have been described, but two are of outstanding clinical interest: the alkaline, which comes chiefly from bone cells, and the acid, which is formed in the prostatic glandular epithelium.[2] Curiously enough, only in man and monkey does the production of acid phosphatase occur in significant amounts, and then only after the onset of puberty.[3] Administration of male hormone to immature male rhesus monkeys leads to a very great increase in the concentration of acid phosphatase in prostate tissue. The suggestion has been put forward that the function of prostatic phosphatase is to split up hexose phosphate and other phosphoric esters in the course of glycogenolysis, upon which human spermatozoa largely depend for the energy requirements of prolonged motility after ejaculation. Although it is unlikely that the enzyme has any function in the glandular epithelium of the prostate, it is probably an important factor in the formation of prostatic calculi. Normally the ferment is excreted in the prostatic fluid, with the result that very little is found in the blood stream. The small amount of acid phosphatase that can be detected in the plasma of a healthy subject is derived from liver, spleen, bone, and kidney.

The information was of academic interest until the discovery of Gutman and his co-workers[4] that tumour cells derived from prostatic epithelium secrete large amounts of acid phosphatase brought the matter into the clinical field. With invasion of blood and lymph vessels by tumour cells a channel is opened to the ferment, so that it can appear in high concentration in the plasma. The Gutmans immediately applied this observation to the differential diagnosis of metastases derived from prostatic carcinoma.[5] They showed that by the method in use not more than 3 units of acid phosphatase per 100 c.cm. appear in the serum of a normal subject. Occasionally a slight increase is detected in the plasma of patients with tumours and other diseases of bone, liver, and other organs not associated with the prostate. Sullivan, Gutman, and Gutman[3] found in a series of 130 patients with bone metastases arising from cancer of the prostate that 110 had acid phosphatase values exceeding 3 units and 95 over 5 units per 100 c.cm. of serum. It would appear, therefore, that a value below 3 excludes bone involvement from prostatic cancer, and that one over 5 almost certainly indicates this. In 3 cases of Paget's disease the acid phosphatase value exceeded 5, but this did not lead to any trouble in diagnosis, because in this condition the alkaline phosphatase is raised, which is not the case with prostatic metastases. In only two instances did any confusion arise: one was in a case of carcinoma of the urinary bladder invading the prostate, and the other in a case of bronchogenic carcinoma with metastases in bone. It should be stressed that an indubitably high acid phosphatase is not usually found unless the skeletal system is involved. The data at present available do not permit one to state precisely how far extracapsular involvement of prostatic carcinoma must extend before a significant increase in plasma acid phosphatase can be detected. Huggins and Hodges,[6] however, showed that injection of testosterone is rapidly followed by an increase of acid phosphatase if there are any metastases in the bones. Accordingly this "provocative" injection of androgen may serve as an excellent diagnostic test of bone involvement when *x*-ray evidence is absent. The same workers went a stage further, and showed that removal of the male hormone by castration[1] or injection of oestrogen[7] led to remarkable clinical improvement, associated with a fall in the acid phosphatase value, which began within 24 hours.

Therapeutic deductions are obvious, but what is of interest here is the opportunity afforded for an objective test to indicate the response to operation. In an excellent review of the whole subject Sullivan and his colleagues[3] have summarized the clinical applications of acid phosphatase estimation. It provides independent evidence of the presence of metastases from carcinoma of the prostate, and it may be helpful in detecting the site of the primary tumour when the prostate is not unduly enlarged. It is of value also in determining when enucleation of the prostate is likely to be of no avail, because any increase in acid phosphatase means that the tumour cells have already reached the skeleton. After removal of a prostate which is afterwards found on histological examination to present signs of malignancy, repeated estimations of plasma acid phosphatase will detect any spread to the skeleton. Finally, if castration or other form of androgen control is carried out, the level of acid phosphatase in the blood serves as a useful means for early assessment of the treatment. The story is not yet finished, because there are hopes of further advances, direct and indirect. Even at this stage, however, there is a strong temptation for the academic investigator to point the moral that even from the most abstruse test-tube investigations matters of great clinical import and therapeutic interest may emerge.

