phenotypic initiation of this kind of disease depends upon the occurrence of one or more—up to at least twelve—specific random events. When more than one random event is involved these may be either statistically "dependent" or "independent" in character. 4) The average rate of the random initiating events appears to be virtually constant throughout postnatal life. This is a most remarkable and totally unexpected property.

5) The average rate of these events in one predisposed individual is approximately the same, within a few per cent, as the average rate in a similar individual. 6) The average rate of a specific random event in females is either equal to that in males or it is twice as high, probably being within a few per cent in each case. No significant departure from this "rule" has been observed so far. 7) The random initiating events are probably a special form of nuclear gene "mutation" in stem cells of the lymphoid series. It is deduced that it probably involves a spontaneous "switch" in messenger ribonucleic acid (RNA) transcription from the "normal" strand of the DNA of a structural gene over to the complementary strand. 8) Specific somatic mutations in specific stem cells initiate the growth of forbidden-clones. The mature cells of the forbidden-clone are either small lymphocytes carrying cell-bound auto-antibody, or they are cells, of unknown type, that synthesise and secrete humoral "auto-antibodies." 9) There is an interval, or latent period, between the initiation of a forbidden-clone and the emergence of symptoms or signs of the associated disease. 10) When the primary pathogen is a cell-bound lymphocytic auto-antibody it appears that the average latent period in women is about twice as long as in men. In this class of disease it is found that the primary target tissue of the auto-immune attack is normally freely infiltrated with small lymphocytes. 11) When the primary pathogen is a humoral auto-antibody in the α and/or β globulin fractions it appears that the average latent period in men is the same as in women, although in special circumstances it can be longer in men. In this class of disease it is found that the primary target tissue of the auto-immune attack lies behind a blood-tissue barrier, for example, in the central nervous system, bone, cartilage, epidermis, odontoblasts and Schwann cells. 12) An endogenous defence mechanism operates against forbidden-clones but it is vulnerable to extrinsic factors such as certain infections and drugs, and also to mental stress; remissions and exacerbations in chronic auto-immune conditions are attributed to the fluctuating balance between defence and attack.

The quantitative aspects of the above conclusions have been drawn from published and unpublished analyses by the author and his colleagues of the age-specific onset-rates or prevalence of presumed spontaneous auto-immune diseases in man. Very recently, however, Holmes and Burnet (1964) have found that the age-specific and sex-specific prevalence of Coomb's positive haemolytic anaemia in the NZB strain of mice and in NZB $\times$ C3H F_1 hybrids reflect the same basic statistical characteristics as those listed above. The kinetics of the onset of this spontaneous auto-immune disease, with a longer latent period in the female, suggest that the primary pathogen is a lymphocytic, cell-bound auto-antibody. The finding of germinal centres in the thymus (Burnet and Holmes 1964) also conforms with this interpretation (Burch and Rowell 1965).

AGE-SPECIFIC AND SEX-SPECIFIC PREVALENCE OF DUPUYTREN'S CONTRACTURE

The finding from Early's (1962) combined surveys of 5,652 men and 1,327 women are plotted in Figure 1. The results for a given age group are plotted for clarity as a point (instead of a histogram) at the centre of the age group on log-log scales. This is not a strictly rigorous procedure but it will not introduce misleading distortion in the present context. It will be seen that fewer women are affected at all ages, but that the age-dependence of the disease in women is steeper than that in men. This suggests one of two hypotheses: either the disease is initiated by multiple forbidden-clones, and more clones are needed to produce the disease in women than in men (Burch 1963*a, b*); or the same number of forbidden-clones (one or more) is involved in the pathogenesis of the disease in men and in women but the average latent period in women is about fifteen years longer than in men (the curve for women lags about fifteen years behind the curve for men). From either interpretation it can be concluded from (9) and (10) above that if Dupuytren's contracture is an auto-immune disease the primary pathogens should be forbidden-lymphocytes carrying cell-bound auto-antibody. In testing the

second hypothesis we note that the latent period difference between men and women should be about fifteen years, and because the average value in women should be about twice that in men, it follows that the absolute average latent period in men should be about fifteen years and in women about thirty years. If these corrections are applied to the data for the prevalence of the disease, then we should obtain the age-specific prevalence, P_t , of the "mutant" stem cell progenitors of the forbidden-clone or clones. These corrections are applied in Figure 2 in which we see that the data for men and women fit the simple equation: $P_t = 100 D_0 (1 - e^{-kt^*})$.

