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THE VALUE OF PENICILLIN IN SURGERY*

BY

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Penicillin is the nearest approach to the ideal antiseptic yet discovered, and its value can scarcely be overestimated. But it has limitations, quite apart from the physical and chemical properties which hamper its preparation and administration. Only certain organisms are susceptible to it (although, fortunately, the sensitive group includes the majority of organisms of particular interest to the surgeon), and even these may not be inhibited or destroyed unless the drug is properly used and the appropriate ancillary treatments given. Good surgery is still essential, and the lavish expenditure of any chemotherapeutic agent will not purchase an indulgence for therapeutic sins.

Penicillin has now been tested in most of the likely and many of the unlikely conditions, and the literature abounds with records of its successes in small groups of selected cases, usually treated without contrasts or controls. Reports on large groups of surgical cases are almost confined to battle casualties because, until just over a year ago, the bulk of the world production of penicillin was devoted to the treatment of the Armed Forces of the Allies. The luckless casualties provided a grim but instructive surgical surfeit, and many Army surgeons did not fail to utilize their unexampled opportunities. The figures quoted below are obtained from such sources.

Value of Penicillin in Prophylaxis

Penicillin, being more active and much safer in use, is a better prophylactic agent than the sulphonamides against the common pyogenic and anaerobic infections, but this theoretical superiority is unlikely to be exploited generally until simple oral methods of administration are perfected. Its use as aerosols in operating theatres or wards to prevent air-borne infections will be impossible until supplies become ample, although it may be employed more economically in the form of nose and throat sprays, as Knott and Blaikley (1946) have suggested, in an attempt to prevent infections produced by staphylococcal and streptococcal carriers. The penicillin pastilles recommended by MacGregor and Long (1944), and the tooth pastes or powders devised by Powell and Colquhoun (1945), may also be employed to combat the development of buccal, faucial, and dental infections; but these methods have more medical than surgical applications, and need not be further discussed.

So far, penicillin has been given large-scale prophylactic trials only in battle casualties. All the dangerous pathogens commonly found in war wounds are penicillin-sensitive, and if penicillin can be maintained in contact with them in a suitable concentration for a sufficient period of time, these organisms should be inhibited or destroyed by the combined

effects of the drug and the normal body defence mechanisms. This knowledge was exploited through all stages of the campaign in N.W. Europe. Casualties were given parenteral or local penicillin, or both, at the most forward surgical levels as soon as practicable after wounding; and once a course of penicillin was started it was continued, no matter how or where the patient went, until a surgeon had decided that the treatment could be terminated or until the patient had been evacuated to an E.M.S. hospital in the U.K. The preparation and administration of penicillin solutions and powders under active service conditions were not easy, and it was feared that complications due to penicillin-insensitive contaminants might be frequent. Actually, such contretemps were astonishingly few considering that at least 100,000 soldiers received penicillin treatment (Mitchell, 1945), and, apart from some impure batches which produced needless pain and irritation, penicillin justified in every way the remarkable claims made for it by Fleming, Florey, Cairns, and others. Reports from all sources contained comments on the marked absence of severe sepsis and the reduced incidence of all wound infections, and, although better facilities, better surgery, better communications, and other factors deserved credit, few doubted that penicillin was the dominant factor in the control of infection—formerly the greatest single problem in war surgery.

Bacteriological Evidence.—The clinical improvement was unquestioned, and confirmation was provided by bacteriological investigations (Porritt and Mitchell, 1946). In the Middle East campaigns "no growth" reports on the first wound swabs taken after admission of casualties to hospital were most uncommon. Thus in a series of 100 consecutive personal cases investigated in No. 1 Orthopaedic Centre, M.E.F., in 1942, a positive culture was obtained in every case. In the N.W. European (B.L.A.) campaigns of 1944-5, "no-growth" reports on wound cultures were common, and staphylococcal, and particularly streptococcal, infections were relatively uncommon (Porritt and Mitchell, 1946). Thus 268 out of 560 wound swabs taken from casualties who had nearly all received prophylactic penicillin gave "no growth" on culture. The findings are contrasted in Table I.