THE PROTEIN RESERVOIR

It has now become so usual to estimate the serum proteins in the study of nutrition, shock, and metabolic disease that Peters[1] has done well to emphasize the implications of physiological work on this subject. Modern studies began when Starling showed that the exchange of fluid between the blood stream and the tissues depended on the balance between the capillary blood pressure and the colloid osmotic pressure of the proteins. The probability of a dual causation should always be remembered in the treatment of oedema. In heart failure oedema may prove intractable if, as the result of malnutrition, serum proteins are even slightly reduced. The ascites and oedema of cirrhosis are as much dependent on a fall in serum albumin as a rise in portal pressure. Because of its smaller molecular size and other properties, the serum albumin is the all-important factor in the maintenance of the colloidal osmotic pressure. Moreover, the globulin is but little reduced by albuminuria or malnutrition, and it may, indeed, be greatly increased in cirrhosis and other diseases in which albumin is diminished. Albumin and globulin are in fact independent variables in the serum, and no determination of the proteins that does not include separate measurement of these fractions is satisfactory. When the clinician finds the serum proteins reduced he is tempted to think they may be rapidly increased by the transfusion of plasma. This is a false analogy with the transfusion of red cells, which exist in a closed system within the blood vessels. Proteins, as Beattie and Collard have shown, flow freely in and out of the vascular system,[2] and the serum proteins are in equilibrium with the tissue proteins. The level of the proteins in the serum can be likened to the level of the fluid in a manometer which communicates with a much larger system. When a dog was starved of protein for 80 days the serum albumin was reduced by 70%, the haemoglobin by 50%, and the body weight by about 20%. But if the percentages are converted into total values, it is seen that of the total protein lost about 80% came from the tissues, only about 3% from the serum proteins, and the remainder

[2] Kutscher, W., and Wolbergs, *Z. physiol. Chem.*, 1935, **236**, 237.
[3] Sullivan, T. J., Gutman, E. B., and Gutman, A. B., *J. Urol.*, 1942, **48**, 426.
[4] *Amer. J. Cancer*, 1936, **28**, 485.
[5] Gutman, A. B., Tyson, T. L., and Gutman, E. B., *J. clin. Invest.*, 1938, **17**, 473.
[6] *Cancer Res.*, 1941, **1**, 293.
[7] Huggins, C., Scott, W. W., and Hodges, C. V., *J. Urol.*, 1941, **46**, 997.

[1] *J. Mt. Sinai Hosp.*, 1942, **9**, 127.
[2] *British Medical Journal*, 1942, **1**, 459; **2**, 301, 507.

from haemoglobin. A moderate deficiency of serum albumin, then, may denote a severe depletion of tissue protein, and for every gramme by which we wish to raise the level of serum albumin 30 grammes must be put into the tissues. If this were more generally appreciated there would be less surprise that in malnutrition serum albumin cannot be restored with great celerity or that the transfusion of plasma is relatively ineffective in the treatment of oedema. A similar line of argument will fortify us against disappointment with the results of parenteral administration of protein autolysates, such as is being developed in the United States.[3] To give only the minimum daily requirement of nitrogen in the form of intravenous injections of amino-acids requires an unpleasantly large volume of fluid. Many lives have been saved by the transfusion of plasma in shock and acute perturbations of the blood volume, but these are conditions in which the body reservoir of protein is intact. Once this reservoir is emptied it is not practicable to refill it by pouring liquid into the manometer—i.e., by parenteral administration of proteins or amino-acids. Reliance must be placed on the natural channel of supply—the assimilation of proteins via the alimentary tract.