The closeness of the fit strongly favours the second hypothesis and the chance of a coincidental fit of this nature is very small. The equation describes the age-specific prevalence,

FIG. 1

FIG. 2

Age-specific and sex-specific prevalence, P_t , of Dupuytren's contracture as a function of age, t , for the combined population surveys of Early (1962) (log-log scales). For clarity, prevalence is plotted as a point at the centre of each age group instead of a histogram. In Figure 2 it is assumed that the average interval or latent period between the initiation of a forbidden-clone and the diagnosis of the disease is fifteen years for men and thirty years for women. The curve is the graph of the equation: $P_t = 100 D_0 (1 - e^{-kt^*})$ which describes the age-specific prevalence of a condition that is initiated in predisposed individuals by four random, dependent-type events (see text). (Plotted from the data given by Early (1962) in his Table I.)

P_t (in per cent) at age t , of a forbidden-clone or clones that is or are initiated by four dependent-type random events. K is a constant which, in the theoretical model for the initiation of a single forbidden-clone, is proportional to L , the number of stem cells at risk multiplied by $(m_s)^4$ —that is, the average somatic mutation-rate, per gene at risk, per cell at risk, raised to the fourth power (Burch and Rowell 1963, 1965; Burch 1964c, d, e). D_0 is the proportion of the population at birth that is at risk with respect to the disease. The equation will be valid at all t provided: the mortality in the predisposed population is effectively the same as that in the general population; m_s is constant throughout life; and $m_s t$ is very much less

than unity for all t . From Figure 2 it is deduced that D_0 is about 0.2 in the population studied by Early (the theoretical curve approaches D_0 asymptotically, as t (age) tends to infinity).

The closeness of the fit to the equation when the data are adjusted for the latent period suggests, therefore, that Dupuytren's contracture is, first, confined to a sub-population constituting about 20 per cent of both men and of women in the general population studied by Early (1962); that, second, it is initiated by four dependent-type random events, the average rate of the random initiating events being the same in men and women and constant from the age of fifteen years or earlier to the end of the life span; and, last, that it is associated with an average latent period of fifteen years in men and thirty years in women. (There is a very slight suggestion—based on only one case—that the average latent period for males in the age group fifteen to twenty-four years might be less than fifteen years; it appears from other evidence (Burch and Rowell 1965) that the average latent period in infants and children is in fact shorter than in adults, but in any event, the absolute latent period for the disease in a patient aged fifteen years cannot, of course, exceed fifteen years—plus an appropriate fraction of the gestation period.)