TABLE I

Organisms Isolated	M.E.F. Casualties	B.L.A. Casualties
Streptococci	68% (50% haem.)	5% (3% haem.; 2% anhaem.)
Staphylococci	58% (46% aureus)	25% (11% coag. +; 5% coag. -; 9% no details given)
Clostridia	28%	2%
Pyocyanus	16%	—
Coliforms	6%	10%
Proteus	14%	—
"No growth"	—	48%

* A lecture delivered at the Royal College of Surgeons, London, on Oct. 29, 1946.

In both the above-quoted series the infections were usually mixed, so the percentages merely give an indication of the incidence of the various organisms in the wounds. And it must be recorded that penicillinase was not employed in many of the cultures, so it is probable that a number of false negatives were obtained. Nevertheless, these laboratory findings confirmed the clinical impression that the great majority of the wounds were cleaner than were those commonly seen in former campaigns. Incidentally it is interesting to recall that in the war of 1914-18 haemolytic streptococci were the predominant pathogens (Fleming and Porteous, 1919).

Factors Influencing Results.—Clearly it would be very important to discover the reason for the improvement, and after consideration of all possible factors influencing the occurrence of infection in wounds there is no doubt that the widespread prophylactic use of *both* parenteral and local penicillin at the most forward surgical levels in the N.W. European campaigns was the principal factor in producing the improved results. Time does not permit discussion of all these factors—nature of wounds and missiles, degree of contamination, terrain, climate, time-distance factors, resuscitation, anaesthesia, primary surgery, pre- and post-operative care, etc.—which do influence the state of wounds; but two common misconceptions must be corrected: (1) that the surgeons of 21 Army Group (the combined British and Canadian Armies constituting the so-called B.L.A.) were all specially experienced; and (2) that the time-distance factors were much more favourable in Europe than elsewhere.

1. The majority of the surgeons, anaesthetists, and transfusion officers who landed in Normandy in June, 1944, had no previous experience of field surgery, and while their work was generally excellent, it was no better, for example, than that achieved by the Eighth Army surgeons. Yet their results, as judged by the condition of the wounds, were much better.

2. Some have assumed that more favourable time-distance factors in N.W. Europe explained all the improvements, it being ignored or forgotten that men wounded in the same theatre in 1940, even before the final disastrous days, had shown no comparable absence of sepsis. Two time-distance factors require consideration: (a) the interval between wounding and primary surgery; and (b) the interval between the primary surgery performed in forward units and the secondary surgery done in hospitals. These in turn are related to important subsidiary factors such as rest, frequency of dressings, etc.

The first interval is the more important in respect of prophylaxis, and, although this may surprise many, it was not significantly different in the N. African, Italian, or N.W. European theatres, being 12 to 14 hours on an average.

The second interval was often prolonged in the desert, especially in the earlier phases, and this probably explained the almost universal occurrence of moderate to severe wound sepsis. Exhausting journeys, lack of rest, inadequate fluids, frequent pain, and the irrepressible tendency to change dressings in each medical unit on the line of evacuation, all led to inevitable infection. But this state of affairs did not always prevail. At Alamein, where the greatest desert battle was fought, the front remained static for weeks on end. At that time casualties were evacuated to hospitals more easily and rapidly than was often possible during the campaigns in N.W. Europe, and the Medical Services were as efficient as anywhere during the war, yet the wounds were all infected to a greater rather than a lesser degree when the patients reached hospital.