PEPTIC ULCER OF THE OESOPHAGUS

Chronic peptic ulcer of the oesophagus has for long been recognized, though it has generally been regarded as almost a medical curiosity. In recent years, however, Jackson and others have suggested that the condition is much less rare than was previously thought, and in a paper recently published R. C. Dick and Sir Arthur Hurst[4] agree with this view. They describe a further series of cases and bring out a number of important points on aetiology, symptomatology, and treatment. Chronic oesophageal peptic ulcers differ in no way in their morbid anatomy from ulcers of the stomach or duodenum; they may vary in size but are usually single. The majority appear to heal completely, causing scarring with or without cicatricial stenosis; malignant degeneration rarely or never occurs. On oesophagoscopy they appear as flat ulcers, with yellowish exudate and hyperaemic zone around, and without the raised fungating edges of a carcinoma. Jackson was able to demonstrate scars of healed ulcers in 67 cases by oesophagoscopy, as well as 21 active ulcers. As with peptic ulcers elsewhere, the acid gastric juice appears to be an essential factor in causation. Dick and Hurst note that in the majority of cases this regurgitates through the cardiac orifice of the stomach owing to incompetence of this opening associated with a congenitally short oesophagus. They quote the findings of Johnstone, in all of whose seven cases there was definite shortening of the oesophagus, but they themselves consider that this shortening is congenital and not cicatricial, being in most cases found with a diaphragmatic hernia of a portion of the stomach. In a very few cases an ectopic patch of gastric mucous membrane occurs in the oesophagus and secretes acid and pepsin just as in the stomach itself.

The symptoms of chronic ulcer of the oesophagus differ from those of carcinoma or of "cardiospasm" in a number of ways. Pain is often severe and appears during eating or drinking—at first only with hard or irritating food, but later with almost every meal. It may also be felt later after eating if the patient bends forward or lies down; it may be relieved by sitting up, or by stretching the arms above the head, though this only happens in cases associated with a diaphragmatic hernia. The pain is situated deeply in the middle line behind the lower end of the sternum, and may come and go just as in ulcer of the stomach, with periods of freedom lasting even for years. The natural tendency is towards recovery, but in about half the cases there is gradual dysphagia due to spasm; occasionally organic stricture develops. With stricture, retention of gas in the stomach may take place as well as obstruction to the passage of food from above, and the rare condition described as "aérogastrie bloquée" may then result, with intense gastric dilatation. The diagnosis may be confirmed by *x*-ray examination or oesophagoscopy may be employed, though, owing to associated spasm, the ulcer cannot always be seen. If there is clinical suspicion of oesophageal ulcer—as suggested by the symptoms, findings of occult blood in the stools, and perhaps haematemesis—special methods of *x*-ray examination should be adopted. The simple fluid barium emulsion does not often reveal the ulcer, and a semi-solid meal is required: the patient should swallow it lying down, the foot of the bed being raised. The characteristic picture of spastic narrowing with a central ulcer niche can often be recognized, as well as a portion of the stomach lying within the thorax above the diaphragmatic opening.

In treatment, fluid feeds are necessary at first, but need not be given as frequently as in gastric or duodenal ulcer; the patient is better sitting up; the bed should be raised at night so that the head is high, in the hope that regurgitation of gastric contents into the oesophagus will thus be prevented. Atropine and olive oil are also recommended. If such medical measures fail, gastrostomy is advisable, and was required in 2 of the 16 cases described by Dick and Hurst. Some after-care on similar lines to the active treatment is important to prevent recurrence.

With careful diagnosis and thorough treatment the prognosis is good, and although oesophageal ulcer is not common, it is important that it should not be forgotten when obscure cases of early gastric pain or dysphagia are encountered.

[3] *J. Amer. med., Ass.* 1942, **120**, 1176.
[4] *Quart. J. Med.*, 1942, **11**, 105.