COMMENT

It has been suggested above that the age pattern of Dupuytren's contracture indicates that it is initiated by four statistically "dependent-type" random events. The rate of each of these events is more or less constant in men and in women throughout adult life and perhaps earlier. It is reasonable to suppose that there should be some link between the predisposing genotype and the random initiating events, and these events may be spontaneous somatic "mutations" of autosomal genes that are related—directly or indirectly—to the predisposing alleles. To this hypothesis it is necessary to add another to explain how four somatic gene mutations can give rise to the complicated pathological changes seen in the palmar and plantar nodules; some form of amplification of the effect of only four gene mutations is clearly necessary to account for these severe changes. In principle, many possibilities would seem to be open, but Burnet's (1959) "forbidden-clone" hypothesis is very attractive at the theoretical level and it also offers an elegant interpretation of many of the clinical, genetical, laboratory and statistical features of recognised disturbed-tolerance auto-immune diseases. Should this be the proper interpretation then we have to inquire whether the mature cells of the forbidden-clone are small lymphocytes bearing cell-bound auto-antibodies, or whether they are other types of cell synthesising and secreting humoral auto-antibodies. Here the deduction concerning the sex-differential in the latent period, taken in conjunction with the evidence for other diseases, suggests that the primary pathogens should be forbidden small lymphocytes. A common result of the presumed auto-immune interaction between lymphocytic cell-bound auto-antibody and target cells is the proliferation, or hyperplasia, of target tissue, and an example of this is the pannus formation in rheumatoid arthritis; this phenomenon is in full accord with Burwell's view (1963) that the primary and intrinsic role of the normal lymphoid system is the regulation of symmetrical mitosis in "target" tissues throughout the body. The normal mitogenic sub-immune interaction between, say, small lymphocytes and target cells should, according to Burwell, produce normal symmetrical mitosis. However, when in auto-immunity the sub-immune interaction is replaced by a strong immune-type interaction, it is not surprising that abnormal and excessive mitotic activity often results. The pathology of Dupuytren's contracture can be accounted for in these terms, and the histological picture has been described as "... a combination in varying proportion of fibroblastic proliferation and collagen formation ... " (Hueston 1963). The finding of hyperplastic foci of fibroblasts around the sheaths of branching blood vessels fits in with the concept that the abnormal mitogenic agent (the "forbidden" small lymphocyte) is blood-borne. However, the identity of the cells that constitute the primary target of the (presumed) auto-immune attack is still not clear. The proliferating fibroblasts may represent a stage of metaplasia, and MacCallum (quoted by Hueston 1963)

believed that the changes represent a dedifferentiation of muscle fibres to Dupuytren's tissue. Presumably the "small round-cell collections" (Hueston 1963) formed by perivascular infiltration include concentrations of small lymphocytes.

One of the more unusual features of this disease is the long duration of the latent period. The deduced average values of fifteen years for men and thirty years for women are the highest I have so far encountered. It has been proposed that one of the important features determining the duration of the latent period is the efficiency of the endogenous defence mechanism directed against the developing forbidden-clone (Burch 1963*a, b*, 1964*c, d, e*; Burch and Rowell 1963, 1965). Where forbidden-clones result in lymphocytes the efficiency of defence appears to be twice as high on the average in women as compared with men. Another interesting aspect of this sex-differential is seen in connection with Dupuytren's contracture. Thus Hueston (1963) found that 27.6 per cent of men over sixty years old with Dupuytren's contracture show flexion deformity while only 14.3 per cent of women with the disease in the same age group show the deformity. It has been proposed (Burch and Rowell 1965) that the germinal centres found in the thymus in connection with rheumatoid arthritis, systemic lupus erythematosus and myasthenia gravis (Burnet and Mackay 1962, Mackay and deGail 1963) represent one phase of this defence mechanism. Cell-bound auto-antibodies would appear to be auto-antigenic, and forbidden small lymphocytes are probably attacked by classical immunoglobulins (either 19S or 7S or both) (Burch and Rowell 1965); it is interesting, therefore, that the thymic germinal centres contain plasma cells which are now known to be the main producers of classical immunoglobulins. Much evidence (Burch 1963*a*, 1964*c*; Burch and Rowell 1963, 1965) indicates that this endogenous defence mechanism is vulnerable to various extrinsic factors such as certain drugs and infections and also to mental stress. Competition for finite defence resources appears to be involved where infections are concerned, and in principle it is expected that other forbidden-clones, antigenically related to the first, would also compete for the defence mechanism and would shorten the latent period for both or all auto-immune diseases. This kind of consideration might account for the relatively early onset of Dupuytren's contracture in patients with epilepsy, alcoholism, pulmonary tuberculosis and in other chronic invalids (Hueston 1963). However, the fact that at sixty or more years of age the prevalence of Dupuytren's contracture in epilepsy and chronic alcoholism is nearly twice as high as in normal persons suggests that there is, in addition, one or more genetic factors that are common to each of these diseases and conditions. Ling (1963) has proposed that most, and perhaps all, cases of Dupuytren's contracture are caused by a dominant mutant gene. He also points out that, with such a high gene frequency in the population, the existence of homozygotes is likely. However, the homogeneity of the age pattern suggests that, from the point of view of initiation, the population at risk is homogeneous. Although Ling's familial study is reasonably consistent with the single Mendelian autosomal dominant gene hypothesis, it is also consistent with a single autosomal recessive gene hypothesis. If the typical frequency of individuals predisposed to Dupuytren's contracture is about 25 per cent of all individuals at birth in British and Australian populations, then the frequency of the predisposing allele (for simple, monogenic, recessive inheritance) will be in the region of 50 per cent. On this scheme the average proportion of the siblings of a proband who will also be predisposed to Dupuytren's contracture will be 1 in 2.25 or 45 per cent. The total number of first degree (male and female) relatives of probands found to be affected was forty-one out of a "weighted total" examined of eighty-six (Ling 1963). The "weighted total" involves a correction for incomplete penetrance. Hence the corrected proportion of forty-one out of eighty-six, or 48 per cent, of affected first degree relatives is also consistent with the single recessive autosomal gene hypothesis. Investigation of the offspring of parents, both of whom have Dupuytren's contracture, could, in principle, distinguish between these alternatives. On the simple recessive hypothesis all offspring would be predisposed. If on the dominant gene hypothesis only heterozygous individuals are predisposed to the disease then 50 per cent of

