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E. W. Horton B.Sc.



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Pulmonary tuberculosis was first described by Greek physicians about the time of Hippocrates. They called the condition - phthisis - the wasting disease. It

(3) The resistance of the body may be increased locally. (collapse therapy)
(5) The bacilli may be removed by local treatment (surgery)
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(4) The bacilli may be destroyed by systemic treatment. (chemotherapy)
tuberculosis is a morbid process which can occur in various parts of the body, and that phthisis or consumption is

tuberculosis of the lungs. The causal agent, Mycobacterium tuberculosis, was discovered by Koch who published his work in 1882. In the past it has been customary for each

medical practitioner. The pathological processes which occur in response to infection with tubercle bacilli will not be discussed here in any detail, but they are most adequately described in the standard textbooks (e.g. Boyd 1953, Florey 1954.) For the purposes of the discussion of treatment, the disease may be regarded simply as a struggle between the tubercle bacilli and the defences of the human body. The aim of therapy must be to swing the battle in favour of the body's defences; but it is important to remember that without these natural defences no amount of therapy will be of any avail. Keeping this struggle in mind, the methods of treatment can be reviewed. Briefly they are of four types; two aim to increase the body's resistance and two are directed against the tubercle bacilli. The planning of a therapeutic trial with adequate controls, objective

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Assessment of Treatment.

In the past it has been customary for each medical practitioner to base his treatment on methods hallowed by tradition, the therapy being modified only in the light of the practitioner's own experience and adjusted to the particular needs of the individual patient. The doctor assessed the value of any form of therapy by means of his clinical impressions. It is not surprising that such methods of assessment should have persisted for so long, for the very nature of the doctor-patient relationship lends itself to evaluation by clinical impression rather than by objective methods which are now becoming prevalent.

The introduction of the scientific method into medicine and in particular the introduction of statistics has changed the whole outlook. The planning of a therapeutic trial with adequate controls, objective

(all of whom had bilateral tuberculous bronchopneumonia) methods of assessment by unbiased observers, and statistical analysis of the results, is often a vast undertaking but the supreme advantage is that definite information is obtained. Fox (1954) gives an interesting account of the methods used in the Medical Research Council trials.

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(1) General Measures to Increase the Body's Resistance.

Four factors are to be considered under this heading:- rest in bed, diet, fresh air, and the psychological attitude of the patient to his disease.

Rest in bed. For centuries consumptive patients have been treated by rest in bed. Their wise physicians, though ignorant of the real cause of the disease, were ardent believers in the healing power of Nature - *Vis Medicatrix Naturae*. However, no series of cases treated by bed rest alone, compared with controls (patients not at rest in bed) has been reported. In the first trial by the Medical Research Council, the control patients were treated by bed rest alone; and it was found that 33% of those patients

(all of whom had bilateral tuberculous bronchopneumonia) showed an improvement in the radiographic picture after six months bed rest, (M.R.C. 1948) and were still alive after five years (see Livingstone 1955). Whether such improvement was due to spontaneous regression of the disease or to the effect of rest in bed, cannot be stated definitely. For a variety of reasons, however, it seems reasonable to suppose that rest in bed is advisable. In some cases the patient is unfit for activity of any kind and is obliged to confine himself to bed, but nowadays the majority of cases are detected early, and would normally have continued with their occupations. In these people confinement to bed for a period should aid the processes of recovery by enhancing their powers of general resistance.

Livingstone (1955) believes that extension of the disease in a newly diagnosed case is largely prevented by bed rest. He recommends that such patients should be confined to bed at home throughout the twenty-four hours, until hospital accommodation can be provided. Dillwyn Thomas advises postural retention for cavitated cases. The patient is immobilised in a plaster cast and his bed is raised at the foot. Continued for ten weeks together with chemotherapy this form of treatment results in the decrease of cavity size thus enabling less extensive surgery to be carried out. (Thompson, Savage & Rosser 1954).

In a study carried out under the auspices of the Committee on Non-Surgical Collapse Therapy of the

American College of Chest Physicians, Trimble found that very few of the one hundred physicians questioned would treat even minimal pulmonary tuberculosis with rest in bed alone.

Fresh Air and Sunlight.
(Trimble 1955). Whereas in 1948 the treatment was often recommended. There are many who consider that the value of rest is overestimated, and a preliminary report from the University of Colorado suggests that ambulation of patients with pulmonary tuberculosis gives no worse results than those of prolonged rest in bed, provided that adequate chemotherapy is instituted. (Dressler et al.) 1954).

Although no statistically valid evidence is available, it is probable that rest in bed is often a useful adjuvant to other forms of therapy. However, the disadvantages of prolonged recumbency must be taken into account, and weighed against the possible advantages. When the disease process has been arrested, it is likely that further bed rest is unnecessary.

Diet.

The value of an adequate diet in the treatment of pulmonary tuberculosis cannot be estimated, but it would seem unreasonable to curtail the intake in any respect. Meals should stimulate the appetite, should be small and frequent and should include abundant milk, butter and raw fruit. The calorific value of the diet should be high, and vitamin supplements should be prescribed. A liberal supply of essential food factors should ensure that there

is no lack of materials for the synthesis of the body's various protective agents.

Fresh Air and Sunlight.

Before the days of chemotherapy, when the tuberculosis hospitals and sanatoria were filled with open cases of tuberculosis, it was important to cut down cross-infection not only from patient to patient, but from patient to the nursing staff. This was achieved in some measure by treating the patients out of doors or in wards with uncomfortably adequate ventilation. The sun's rays are definitely lethal to the tubercle bacilli, thus "out-of-door" treatment had a rational basis. With the coming of antibiotics, the proportion of open cases has been considerably reduced and the danger of cross-infection consequently minimised. However, the psychological benefits of fresh air and sunlight are probably of sufficient importance for this type of therapy to be retained, but there can no longer be any justification for an unheated ward during the cold months.

The treatment of tuberculous cases at mountain altitudes has been advocated since the time of Celsus, but the Sanatorium regime is of more modern origin and was introduced in the last century. The isolation of these mountain resorts with their clean fresh air is undoubtedly associated with a low tuberculosis morbidity rate, (i.e. amongst the native population) but the superiority of

therapy in these places over simple rest in bed in a hospital nearer civilisation, remains unproved. No statistical investigations comparing such forms of treatment have been reported. Miller (1928) found little difference in progress amongst cases treated in mountain sanatoria and those in other hospitals, his opinion was based purely upon clinical impressions. Sewell (1932) also expressed his doubts about the value of high altitude treatment.