REFRIGERATION ANAESTHESIA

Baron Larrey, Napoleon's army surgeon, is said to have amputated limbs painlessly at the Battle of Eylau in a temperature of −19° C. The deliberate use of cold, however, to obtain anaesthesia, while well known, and subjected to spasmodic attempts at popularization,[1] has never been taken up seriously, largely through the fear of damaging the tissues and the practical difficulties of refrigerating more than small areas of the body surface. The experience of Crossman, Allen, Hurley, Ruggiero, and Warden[2 3] suggests that it is a useful method of anaesthesia for amputation in "poor-risk" patients in whom the circulation in the limb is already failing. For efficient refrigeration of a limb—and their report deals with the lower limbs only—a tourniquet is essential. They emphasize that the main harmful effect of a tourniquet is by direct pressure, particularly on nerves, and to minimize this they advise narrow gum-rubber tubing. Experiments on animals have shown[4] that a limb will survive up to 12 to 15 hours' deprival of blood supply at ordinary temperatures, and very much longer when cooled to just above freezing-point. Ligation of a limb causes shock, which after 6 to 8 hours may be sufficient ultimately to kill the patient. Human resistance to this form of shock is high, and little ill effect of the sort need be expected from a ligation lasting 2 to 3 hours. Cold lowers the resistance of the tissues to infection, but the activity of bacteria present is decreased. Objection to cold might be made on the ground that the trickle of blood in the arteriosclerotic limb threatened with gangrene would be still further reduced and real danger

[1] Arnott, *Lancet*, 1848, **1**, 287.
[2] *Anesth. & Analges.*, 1942, **21**, 241.
[3] *Arch. Surg.*, Chicago, 1942, **44**, 139.
[4] Allen, *Surg. Gynec. Obstet.*, 1939, **68**, 1047

arise of sloughing flaps. This is more than offset by the lowering in metabolic activity of the tissues, with consequent reduction in oxygen need and carbon dioxide production. One great advantage of the use of refrigeration is that no preparation other than a mild sedative in the occasional apprehensive patient is required. The authors use either ice or electrical refrigeration to cool the limb, and have found that the time of cooling to produce anaesthesia varies from 1 hour for a foot to 2½ hours for a thigh amputation. Frostbite does not occur, and the skin temperature does not usually fall below 40° F. As Rupp[5] points out, refrigeration may prove useful in other directions. It would probably lengthen the time during which embolectomy could be undertaken, and it might be invaluable for cases inoperable by any other method.

VENEREAL DISEASE IN SWEDEN

The large rise in the incidence of venereal diseases in Britain since the beginning of the war has attracted widespread comment. In discussions on the thorny problem of prevention and control comparison has been made with the experience of Scandinavian countries, where legislation has been in operation for some years. A law to combat venereal disease was introduced in 1918 in Sweden, and this lends special interest to an examination by Dahlberg[6] of the trend of the incidence of venereal diseases in that country from 1913 to 1938. Legislation and the methods adopted for the control of venereal disease were, it appears, very successful in the case of syphilis, but made little impression on the trend of gonorrhoea. After a slow rise in the incidence of venereal diseases during the first years of the last war a rapid increase occurred in 1918 and 1919. By 1919 the number of cases of soft sore and of syphilis at ages over 1 year had been almost trebled, and the incidence of gonorrhoea was double that of 1913-14. At ages under 1 year the number of cases of syphilis rose suddenly in 1919 (followed by another small rise in 1920) to three times the previous figure. Between 1919 and 1923 the incidence of syphilis fell rapidly from 6,354 cases in the former year to 1,127 in the latter—i.e., to about half of the pre-war level. The fall continued more slowly, and in 1925 only 723 cases were recorded. This trend was interrupted by a rise to over 1,100 cases in the boom years of 1927-31. After this the prevalence of the disease again fell rapidly, and the average number of cases annually in 1936-8 was only 352, compared with 2,478 in 1913-15. Soft sore followed a similar course but with a relatively greater decrease: the annual cases numbered only 81 during 1936-8, compared with 1,387 during 1913-15. Congenital syphilis declined at a much slower rate, and it was not until 1928 that the trend returned to the pre-1914-18 level. In the last three years an average of 9 cases was recorded, as against 30 during the first three years of the period (1913-38). The curve for gonorrhoea differed from that of syphilis in the later years, though to begin with it was similar. Between 1919 and 1923 notifications of gonorrhoea diminished from 20,594 to 10,321—to pre-war level. They then rose until 1930, when 14,388 cases were recorded, and afterwards decreased but remained above the pre-war level. The annual average number of notifications of gonorrhoea in 1936-8 was 12,125, compared with 10,621 in 1913-15. The percentage of male to female patients was approximately 70 for syphilis and 90 for soft sore, and only small fluctuations occurred in this percentage during the twenty-six years. The male percentage for gonorrhoea, however, has shown a progressive fall from 80 in the beginning of the period to 70 at the end.