Air transport was not used in evacuating the wounded from the battlefield to the forward surgical units a few miles

behind and therefore did not influence the more important time-distance factor from the prophylactic point of view—that between wounding and primary surgery. It did influence the period between primary and secondary surgery, however, as from the time of Alamein in 1942 onwards air-ambulances were used increasingly between forward and base medical units. It was possible to obtain information about this interval from special surgical reports submitted by many of the surgeons in 21 Army Group hospitals. Thus, of 2,153 men who had wound sutures performed, 1,290 were operated upon within 1 to 7 days of having been wounded, and 863 were operated upon 8 days or more after they had been wounded. It was the general rule to suture nearly every wound within 1 to 2 days after the patient had been admitted, so it is obvious that about 40% of the casualties in N.W. Europe did not reach a hospital where secondary closure was possible until about a week or more after they had been wounded. From late 1942 onwards the average intervals in other theatres were not greater.

Penicillin v. Sulphonamides in Prophylaxis.—Many surgeons are still undecided about the relative value of sulphonamides and penicillin in prophylaxis, and assume that because the former are of great therapeutic value in many conditions they must also be very effective prophylactic agents. The evidence, however, favours the view that they usually prevent spreading or generalized infections from wounds, but have no appreciable effect on the incidence or severity of local infections. This was well exemplified in the later desert campaigns. By then the administration of prophylactic sulphanilamide was extremely efficient and, although the spreading infections commonly seen in the pre-sulphonamide phase were comparatively rare, the great majority of the wounds showed evidences of active local infection. In the N.W. European campaign both penicillin and sulphonamides were used and there was a remarkable change for the better in the condition of the wounds. As the one completely new factor was the prophylactic exploitation of penicillin, it must be accorded most credit for the dramatic improvement.

An attempt was made to discover whether penicillin alone was as effective in prophylaxis as penicillin plus sulphonamides. Once the former was freely available it seemed to be unnecessary to give both if penicillin alone was equally effective, especially as the sulphonamides occasionally produced annoying or even dangerous complications. Casualties with comparable wounds were divided into two groups in forward surgical units. Except for the drugs employed these men were all treated alike, but one group received only the routine prophylactic doses of parenteral and/or local penicillin, while men in the other group were given both penicillin and sulphonamides. The wounds of these patients were carefully compared when they were first examined in base hospitals. In the assessment of infection, four categories were used: 0 (none); + (slight); ++ (moderate); and +++ (severe). The results compiled from the reports of 17 surgeons are given in Table II.

TABLE II

Agents	Total Cases	Degree of Infection				Percentage 0 and +
		0	+	++	+++	
Penicillin only (parenteral and/or local)	497	298	165	28	6	93.1
Penicillin (parenteral and/or local) plus oral sulphonamides	480	275	159	37	9	90.4
Sulphonamides only (oral and usually local)	157	74	41	25	17	73.2
Totals	1,134	647	365	90	32	88.8

The number of severe infections was highest in the "sulphonamide only" group, but most of these were in prisoner patients, and it would be misleading to compare them directly with the others. Study of the other groups shows that the men who received penicillin only did not suffer from the absence of a sulphonamide. Although the difference between the results is small, it is significant that a higher proportion of the men in the "penicillin only" group received parenteral penicillin, suggesting (a surmise confirmed by personal investigations) that this group contained a higher proportion of men with severe wounds, these being the ones more likely to receive parenteral penicillin. Thus the interesting fact emerges that in this series of about 1,000 cases the men with the severer wounds received more prophylactic parenteral penicillin and had less infection. The moral of this and similar observations in many other cases is obvious: in order to secure maximum protection for those with severe open injuries penicillin should be used *both* parenterally and locally.