Psychological Attitude of the Patient.

As a result of the recent advances in treatment, most sufferers from pulmonary tuberculosis can now be assured of the prospect of an ultimate cure. Cases entering a tuberculosis hospital for the first time are able to watch their fellow-patients responding to therapy and being discharged, cured. The psychological effect of this does much to enhance their own progress, for a patient's co-operation and determination to overcome the disease are as important as any drugs the physician may possess. This is especially true in a disease like tuberculosis, where prolonged treatment may be necessary, testing the patience and perseverance of both patient and doctor. It is imperative to prevent boredom by appropriate diversional therapy and the provision of light recreational facilities (e.g. library, radio & television.). The acquiring of new skills, which would enable the patient to earn a living after discharge, should a change of occupation be necessary complications. Furthermore, the coming of chemotherapy

is an important aspect of later therapy. Such provisions give the patient new hope and purpose in life, and help to dissipate any feeling of inferiority he may have towards his associates outside; for there is still much prejudice against the tuberculous patient amongst the lay population and so it is essential that the patient should be discharged with a well-informed attitude towards his past disease.

(2) Measures to Increase Local Resistance.

The adequate healing of a tuberculous cavity in the lung cannot take place until its walls are approximated. If this does not occur and the cavity persists, provided the patient's resistance is sufficient, the lesion will fibrose and drift into chronicity. Collapse of the whole or part of a lung may eliminate the cavity and thus hasten the process of healing. When healing has occurred, the collapsed pulmonary tissue is allowed to re-expand. Collapse may be achieved by artificial pneumothorax, pneumoperitoneum or thoracoplasty.

Artificial Pneumothorax. (A.P.)

Treatment by A.P. was widely used before the introduction of chemotherapy. Due partly to misuse in less expert hands and partly to dangers inherent in the method itself, this form of treatment has led to many complications. Furthermore, the coming of chemotherapy

and other collapse methods have decreased the need for its use. Trimble and Easton (1955) in their analysis have shown that nowadays, (1953) few practitioners would recommend A.P. therapy in any form of pulmonary tuberculosis, whereas in 1948 a fairly high proportion of cases would have received such treatment. As pointed out by Scadding (1954), it would be wrong to discard a form of treatment because its indications and limitations have not been fully appreciated.

Though there is a voluminous literature on the subject, it is difficult to find any reports of controlled series of cases. Foster-Carter (1952, 1954) has given an account of the results of A.P. treatment after a minimum of eight years. He concludes that in selected cases excellent results are obtainable. A patient with a unilateral cavitation under 4 centimetres in diameter is regarded as suitable. If adhesions are present they should be divided within the first week of therapy, but if they prevent closure of the cavity the A.P. should be discontinued. Rafferty (1947) has shown that the prognosis is worse if A.P. is continued in the presence of an unclosed cavity than if no treatment is given. Empyema is a dangerous complication. Foster-Carter and his co-workers (1952) had an overall incidence rate of 17 per cent in their series. The highest incidence occurred in lungs where adhesions had prevented satisfactory collapse of the cavity. There was no significant difference between the incidence of empyema in cases with adhesions and in those without adhesions,

provided that the A.P. is satisfactory. Thus adhesions, in themselves, are not a contra-indication to A.P. therapy, if the cavity is effectively closed.

Scadding considers that the following are definite contra-indications to the use of A.P. therapy:- Tuberculous pneumonia, because pleural effusion and empyema are likely complications - tuberculoma of the lung, because A.P. therapy has no effect; chronic tuberculosis with extensive fibrosis, because adhesions prevent relaxation; large peripheral cavities which are receiving a blood supply from the chest wall, because vessel rupture may occur; and tuberculosis of major bronchus associated with a tension cavity or atelectasis or both, unless the tension element can be overcome. (Scadding 1954).

Closure of cavities is usually completed after 2-6 months. The development of a small pleural effusion during the A.P. treatment is of no significance, but a large effusion not absorbed after rest and aspirations is an indication for discontinuing the treatment. A "Frozen Lung" results from extensive fibrosis involving the wall, or from pleural effusion or atelectasis. If it is fully developed there is little hope of functional recovery. (Wright et al.) 1949.)

An A.P. should be maintained for 3 - 5 years, though this period may be shortened by chemotherapy. Then the re-fills are progressively reduced to avoid the risk of pleural effusion or of rupture of the visceral

pleura. A tomograph should be taken before the lung reaches the chest wall, so that the A.P. can be re-induced if adequate recovery has not taken place.

Although it is possible that A.P. therapy may be a useful adjunct to chemotherapy and rest in bed in certain selected cases, the protagonists of the treatment have not convincingly shown that it has any advantages over other collapse procedures, in particular pneumo-peritoneum.

with a chronic cavity in the upper lobe in preparation for

Pneumoperitoneum. (P.P.).

There is no reliable evidence to suggest that phrenic crush is advantageous in the maintenance of P.P., though many workers believe that such a combination is essential for good collapse therapy.

Banyai introduced this treatment in 1934. (Banyai 1946.) Its real value is hard to estimate, for, though many papers have appeared on the subject, there have been no reports of any adequately controlled series. The whole of the literature on P.P. therapy consists of innumerable articles describing the results of treatment on isolated series of cases, comparison between which is hopeless and in any case statistically invalid. There have been great differences in the amount and type of chemotherapy used (if any), in the use of phrenic crush, in the type of lesion treated and in the use of rest, from one series to another.

Since pleural surfaces are not separated, the complications seen in A.P. are not encountered.

Livingstone (1955) estimates that the incidence of serious complications is less than 5 per cent; these include air embolism and peritoneal effusion. The likelihood of appen-

dicitis occurring is increased in patients with pneumoperitoneum (Rilance & Waring 1944).

Technically, P.P. is preferable to A.P. because it is easier to induce. It has the added advantage that it can be terminated at will and can be used in patients living at home. Scadding (1954) recommends the induction of P.P. in patients with acute exudative lesions, especially where there are signs of early cavitation and in the patient with a chronic cavity in the upper lobe in preparation for resection.