offspring would be at risk; if, however, heterozygotes and homozygotes are both predisposed, rather more than 75 per cent of offspring would be at risk. In view of the changing penetrance of the disease with age it will not be easy to distinguish between these various possibilities—and there may be others. It has previously been found that the probable allelic frequencies associated with auto-immune, or possible auto-immune, diseases tend to lie in the region of 0·3 to 0·7 (Burch 1963*a*, 1964*b*, *c*, *d*) although exceptions, above and below these limits, have been found. It should be mentioned that the efficiency of the endogenous defence system should be affected by genetic factors other than the X-linked ones, and hence the severity of the disease may to some extent be governed by additional autosomal genetic factors.

The relation of the disease to injury has long been a source of controversy. However, it now seems to be agreed that there is little or no association between Dupuytren's contracture and occupation (Early 1962, Hueston 1963). This is to be expected on the basis of the current theory. However, a specific injury to the hand or arm—with bruising or bleeding—does appear to be a precipitating factor (Hueston 1963). This again is to be expected on theoretical grounds because repair of target tissue should require a specific mitotic stimulus, which should evoke the flow of efferent small lymphocytes, and, furthermore, injury to blood vessels should facilitate the diffusion of "forbidden" lymphocytes to the target tissue.

In treatment the present etiological theory gives little ground for optimism. At the fundamental level the therapeutic problem would appear to be closely similar to that associated with, for example, rheumatoid arthritis and systemic lupus erythematosus. If any way of potentiating the endogenous defence mechanism could be discovered this should in theory have a palliative effect; at present, however, there would seem to be no obvious alternative to surgery.

SUMMARY AND CONCLUSIONS

1. On the basis of, first, a mathematical analysis of the age-specific and sex-specific prevalence of Dupuytren's contracture; second, the genetical aspects; and last, the pathology, it is concluded that Dupuytren's contracture is probably a spontaneous disturbed-tolerance auto-immune disease.
2. The proportion of predisposed individuals at birth is about 20 per cent of males and females in the population studied by Early (1962), although it differs between populations and races.
3. The disease is probably initiated by four random, dependent-type, autosomal somatic gene mutations in a stem cell of the lymphoid system. With the accumulation of the fourth and final somatic mutation, a "forbidden-clone" of lymphocytes is probably generated. There is a latent period between the occurrence of the last initiating event and diagnosis.
4. In men the average latent period is about fifteen years, in women it is about thirty years.
5. The target tissue primarily attacked by forbidden lymphocytes is unknown, although proliferating fibroblasts are evidently a consequence of the auto-immune attack.

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