

ation following contact with sclerosing substances like silica crystals.

Regarding the experimental results and the rarely diagnosed clinical lymphostatic disturbances in organs, further investigations should be enhanced to get more

information about the pathogenetic effect of lymphostasis in organic diseases. First investigational results in that direction have been achieved for organs like the cerebrum, the heart, the liver, the pancreas, and the kidney.

The Medical Treatment of Lymphoedema

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The benzo-pyrones

These are a group of drugs with many actions on the body^{1,2}. One of the most potentially important of these is that they can greatly increase the normal lysis of proteins in the tissues^{2,3}. Since lymphoedema is a disease where there are too many proteins which cannot be removed from the tissues⁴ they would appear to be very useful in its treatment, as has been shown by animal experiments and clinical trials². (This does not apply to long-standing cases where there is much fibrosis, although even here a relief of symptoms is often experienced and, since the collagen of the body is being continually remodeled, it may be that long-term treatment will permit its removal, but this has not yet been tried.)

The elucidation of the mode of action of the benzo-pyrones in high-protein oedemas has been made difficult by the multiplicity of their actions^{2,3}. They could have acted by decreasing protein leakage from the blood vessels; this sometimes seems to happen, but most of the time many (but not all) of the members of this group actually damage the blood vessels by releasing histamine. (This effect is more than compensated for by their action in removing proteins.) Again, they could have increased lymphatic function and indeed they do this in normal conditions: in oedema, however, the lymphatics are usually functioning as well as they can (they may even be completely and irreversibly occluded). The drugs could have removed the proteins by simple endocytosis, but this does not occur. In the end, it has been shown that they remove proteins by increasing their lysis in the tissues – whether intracellularly or extracellularly, or both, is unknown. In effect, the benzo-pyrones allow certain cells in the tissues to bypass the malfunctioning lymphatics and remove the proteins by lysing them *in situ*. The fragments can then pass rapidly into the blood vessels because they are small enough to pass between the cells, have high diffusion coefficients, suffer little molecular sieving, and have their concentration gradients directed towards the tissues. The cells involved are likely to be the macrophages, as has been shown *in vitro* and by poisoning them with sili-

ca^{2,5,6}. It is singularly fortunate that these are just the cells (in their stimulated form) which so readily accumulate in lymphoedema^{7,8} as well as in the other forms of chronic inflammation. It appears⁸ that lymphoedema has many of the features of chronic inflammation and, if this is the case, the removal of excess protein may well have a beneficial effect in itself since it may be that altered plasma proteins are the initial stimulus causing this⁹. Thus these drugs particularly enhance the normal proteolysis of the cells which accumulate just where they are needed. It may be that this is the reason why the benzo-pyrones are so free of side-effects when compared with other treatments using proteolysis.

These drugs have also been shown to be very helpful in many other pathological conditions². The number of these is at first sight surprising, but is not so when one reflects upon how many diseases have a lymphostatic component, either directly implicated in their aetiology, or as a side-feature which increases their debilitating effect^{10,11}. Such conditions include burns and inflammations in general, venous insufficiency (including varicose ulcers), post-surgical oedema and that caused by fractures and torn ligaments, and other conditions in which high-protein oedemas occur.

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