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Frequent re-fills are necessary, as the air is completely absorbed within 6-8 weeks. The duration of treatment **must** be adjusted to the particular case, in general it may be said that it should be kept up for at least one year, though if it precedes surgery it may be either terminated before the operation or carried on into the post-operative period.

High relapse rates are being reported in patients who have had P.P. as their main line of therapy (Morris et al. 1952, Edge 1953), it is possible that poor selection of cases was the real cause of this failure.

In view of the relatively innocuous

nature of the procedure, it would seem worth while carrying out a therapeutic trial of this method. Supposedly suitable cases should be randomly distributed between P.P. and control treatment, both test and control subjects receiving adequate chemotherapy and equivalent amounts of bed rest and general nursing attention.

Thoracoplasty.

The principle of thoracoplasty is to remove part of the bony chest wall, and thus allow collapse of the underlying portion of lung. The idea was first put forward by Tuffier and developed by Sauerbruch who used the para-vertebral operation, involving the removal of as many as 10 ribs. The method was not ideal and carried a high mortality rate. Holst and Semb approached the problem from a slightly different angle. They argued that concentric collapse of the diseased area was required so that the lung should be allowed to collapse from above as well as from the side. This new technique was accompanied by a lower mortality rate and was more efficient in closing cavities.

Price Thomas (1942) advises the extension of the number of stages in the operation up to three. The detailed operative procedures cannot be discussed here, but they have been described by various thoracic surgeons.

(see Price Thomas 1952, Belcher 1954.)

surgery. Improved Now that the morbidity and mortality rates following thoracoplasty have been reduced (Price Thomas 1952, Sellors 1947, Laird 1953.), perhaps its greatest disadvantage is that it is not always effective in closing the cavity. It is most applicable to lesions in the apical and posterior segments of the upper lobe - the situations where pulmonary tuberculosis is commonest. Thoracoplasty will be of little value in solid lesions, or in areas of bronchiectasis or of gross tissue destruction. If the operation entails the collapse of much normal lung tissue in order to close a cavity, it cannot be justifiable.

After a patient has Extraperiosteal plombage and extrapleural pneumothorax are essentially variations of thoracoplasty designed to overcome some of its disadvantages. They should be considered in special cases, but have no wide application. Their disadvantages may outweigh their usefulness. (Belcher 1954).

(3) The Removal of Bacilli by Locally Excising

Diseased Tissue - Resection.

The tuberculous lung has, until recently defied surgical treatment since such interference almost inevitably ended in disaster due to spread of the infection to other parts of the lung. However, during the last decade a number of advances have contributed to improved thoracic

surgery. Improved anaesthetic methods which prevent aspiration of infected tuberculous material, a more exact knowledge of pulmonary anatomy and the discovery of streptomycin have ^{increased} the surgical possibilities in the field of pulmonary tuberculosis. Depending upon the extent of the tuberculous lesion, a total pneumonectomy, a lobectomy or a segmental or sub-segmental resection may be carried out. The aim of such treatment is to remove those lesions which the body's defences are unable to cope with, leaving the smaller foci which should be overcome with the aid of chemotherapy.

What are the indications for resection?

After a patient has been on conservative treatment - rest, good food, minor collapse therapy (possibly) and chemotherapy - and ceases to show any further improvement as revealed by clinical and radiological examination, it is well to consider surgical intervention. The choice will lie between thoracoplasty (already discussed) and resection. Resection is absolutely indicated in all solid tuberculous lesions over 2 centimetres in diameter (Cleland 1954); such lesions can be detected easily on radiological examination. Tuberculous foci associated with broncho-stenosis should be resected since the stenosis will prevent healing and the condition is usually aggravated by attempts at collapse therapy. Cavitation in the lower lobe which has not responded to conservative treatment is treated by resection in preference to thoracoplasty, since the latter

procedure would require the collapse of nearly the whole lung on that side. Where collapse therapy, either surgical or medical, has failed to procure healing of a cavity, the diseased area should be resected. The presence of bronchiectasis or a portion of completely destroyed lung is an indication for resection. It is perhaps more open to argument whether resection should be employed in fibro-caseous disease of the upper lobe, for the removal of tension cavities or in segmental lesions.

If there is doubt whether to resect or to perform thoracoplasty, the following factors must be taken into consideration. Removal of part of a lung will be followed by compensatory expansion of the remaining lung tissue on both sides, so any latent foci of tuberculosis may become activated. This is of particular importance with regard to cavities which may be considerably enlarged after resection of another portion of the lung. Resection is contraindicated in the presence of an active lesion. Activity may be assessed by the presence or absence of fever, the E.S.R. reading, change in weight and changes in the radiological picture. The active lesion is preferably treated by rest and chemotherapy, surgery may follow when the lesion is again quiescent.

The importance of streptomycin in the development of thoracic surgery for pulmonary tuberculosis has been stressed. Isoniazid and sodium p-aminosalicylate

have now been added to the armamentarium. If the patient coming to surgery is infected with organisms which are resistant to one of these drugs, it is essential that chemotherapeutic cover should be provided with drugs to which his bacteria are still sensitive, otherwise the risk of complications is much increased.

The supreme advantage of resection is that the main focus of disease is removed, leaving the body to deal with only minor foci. Less functional impairment follows resection than thoracoplasty. From an economic point of view, resection is a most satisfactory form of treatment, for it favours earlier re-habilitation, increases hospital turnover, results in fewer re-admissions and converts the positive sputum so that spread of infection is reduced. (Conklin 1955). On the other hand, complications including empyema, broncho-pleural fistula and atelectasis are more common and usually more serious after resection than after thoracoplasty. (Cleland 1954). The inadvisability of resection where cavities are to remain must be re-emphasised.

(4) The Destruction of Bacilli by Systemic Treatment - Chemotherapy.

The discovery of streptomycin by Waksman and his co-workers (Schatz, Bugie & Waksman 1944), and the

experimental work and clinical trials of Hinshaw (Hinshaw & Feldman 1944, Hinshaw & Pfuetze 1946) revolutioned the treatment of pulmonary tuberculosis. Not only did curative medical treatment become possible but the dangers of thoracic surgery from dissemination of the disease were considerably reduced. It soon became evident that tubercle bacilli were remarkably efficient in developing resistance to the drug. This stimulated further research in the hope of finding substances to which the bacteria would not become easily resistant. Sodium para-aminosalicylate in large doses was found to delay the development of resistance to streptomycin, and oxytetracycline, introduced in 1950, was shown to have some anti-tuberculous activity. The following year a real advance was made when isoniazid was produced, for it was found to have high anti-tuberculous activity and to be effective by mouth producing no toxic effects, but again drug resistance soon developed.