Anaerobic Myositis.—The value of penicillin in prophylaxis, and possibly in therapy, is further confirmed by studying the figures for anaerobic myositis. The high incidence of this serious infection in the war of 1914–18 and in the disastrous struggle in 1940 gave rise to inevitable fears of a similar high rate when fighting was renewed over the same ground. The penicillin memorandum issued for the guidance of medical officers just before the invasion of Normandy in 1944 drew particular attention to the "gas-gangrene prone" type of case and placed these patients in the highest priority for penicillin prophylaxis. The recommendations were interpreted generously, and the rate of penicillin expenditure was high, but the policy was justified by the results. In the desert campaigns MacLennan (1944) calculated that the incidence of gas-gangrene was 3.4 per 1,000 and in Tunisia 6.7 per 1,000. Jeffrey and Thomson (1944) estimated that the rate in Italy was not less than 10 per 1,000. It is unknown whether the above figures include cases among prisoners. In N.W. Europe the incidence in Allied troops (Porritt and Mitchell, 1945) was 1.5 per 1,000, and, although no exact figures are available, it was very much higher in enemy troops. Incidentally, it is worth noting that sulphonamides were used freely by the Germans both in prophylaxis and in therapy. The death rate in cases in N.W. Europe was also exceptionally favourable, being 21.5% in Allied troops—the lowest recorded mortality in any large series of cases. The actual figures for the entire campaign in N.W. Europe are given in Table III.

TABLE III.—*Anaerobic Myositis Cases treated by 21 Army Group Surgeons, D Day (June 6, 1944) to VE Day (May 8, 1945)*

Categories	Cases	Deaths	Percentage Mortality
Allied troops	251	54	21.5
Prisoners	133	59	45.1

The existence of many variables in wounds sustained and treated in the field renders the exact assessment of their individual importance difficult or impossible. But the one really new factor in the N.W. European campaigns was the widespread prophylactic use of penicillin, both parenterally and locally, and in any reckoning it must be accorded a good deal of the credit for the diminished incidence and improved results.

I have deliberately focused attention upon the prophylactic value of penicillin because to date its therapeutic applications have secured almost all the publicity. Penicillin may produce brilliant results in many established and hitherto mortal infections, but it would be far better for the patients, if less spectacular, to prevent the infections or modify their virulence. Herein lies the greatest promise of

penicillin in surgery—to abolish or reduce the incidence and severity of pyogenic and anaerobic infections by the judicious combination of surgery and penicillin.

Prophylactic Administration.—In minor wounds local applications are usually adequate. The wound should be dusted with penicillin powder at the first examination, and this procedure may be repeated if necessary, but unnecessary dressings or interference should be avoided. In war wounds we used 5,000 Oxford units of penicillin per gramme, the diluent being sulphonamides or powdered plasma. For the average civilian case, which is treated sooner and is less heavily contaminated, a smaller concentration of penicillin should be adequate. In more severe wounds, particularly in those with much tissue damage, associated vascular lesions, retained foreign bodies, or open bone and joint injuries, penicillin should be used *both* parenterally and locally as soon as practicable after the accident—e.g., on admission to the casualty department of a hospital. For prophylaxis intermittent injections are most often used, and, depending on circumstances, dosages between 15,000 and 100,000 units per injection have been employed; the smaller doses are given three-hourly and the larger every five to six hours. The lower dosages should be sufficient in civilian practice. With the increasing availability of penicillin in slow-release vehicles, such as the oil and beeswax suspensions, these may be employed to reduce the number of injections and give more prolonged protection; they have the disadvantage that they are difficult to inject. Reliable and economical oral methods of administration have not yet been perfected. When they are they will become the method of choice except in those patients who have been exposed to great infective hazards or who show evidence of developing a fulminating infection. If the patient is admitted to hospital continuous methods of administration may be instituted from the start and the prophylactic administration may then merge into the therapeutic; the average daily dosage by this method is 100,000 to 120,000 units, and most practitioners will be familiar with the various forms of apparatus that may be employed.

Penicillin administration should be started at the first available opportunity and should be continued until the satisfactory state of the patient's local and general conditions shows that the danger of infection is past.

In patients with heavily contaminated wounds the initial prophylactic dose may be boosted up to 100,000 units, or, if continuous methods of administration are employed, 300,000 units may be given during the first 24 hours. The larger doses are specially indicated if there has been any delay in instituting treatment or if there are associated vascular lesions. The higher blood titre thereby obtained may produce an adequate penicillin level in partially devitalized or devascularized tissues, but it is re-emphasized that surgery is still the main bulwark in these cases both in prevention and treatment. Unless there is some specific indication for their use, prophylactic sulphonamides may be withheld if penicillin is being administered.