Dahlberg considers that the difference between the trends of gonorrhoea and of both syphilis and soft sore may be due partly to the difference in the diseases. Gonorrhoea, being more contagious, is consequently far commoner than the other two diseases. The symptoms are milder and the patient may optimistically but erroneously believe he is no longer a source of danger to others. There is also a possibility that gonorrhoea may be transmitted during the initial period before the patient is sufficiently aware of it to seek treatment. After discussing various alternative explanations, Dahlberg concludes that the law of 1918 has played an important part in the large reduction of syphilis and soft sore. Diseased males behave with less irresponsibility to prostitutes for fear of penalties, and the instructions which every infected person receives may also have been a factor in the decline of these two diseases.

DIET IN PULMONARY TUBERCULOSIS

The part played by malnutrition in the aetiology of tuberculosis is now generally recognized; yet it is remarkable how scanty is the scientific evidence for this widespread belief. Malnutrition is invariably associated with poverty, and poverty is associated with other factors besides malnutrition. Among these, just how important is the lack of proper food in determining lowered resistance to tuberculous infection? Perhaps the statistical investigation carried out by Knud Faber[1] into the incidence of tuberculosis in Denmark during the war of 1914-18 provides the most trustworthy evidence of the effect of food deficiency on the incidence of tuberculosis. According to Faber it was shortage of first-class protein that caused the rise in tuberculosis in Denmark during the early part of that war, the shortage being due to increased exports. When, later in the war, the blockade prevented these exports, the death rate from tuberculosis in Denmark fell rapidly, though in other countries the rise continued. Dr. George Day, of the Mundesley Sanatorium, has published some interesting observations[2] in relation to the present war and the rationing compelled by it. Over varying periods of time during the past five years several groups of patients suffering from pulmonary tuberculosis have been given different diets. These were: (*a*) restricted pre-war diet, (*b*) unrestricted pre-war diet with extra sugar and injections of insulin, (*c*) wartime-rationing diet, (*d*) wartime-rationing diet with extra sugar. (The extra sugar necessary for the experiment was obtained through the Medical Research Council.) The progress rate of the average patient in each of these groups was calculated from the rate at which his body weight increased, and the rate at which his sedimentin index decreased, as worked out by Day.[3 4] He found that the patients on (*c*) made much poorer progress than any of the other groups. It appeared, too, that the rate of progress was proportional to the calorie value of the diet. There was not enough evidence to decide whether carbohydrate was the most effective ingredient as a calorie provider. It has always been believed that a diet low in fat predisposes to development of tuberculous disease. Faber blamed protein deficiency. By implication Day suspects the third proximate constituent, and more directly what is common to all three—energy value.

The Honorary Fellowship of the Royal College of Surgeons of England has been awarded to Mme. Chiang Kai-shek in recognition of her great services in the relief of suffering and the advancement of medicine in China.

[5] *Anesth. & Analges.*, 1943, **22**, 46.
[6] *Amer. J. Hyg.*, 1941, **33**, Sec. A, 51.

[1] *Acta tuberc. scand.*, 1938, **12**, 287.
[2] *Tubercle*, 1942, **23**, 215.
[3] *Lancet*, 1940, **1**, 1160.
[4] *British Medical Journal*, 1940, **2**, 376.