Other drugs including Viomycin, Amithiozone, and Pyrazinamide have been used but owing to their toxicity have not found wide application. They may be required where resistance has developed to the three main antibiotics.

Pharmacology of the Anti-tuberculous Drugs.

Streptomycin.

Streptomycin is not absorbed from the gut. It is administered intramuscularly, as its sulphate

The toxic effects of P.A.S. are mainly gastro-intestinal in origin. (Lancet Annotation 1955) Toxic effects may occur after prolonged treatment and include vertigo and deafness due to damage to the eighth cranial nerve. Maher-Loughnan (1952) has shown that toxic effects are much less frequent when doses of 1 Gm./day are used instead of the 2 - 3 Gm. recommended in the earliest days of chemotherapy. The incidence would possibly be even less if twice weekly injections were universally substituted for the daily regime, at present widely used. There is evidence that therapeutic efficacy is not impaired by the lower dosage. (M.R.C. 1955).

Oxytetracycline.

Sensitivity reactions to streptomycin are liable to occur amongst the nursing staff who constantly handle the drug. Crofton (1952) has reported success in desensitising these people; but prevention by the wearing of gloves is obviously preferable. Intramuscular injections of streptomycin are at best unpleasant and may be extremely painful, this should be considered when a choice of therapy is available.

Sodium p-Aminosalicylate. (P.A.S.).

Viewpoint. P.A.S. is given by mouth. The daily administration of 20 Gm. (5 Gm. four times a day) in 1 Gm. cachets, has been recommended in the past. Reduction of dosage to 10 Gm. did not result in any diminution of therapeutic effect in a recent trial (M.R.C. 1955).

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Isoniazid.

Isoniazid is taken orally in daily doses of 200 mg. It has a high level of activity, and few toxic effects, none serious, have ever been reported at therapeutic dose levels. Disturbances of the central nervous system including psychological changes, may occur when as much as 600 mg. is administered daily (D'Esopo 1954).

Oxytetracycline.

Oxytetracycline is a wide spectrum antibiotic. It is effective against tubercle bacilli in doses of 5 - 7 Gm. daily. The drug is absorbed from the gastro-intestinal tract and is normally given orally, but special preparations may be administered intravenously if necessary. By eliminating the normal flora of the gut, oxytetracycline may predispose to invasion by yeasts, such as monilia; thus, stomatitis, proctitis and diarrhoea are possible toxic effects.

Viomycin.

Viomycin like neomycin is very toxic to the kidney. It is much less effective than streptomycin, and is little used.

Amithiozone.

Amithiozone is a thiosemicarbazone with low efficacy and high toxicity. It has been used effectively in mucous membrane lesions. (see D'Esopo 1954).

Pyrazinamide (aldinamide).

There have been a number of enthusiastic reports of the high activity of pyrazinamide. (D'Esopo 1954, Veterans Administration 1955.) However, some clinicians have found that it may produce serious toxic effects, especially on the liver, and advocate its abandonment for that reason (Potter & Chang 1955). Drug resistance develops rapidly, but it may be of value in combination with isoniazid to which it delays resistance.

Drug Resistance.

If any of the anti-tuberculous agents is administered alone for a period of 3 - 4 months, bacterial resistance to that drug will occur in 30 - 40 percent of patients. (Veterans Administration 1948, Tempel 1952, Dye et al. 1953, M.R.C. 1950, 1953, Daniels & Bradford Hill). Whereas the administration of two drugs in full therapeutic dosage has been shown to reduce the development of resistance to both. (M.R.C. 1950, 1952a, 1953a, 1953b, Dye 1952, Tempel 1952, Miller et al. 1952, Friedman et al. 1952,

(Daniels & Bradford Hill 1952, Pitts et al. 1953.)

Without discussing the detailed mechanism of drug resistance (see Work & Work 1948), these findings may be explained as follows. During the growth of a bacterial colony, a mutation may occur spontaneously which renders the new strain so produced relatively insensitive to one or other of the antibiotics. If such a mutation occurs in one of the patient's organisms while under treatment, or if his organisms already contain a small proportion of such insensitive bacteria, then these will thrive in the presence of the particular chemotherapeutic agent, while the vast majority of his organisms will be inhibited. Eventually, the patient will be infected with a strain which is composed predominantly of resistant bacteria. If however two drugs are used simultaneously, the chances of drug resistance developing are considerably reduced. Such an event would require that a sensitive organism should undergo two mutations. The chances of that occurrence may be expressed as the square of the chances of one mutation taking place. Thus the exhibition of two drugs to which the organisms are sensitive, practically ensures that bacterial resistance to either will not occur. On the other hand, the administration of two drugs, one of which has been given before so that the patient's organisms are no longer sensitive to it, would be expected to have an effect equivalent to the administration of the second drug alone. This is

borne out in clinical practice. (Turnbull et al. 1953). Similarly, if the dose of one of the antibiotics is insufficient, the emergence of drug resistant organisms will not be prevented. (M.R.C. 1952a.) If one of the drugs has insufficient antituberculous activity, resistance may develop to the other. (Greenberg 1952.)

It is concluded, on theoretical grounds as well as from clinical evidence, that adequate chemotherapy in tuberculosis must include the simultaneous administration of two drugs, to which the patient's organisms have been proved to be sensitive, in full therapeutic dosage. A drug which has previously been administered alone to the patient must not be used unless it is shown that the organisms are still sensitive to it, usually resistance will have developed.

The Results of Combining Two Drugs.

The value of any drug combination in the treatment of pulmonary tuberculosis must be assessed by (1) its antituberculous activity and (2) its ability to prevent the development of drug resistance. The various combinations will now be considered.

Streptomycin and P.A.S.

