and carbon labelling demonstrated them to be insufficient. There is intracellular edema of the endothelial cells and of smooth muscle cells of arteries and veins. More marked is the thickening and edema of the subendothelial basement membrane and of the basement membrane of smooth muscle cells. Due to the endothelial damage, fibrin thrombi are encountered frequently in blood and lymph vessels. The interstitial tissue both of the epi- and subfascial space of the extremity is massively edematous, multiple lymphocytes and phagocytes are present. Similar, but less pronounced transitory changes of blood and lymph vessels are found in acute lymphedema[12–15], but they regress almost completely, following subsidence of the edema. In our experimental, manifest chronic lymphostatic lymphedemas of 2 and more years duration, the tissue changes were found to be irreversible. The lymphatics of the epi- and subfascial space become enormously dilated. They are massively increased in number, as observed in lymphangioma-like alterations. The walls of lymph collectors and precollectors are thickened and sclerosed, and these structures are difficult to differentiate from veins without carbon labelling. The basement membranes of the lymph capillaries are continuous and thickened, the anchoring filaments are increased in number. The thrombi within the lymph vessels, found during the latent phase, become organized and recanalized. Also, the walls of the arteries and veins are affected by marked localized arteriosclerosis, consisting in connective tissue sclerosis of all tissue layers, predominantly involving the adventitia. The blood vessel sclerosis leads in many arteries and veins to thrombus formation. The connective tissue of cutis and subcutis as well as of the subfascial space is increased, heavily sclerozed and contains infiltrates of chronic inflammation. The deep fascia, anatomically dividing the epi- from the subfascial space, is thickened, but is found to be traversed by many ectatic lymph vessels. This leads to a free functional communication between the two compartments and is especially important if the lymphatic system of only one compartment is obstructed. The structures of the nerves and muscles were not found to be altered by chronic lymphostasis[16].

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Pathology of Lymphoedema

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The histological equivalent of the macroscopic appearance in acute and chronical lymphoedema is not very easy to recognize. Lymphoedema cannot be distinguished from other oedema rich in protein with morphological methods. Lymphostasis induces dilation of lymph vessels, but, lymphangiectasia can also be observed under increased load of the lymph vascular system. For instance, dilated lymphatics can be observed accompanying ovarial cysts, lung oedema, and within almost every inflammatous tissue, although there is no blockage of lymph outflow. In spite of these difficulties in interpretation of dilated lymph vessels, it is of great importance from the clinical and morphological point of view to get more information about the appearance of lymphoedema caused by blockage of lymph vessels.

For this reason, experiments have been performed with ligation of lymph collecting vessels and of lymph trunks to induce renal lymphostasis, lymphostasis of the liver, and cardiac lymphostasis. Interruption of renal lymph outflow induces nephrotic changes with disturbances of renal concentration. Blockage of lymphatic outflow from the liver aggravates considerably the effects of other loads, as for instance that of cholostasis. Cardiac lymphostasis causes myocardial oedema and oedema of the cardiac valves leading to rather severe fibrosis of the valve leaflets. The experimental lymphostasis, as mentioned above, cannot be maintained for longer than 1 week since regeneration of newly formed lymph vessels and opening of anastomoses will soon permit a sufficient outflow of lymph. First experiments with 'malignant' complete and continuous lymphostasis by encapsulating the liver or other organs with plastic material seem to induce severe degenerative effects within the enclosed organs. In addition, complete lymphostasis of organs can be controlled by non-morphological investigation methods, as for instance cardiac lymphostasis leads to electrocardiographical disturbances like ST-depression. Lymphostatic liver damage increases SGPT and alkaline phosphatase during the first 2 weeks after blockage of hepatic lymph flow.

Signs of lymphostatic organ diseases in man are rare and hard to prove. Classical lymphostasis of extremities and of organs can be observed in cases with malformations, hypoplasia or aplasia of the lymph vascular system. In addition, blockage of lymphatic outflow can be caused by tumorogenic lymphangiosis, inflammatous lymphangiosclerosis, and sclerotic vascular obliter-

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 tissues[4] they would appear to be very useful in its treatment, as has been shown by animal experiments and clinical trials[2]. (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 was well as they can (they may even be completely and irreversably 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 silica[2,5,6]. It is singularly fortunate that these are just the cells (in their stimulated from) which so readily accumulate in lymphoedema[7,8] as well as in the other forms of chronic inflamation. It appears[8] that lymphoedema has many of the features of chronic inflamation 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 this[9]. 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 conditions[2]. The number of these is at first sight surprizing, 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 inflamations 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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