In the earliest M.R.C. trials, a combination of P.A.S. (20 Gm./day) and streptomycin (1 Gm./day) was shown to be superior to either of these drugs used alone. (M.R.C. 1950.) It is a highly effective combination, and

only a small proportion of the cases develop resistance to one or other of the drugs. (M.R.C. 1950, 1952, 1953a, Daniels & Bradford Hill 1952). If streptomycin is given twice weekly instead of daily, the combination is equally effective, (M.R.C. 1955.) and drug resistance is not more likely to occur (Dye 1952, Pitts et al. 1953).

Streptomycin and Isoniazid.

The combination of streptomycin (1 Gm./day) and isoniazid (200 mg./day) has been shown to be superior to any other, when progress is assessed by radiographic methods. (M.R.C. 1955). Bacterial resistance emerges in only a very small proportion of cases. (M.R.C. 1953a). In this respect the combination is equivalent to P.A.S. and isoniazid or streptomycin and P.A.S. (M.R.C. 1955).

If streptomycin is given in twice weekly injections of 1 Gm. with 200 mg. daily of isoniazid, the incidence of bacterial resistance is not increased and the efficacy is equal to that of any other combination on clinical grounds, though radiologically the higher dose of streptomycin gives a better result. (M.R.C. 1955).

P.A.S. and Isoniazid.

The combination of 200 mg. isoniazid with either 20 or 10 Gm. of P.A.S. is equivalent to treatment with P.A.S. and streptomycin (M.R.C. 1953b, 1955.). It has the advantage that both drugs are taken orally, thus

no injections are required.

Combinations with Oxytetracycline.

Oxytetracycline (5 Gm.) when combined with streptomycin prevents the development of streptomycin resistant organisms (Miller et al.)1952). Similarly, it prevents to a great extent, the emergence of isoniazid resistant organisms. (Stewart et al.)1954). Resistance to oxytetracycline does not occur.

Clinical Applications.

Chemotherapy is indicated when an unhealed tuberculous lesion is present in the lung, whether other forms of treatment are required or not. It is important that at least two effective drugs should be used simultaneously, because of the dangers of drug resistance. No drug should be used if it has been previously used alone. Regular bacterial sensitivity tests must be carried out, if these show at any stage that resistance has developed to one of the drugs, or if the patient is not making satisfactory progress, the drug regime should be changed without delay. If the bacilli are sensitive to the three main drugs choice may be influenced by consideration of their toxic effects and ease of administration.

Conclusion.

Annotation (1955) At the present day the multiplicity of available therapeutic measures tends to cause confusion in the treatment of pulmonary tuberculosis. Unfortunately, the formal assessment of all the possible combinations is not feasible. As a result of the statistically controlled trials carried out in the United States and Great Britain definite information on the most effective chemotherapeutic regimes has been obtained.

D'Esopo (1952) Treatment may be summarised as follows:- All patients with pulmonary tuberculosis should receive adequate chemotherapy in the manner described above. If a cavity results pneumoperitoneum may be indicated, but if it is situated in the upper lobe, thoracoplasty will probably be efficacious. When the disease has become quiescent, leaving a cavity in the lower lobe, a portion of grossly diseased lung or bronchiectasis, resection under antibiotic cover should be considered.

Fox (1954) Tuberculosis presents such a variety of anatomical and immunological features that the physician may still have to exercise judgement based upon experience in treating the case which is not quite typical.

Hinshaw & Pruetze (1946) *ibid.* 35, 181.

Daird (1953) *Lancet* 11, 319.

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A Physiological and Pathological Discussion of
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Submitted for the Wightman Prize in Clinical Medicine.

1955.

E. W. Horton B.Sc.



Oedema of the ankles is a frequently encountered clinical sign, which is found in a variety of diseases. It is a condition of interest equally to the physiologist, pathologist and clinician, since a complete understanding of the mechanism of its production would help to solve a host of fundamental problems.

Summaries of the positive and relevant negative findings in five patients will be given. Each of these patients presented with oedema of the ankles, though in every case a different diagnosis was reached. No attempt will be made to provide a formal history or a detailed description of the clinical examination, treatment and progress. The cases are put forward as illustrations in a general discussion on the aetiology of oedema.

Definition.

When the ankles are swollen by an abnormal accumulation of fluid in the intercellular spaces, they are said to be oedematous. It is estimated that the limbs may swell as much as 10 per cent before the condition is clinically demonstrable. Oedema is usually detected by pressing firmly on the ankles so that any excess fluid between the cells is pushed away leaving an indentation.

This is called - pitting oedema. Oedema may arise by a re-distribution of the fluids available, with the formation of a localised swelling; or it may be associated with an increase in the total amount of fluid in the body. In the latter case, the total body weight will increase and this may be detected by daily weighing of the patient.

Physiology.

Starling (1895) postulated that water and inorganic salts could pass through the capillary wall but that the large molecules of plasma proteins were retained in the vessels. He maintained that the flow of water through the capillary wall depends upon the hydrostatic pressure of the blood which tends to push water out of the capillaries, and upon the (colloid) osmotic pressure of the plasma proteins which tends to retain water inside the capillaries. Landis (1927) measured the hydrostatic pressure of the capillaries in the frog's mesentery and in general, confirmed Starling's hypothesis. In his textbook, Davson quotes similar evidence for mammals. (Davson 1951). In all cases the colloid osmotic pressure of the plasma proteins lies between the hydrostatic pressure of the arterial end of the capillary and that of the venous end.

Besides the processes of filtration and absorption, there is a third phenomenon which must be

taken into account - that of diffusion. Experiments with deuterium hydroxide have shown that water diffuses in and out of capillaries very rapidly. (Flexner et al. 1942). If water is able to pass through the capillary wall so rapidly, it is likely that there can be little resistance from the wall to its flow. This prompts the question - "How does the fluid leave the capillary?"

The capillary wall examined by ordinary histological techniques can be shown to consist of endothelial cells bound together by intercellular cement. Water and electrolytes must pass either through the cells or through this cement. It has been shown recently that the area available for diffusion or filtration of lipid-insoluble substances is of the order of 0.002 % of the total capillary surface area. Therefore, these diffusible substances must pass through restricted portions only; the capillary may be thought of as a sieve with pores about 3 μ in diameter which allow small molecules to pass but not the large protein molecules. (Pappenheimer et al. 1951.) It is thought that these pores increase in size when the capillary dilates (as in response to histamine) thus permitting larger molecules to penetrate. Such a mechanism accounts for ^{some of} the appearances of the triple response.

mechanism are probably It has been calculated that 0.1 % of the plasma albumin leaves the capillaries each minute and passes into the extracellular spaces. This is a small quantity but may be important in allowing protein hormones to have access to the individual cells. Some of the fluid passing into the extracellular space is removed by the lymphatic system, and the large protein molecules are probably taken up in this way. It has been shown that in oedematous conditions the lymphatic vessels are widely dilated. (Florey & Pullinger 1935.)

The Starling hypothesis deals with the balance between plasma and interstitial fluids, but gives no indication of the processes which control total body fluid. Thirst governs the fluid intake. Output depends upon the kidney, gastro-intestinal tract, sweating and lungs. *The urine is* regulated by hormones from the posterior lobe of the pituitary, the adrenals and possibly elsewhere. Verney (1947) has shown that the osmoreceptors of the hypothalamic region are important in adjusting the urine flow through the mediation of the antidiuretic hormone. The fluid retained in oedema is usually of the same ionic concentration as that of normal extracellular fluid. If the total iso-osmotic fluid volume of the body is increased a corresponding excretion of sodium and water is stimulated in normal persons. The receptors for this homeostatic

mechanism are probably situated in the hypothalamic region. In oedematous patients this mechanism is not completely out of action, since the oedema does not increase indefinitely.

The Production of Oedema.

From the physiological evidence summarised above, it is concluded that the quantity of interstitial fluid is dependent upon five factors. These are:-

- (1) The hydrostatic pressure.
- (2) The colloid osmotic pressure.
- (3) The capillary permeability.
- (4) The lymphatic drainage.
- (5) The total body fluids.

A disturbance of any one of these factors may result in the production of oedema.

(1) Increased Venous Pressure.

If the venous pressure is increased, the hydrostatic pressure at the venous end of the capillary will be raised and tend to neutralise the osmotic pressure of the plasma proteins, thus fluid will collect in the interstitial space. This may occur from local occlusion of the vein by a thrombus or embolus, or from a generalised rise of venous ^{pressure} in cardiac failure.

(2) Decreased Plasma Proteins.

When the protein content of the blood is reduced, the colloid osmotic pressure falls and oedema is produced. The appearance of oedema is related to the level of serum albumin and not at all to the concentration of serum globulin. (Weech 1939). The plasma proteins are decreased when protein intake is inadequate over a prolonged period, (e.g. starvation), when protein synthesis is impaired by gross liver disease or when excessive amounts of albumin are being lost in the urine due to renal damage.

(3) Increased Capillary Permeability.

If the pores in the capillary wall are unduly enlarged, the large albumin molecules will reach the interstitial spaces in high concentration and exert their osmotic effect in the opposite direction, thus oedema will result. Such increased capillary permeability is produced in response to various toxins. It occurs in inflammation, urticaria and other allergic disorders and it may possibly explain the oedema of acute nephritis.

(4) Lymphatic Obstruction.

Excess interstitial fluid is being continually removed via lymphatic vessels. Blockage of the main lymphatic trunks typically results from tumour

deposits or from invasion by filariae. In either case gross oedema of the extremities will be found.

(5) Increased Body Fluids.

If total intake of fluids exceeds the total output, an increase in body fluids necessarily occurs. Much of this excess will be distributed in the interstitial spaces, but its localisation to one region such as the ankle will depend upon other factors (e.g. gravity). Congestive cardiac failure is accompanied by fluid retention which accounts in part for the occurrence of ankle oedema in that condition. (vide infra.)

The factors concerned in the formation and removal of interstitial fluid, and the way in which their disturbance may cause oedema, have been reviewed. When the mechanism of oedema in a particular condition is being studied, all the factors involved must be taken into consideration, for as Starling remarked "It is important to remember that probably under no circumstances can dropsy be ascribed to an abnormal change in one only of these processes."

The patient was treated by rest in bed, phenobarbitone, methylxanthine and digoxin. There was a good response to therapy and the patient was discharged after 5 weeks - well improved.

The location of oedema in congestive

Clinical Cases with Pathological Discussion.

Case I A maintenance fitter aged 61, gave a history of myocardial infarction 5 years before admission, and of increasing dyspnoea and angina of effort over the last six months. For two weeks preceding admission he lost much sleep owing to attacks of nocturnal dyspnoea.

On examination he was found to be dyspnoeic and cyanosed; his neck veins were distended and both ankles were swollen. PITTING OEDEMA WAS PRESENT. The pulse was fast (90) but regular; blood pressure 124/94; apex beat in the 6th. left intercostal space just outside the anterior axillary line. A loud systolic murmur in the mitral area was propagated into the axilla, where it was heard loudest. There were medium crepitations at the base of both lungs. The liver was enlarged 2 fingers breadths below the costal margin.

Electrocardiographic examination showed evidence of recent and old infarcts. Latent heart block was detected and the cardiac hypertrophy confirmed.

A diagnosis of Congestive Cardiac Failure was made. The patient was treated by rest in bed, phenobarbitone, aminophylline and digoxin. There was a good response to therapy and the patient was discharged after 5 weeks - much improved.

Discussion - The location of oedema in congestive

cardiac failure is determined principally by gravity. It will involve the ankles in the ambulant patient, and the sacrum in the one confined to bed.

Production of the ankle oedema may be explained as follows. The failing ventricles are unable to cope with the normal venous return and consequently dilate; but there is a rise in venous pressure and this is reflected at the venous end of the capillaries. Oedema results, with some concentration of the plasma which may, via Verney's osmoreceptors, cause the kidney to conserve fluids and thus lead to fluid retention and decreased urinary output, which is in fact observed in such patients. (Peters 1948).

However, there are other ideas on the production of oedema in heart failure. One school believes that the decreased cardiac output results in tissue anoxia and thus causes increased permeability of the capillaries. Others believe that a combination of these two theories is probably nearer the truth.

From the experiments of Landis and from the laws of physics upon which Starling's original hypothesis was based, it is certain that an increased venous pressure must play some part in the production of oedema. However, it has been shown (Warren & Stead 1944) that in some cases of cardiac failure, there is a rise in body weight due to

increased body fluids before any rise in central venous pressure occurs.

There seems to be no consistent relationship between the height of the venous pressure and the amount of oedema produced. (Altschule 1938.). Ligation of the inferior vena cava producing venous pressures comparable to those occurring in congestive cardiac failure has resulted in only transient oedema. (Ray & Burch 1947).

Since oedema fluid in cardiac failure has a low protein content (Stead & Warren 1944), it would seem unlikely that increased capillary permeability due to anoxia plays any significant part in its production. Furthermore, the oxygen tension in cardiac failure will rarely be so low that the capillaries are affected. In any case, if this were widespread throughout all capillaries then the plasma volume would be fatally reduced before oedema occurred.

Tension of the connective tissues and skin limit the outflow of fluid into the interstitial spaces by opposing the hydrostatic pressure of the blood. This tissue tension can be measured plethysmographically. After the oedema of congestive cardiac failure has resolved it is found to be reduced, presumably because the subcutaneous tissue has been stretched and has lost much of its elasticity. Thus, oedema recurs more readily. (Burch &

Sodeman 1937.) .ent was sitting quietly by the fire. It
 described of a sm By intracutaneous injections of dye it
 can be shown whether lymph flow is diminished or not.
 (McMaster 1937). In congestive cardiac failure the rate
 of flow is reduced whereas in the oedema of nephrosis it
 is increased. However, in lymphatic obstruction the oedema
 fluid contains much more protein than normal whereas in
 cardiac failure the protein content is low. It is unlikely
 therefore, that the oedema in congestive cardiac failure
 could be accounted for by a theory of lymphatic obstruction.

The chest was un From the evidence at present available
 it is concluded that cardiac oedema results from increased
 venous pressure, increased total body fluids and possibly
 capillary damage. The relative importance of these factors
 and the way in which they are inter-related is not understood.
 The primary condition is the myocardial failure. When
 this responds to rest and digitalis (as in the patient
 described), re-absorption of the oedema fluid and diuresis
 follows.

Case II Haem A retired cleaner aged 71, was admitted
 to the R.I.E., following a small haemoptysis on the
 previous day. He gave a history of bilateral thrombo-
 phlebitis 12 months ago, the swelling having persisted,
 particularly in the right leg. The haemoptysis occurred

while the patient was sitting quietly by the fire. It consisted of a small clot of blood. He did not complain of cough or other respiratory symptoms. He had had no previous haemoptysis.

The most striking feature on examination was the intensely red, rather cyanotic, facies. The pulse rate was 70, blood pressure 190/100, apex beat not palpable and the heart sounds were closed. There was Pitting OEDEMA of both ankles. Horman's sign was negative. Respiratory expansion was diminished on the left side. The chest was uniformly resonant to percussion. Vocal fremitus and resonance were both diminished over the left lower lobe. Breath sounds were vesicular but of diminished intensity over the left lower lobe. Fine crepitations were heard at both bases. No enlargement of the spleen or the liver was detected.

X-Ray of the chest showed generalised cardiac enlargement with some congestion of the lung fields. There was evidence of some atelectatic change in the left lower lobe. Examination of the blood gave the following results:- Haemoglobin 147% ; red blood cells 7.04 million; white blood cells 9,800; platelets 310,000. (counts all /cu. mm.) Colour index 1.00 .

A diagnosis of Polycythaemia vera with pulmonary infarction and residual bilateral thrombophlebitis was made. After consultation with the radiotherapists, a

course of deep X-ray therapy was instituted. This resulted in subjective improvement but no reduction in the red cell count occurred; the treatment was curtailed because the platelet count fell to 70,000. During the course of treatment, the respiratory signs resolved and no further haemoptysis occurred, but the ankle oedema persisted though reduced in amount. The patient was discharged improved but not cured.

Discussion: - Thrombophlebitis is a common complication of polycythaemia vera, possibly because there is increased blood viscosity. The formation of a clot in a vein of the lower extremity will impede outflow from the area drained, thus the hydrostatic pressure at the venous end of the capillaries will be raised. The mechanism of fluid distribution will therefore be impaired locally and re-absorption of fluid will be reduced. In addition the inadequate removal of vasodilator metabolites will lead to increased capillary permeability, allowing the large albumin molecules to escape and to exert their osmotic action in the opposite direction. (Wright 1945). In polycythaemia vera and thrombophlebitis there is no reduction in the level of serum albumin so that the normal colloid osmotic pressure of the blood is exerted, but oedema will occur if it is exceeded by the opposing

pressures (described above). There is no increase in total body fluids and the lymphatic drainage is unimpaired in the conditions under discussion.

Treatment in this patient was directed at the primary disorder. It was hoped that, by radiotherapy, erythropoiesis in the bone marrow might be damped down, unfortunately the production of platelets was depressed before any therapeutic effect was observed. Successful treatment would have rendered the patient less liable to thrombotic phenomena, particularly thrombophlebitis, by reducing the red cell count and so the viscosity of the blood. Oedema from the previous attacks of thrombophlebitis would only subside when adequate venous outflow has been established either by the development of anastomotic channels or by the re-canalisation of the thrombus.

Case III. A maltman aged 54, complained of abdominal pain, loss of weight and lethargy of 8 weeks duration. The abdominal pain was a constant diffuse ache in the epigastrium, which did not radiate. It was present day and night but was considerably worse after taking food. Vomiting relieved it to some extent, but prolonged relief was only achieved by abstinence from solid food. He had been living on fluids such as milk and fruit juices since his illness started, but he had little appetite. He had

lost about 2 stones in weight during that time.

On examination the patient was seen to be an emaciated, obviously ill, man with a slight icteric tinge. The abdomen was somewhat distended. There was tenderness but no guarding or rigidity in the epigastrium. The liver was enlarged - one finger's breadth below the costal margin, and its edge was irregular. Shifting dullness was detected in the abdomen, but no fluid thrill could be felt. No abnormality was found on rectal examination. PITTING OEDEMA was present in both ankles. There were no palpable lymph nodes.

The blood picture was as follows:-

Haemoglobin 94%; Red cell count 4.79 million /cu. mm. ;
White cell count 7400 /cu. mm.

The stool benzidine test was negative; the urine contained urobilinogen but was otherwise normal. Tests showed some impairment of liver function:-

Serum albumin 2.40 gm.%

Serum globulin 2.42gm.%

Alkaline phosphatase 24 units.

Non-protein nitrogen 30 mg.%

Thymol turbidity 1 unit.

Cephalin cholesterol test -ve.

Straight X-ray of the abdomen revealed that the right dome of the diaphragm was raised; in view

of the patient's grave condition a barium meal was not carried out.

A tentative diagnosis of cancer of the stomach with hepatic secondaries was made. Treatment was palliative, with frequent doses of morphine latterly. The patient's condition gradually deteriorated; he became comatose and died 2 weeks after admission.

At post mortem a carcinomatous ulcer of the stomach was found. Normal liver tissue was almost absent, being replaced by numerous extensive secondary deposits.

Discussion: Of the five factors controlling the amount of interstitial fluid, it is likely that only two were concerned in the production of ankle oedema in this patient. It is possible that some degree of venous and lymphatic obstruction could occur from tumour deposits, but extensive secondaries outside the liver were not found at post mortem examination, so these factors will not be considered further.

The importance of an adequate level of plasma proteins, especially of serum albumin, in the maintenance of the colloid osmotic pressure of the blood and in the prevention of oedema has already been discussed. The deficiency of serum albumin in this case, due to

impaired protein synthesis in the liver, aggravated by a poor intake of proteins, could probably account for the appearance of oedema of the ankles. However, since the liver is responsible for the inactivation of the anti-diuretic hormone, impairment of liver function is probably accompanied by an increased concentration of this hormone in the blood, resulting in sodium and water retention. (Goodyer et al. 1950). Thus the volume of total body fluids will be increased. The excess is accommodated in the interstitial spaces and the oedema is aggravated still further. The localisation of oedema fluid in the region of the ankles must be attributed to gravity, but it was not relieved by rest in bed.

Case IV. A tractor driver aged 47, a diabetic under treatment with insulin for 18 years, was admitted with staphylococcal septicaemia which responded rapidly to chemotherapy. During the convalescent period, the following signs were found to have persisted:-
 Blood Pressure 170/90 ; Apex Beat in the 6th left intercostal space just outside the midclavicular line; Diabetic Retinopathy and PITCHING OEDEMA of both ankles.

The urine contained albumin in a concentration of 2.0 gm.% (Esbach method). No other urinary abnormalities

were detected. The serum albumin was 2.83 gm.%, the serum globulin 3.26 gm. % and blood urea nitrogen 22 mg.%. The urea range test showed impairment of renal function, all specimens contained 1.5 (± 0.2) gm.% of urea.

In view of the renal failure, albuminuria, oedema and hypertension occurring in a patient with diabetes, a diagnosis of Kimmelstiel-Wilson syndrome was made. The patient's diet and insulin were adjusted, keeping in mind the continual loss of protein in the urine. He was discharged improved and ambulant but unfit for any form of work.

Discussion: The oedema in this patient was due entirely to the low concentration of serum albumin. In contrast to the previous case, however, the hypoproteinaemia was produced by loss from the body and not by impaired synthesis or intake. Kimmelstiel and Wilson (1936) first described a lesion of the kidneys in diabetics, which they called - intercapillary glomerulosclerosis in contrast to intercapillary glomerulofibrosis found in chronic nephritis. In this condition albumin molecules pass through the damaged glomeruli into the glomerular filtrate and so are lost in the urine.

The mechanism of oedema production in the Kimmelstiel-Wilson syndrome is similar to that in

subacute nephritis, in both conditions there is a heavy albuminuria resulting in hypoproteinaemia and a reduced colloid osmotic pressure. The effect of the latter on the distribution of tissue fluids has already been discussed.

Case V. A labourer aged 34, had an attack of influenza with sore throat lasting a fortnight. It was followed by swelling of the face, abdomen and legs a week before admission. He complained of malaise, anorexia and nausea. The patient noticed that his urine was dark and very small in quantity. There was no dysuria.

On examination the patient was seen to be a pale well-built man who did not appear unduly ill. There was PITTING OEDEMA of both ankles but the swelling elsewhere had subsided by the time of admission. The Blood Pressure was 160/100, but the apex beat was not displaced. No other abnormal signs were detected.

The urine was concentrated and had a reddish tinge. Albumin was present in a concentration of 2 gm./litre. Many red blood cells and some casts were seen on microscopic examination. Serum albumin was 3.42 gm.% and serum globulin 3.88 gm.%; non-protein nitrogen 42 mg.% .

A diagnosis of Acute Nephritis was made. The patient was treated with rest in bed and a light diet

containing only 40 gm. of protein. Oedema could not be detected after 4 days and the blood pressure fell to 140/80 within one week of admission. On discharge the patient felt well; his urine contained a trace of albumin only. The plasma proteins were within normal limits.

Discussion: In acute nephritis albumin is lost in the urine and some degree of hypoproteinaemia ensues, but this occurs after the appearance of the oedema, so that it cannot be the initial cause. Since the disorder is thought to have an allergic basis, it has been suggested that the oedema results from a generalised increased permeability of the capillaries. Albumin molecules pass into the interstitial spaces and exert an osmotic action in the opposite direction to normal. According to this hypothesis albumin appears in the urine as a result of the increased permeability of the glomerular capillaries, which occurs in common with all the other capillaries of the body. The main snag to this convenient explanation, is that the oedema fluid in acute nephritis has a low protein content. In addition such a generalised increase in permeability would lead to circulatory collapse before oedema was clinically detectable. The localisation of the oedema fluid in acute nephritis is probably due to the tissue tension in different parts of the body. For instance, around the eyes where the oedema

of acute nephritis is particularly marked, the tissue tension is extremely low. (Buch 1940).

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Conclusions:

London: Churchill.

From the evidence available the following conclusions are reached:- The oedema of cardiac failure results from increased venous pressure, a general increase of body fluids and perhaps some increased capillary permeability from anoxia. The oedema of thrombophlebitis is due principally to a local rise in venous pressure but also to the vasodilator action of metabolites. In advanced cancer of the liver protein intake and synthesis are diminished, and fluid retention may occur if the anti-diuretic hormone is not destroyed. The hypoproteinaemia and consequent oedema of the Kimmelstiel-Wilson syndrome results from urinary loss of albumin. Finally, the oedema of acute nephritis cannot yet be explained satisfactorily.

The five cases described have demonstrated some of the conditions in which oedema may occur, the inclusion of others such as subacute nephritis, famine oedema, filariasis and toxæmia of pregnancy would have made a more complete picture. It is however evident that the mechanism of oedema production is a complex matter.

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