Value of Penicillin in Therapy

An enormous volume of evidence has been published regarding the therapeutic value of penicillin in a wide variety of conditions. This being so, there is no need to add wood to the pile of well-established facts, and in any case one could not even summarize all the evidence within an hour. It will be more profitable to discuss an experiment (21 Army Group Memo, 1944) which was carried out by Army surgeons in an attempt to discover the relative value of different agents in eliminating or controlling wound infection. Surgeons were asked to treat alternate cases:

(a) with penicillin and (b) with a contrast agent. To avoid complicating the issue, casualties with associated visceral, bony, or articular injuries were excluded. Apart from this, patients treated were consecutive and unselected, and they had wounds of the soft tissues of all grades of severity. The idea was that each surgeon would choose what he regarded as the best alternative to penicillin, and it was emphasized that, apart from the chemotherapeutic agent employed, every other controllable factor, such as surgery, diet, rest, etc., should be of equal quality, with no preferential treatment for any case.

Before describing the results it may be of interest to explain why this investigation was initiated. In the earlier stages of the war surgeons were frustrated by the prevalence of sepsis, and they soon discovered that secondary sutures, grafts, and plastic procedures, however desirable in theory, were not safe in practice. Despite various attempts to evolve improved methods of treatment this state of affairs persisted substantially unchanged until the pioneer work of Florey and Cairns (1943) and their collaborators showed in N. Africa that many wounds could be closed safely under the protective mantle of penicillin. By the time of the invasion of Normandy the much greater supplies of penicillin available permitted its widespread employment as a prophylactic agent. As a result at least 9 out of 10 wounds were clinically clean when they were first examined at base hospital level, and secondary closures became the commonest operations performed. They were carried out regularly and with impunity not only on clean wounds but on many which, in pre-penicillin days, would have been regarded as quite unsuitable for suture. This notable advance conferred untold benefits in the prevention of pain, in providing better functional and cosmetic results, in avoiding prolonged suppuration with consequent visceral damage, and in shortening convalescence. As Porritt, Debenham, and Ross (1945) commented: "The results achieved led to a saving of man-power, a reduction in wound complications, and an economy in hospitalization, in supplies of drugs and equipment, in surgeons' and nurses' time which it is quite impossible either to compute or to appreciate fully."

All this is now generally known, but when the medical plans were being made for the invasion of Normandy penicillin was merely a name to most surgeons. Preliminary reports about it were very encouraging, but many surgeons held that the case in its favour was unproved, since the earliest casualties treated had received preferential treatment—e.g. they had been retained in forward hospitals for longer periods than comparable casualties not treated with penicillin, and they had benefited from unusually specialized medical attention. It was therefore decided that the relative value of penicillin could not be assessed accurately until it was tried out on absolutely equal terms against other popular agents. This was the background behind the decision to initiate the investigation mentioned above.

The results proved the superiority of penicillin beyond reasonable doubt as Tables IV and V reveal.

TABLE IV.—Results of Wound Sutures in 4,432 Cases

Agents Used	Total Cases	Grade I		Grade II		Grade III		Percentage Grades I and II
		No.	%	No.	%	No.	%	
Penicillin; local applications only	2,359	1,881	79.73	348	14.75	130	5.52	94.48
Penicillin; local and parenteral	1,485	1,221	82.22	185	12.46	79	5.32	94.68
Penicillin; parenteral only	107	92	85.98	12	11.21	3	2.81	97.19
Sulphonamides; local and systemic	141	88	62.41	30	21.27	23	16.32	83.68
Sulphathiazole-proflavine mixtures—local	183	99	54.09	51	27.88	33	18.03	81.97
Nil	157	114	72.61	25	15.92	18	11.47	88.53

The results may be shown more simply by contrasting the penicillin cases with all the others.

TABLE V

Agents Used	Total Cases	Grade I		Grade II		Grade III		Percentage Grades I and II
		No.	%	No.	%	No.	%	
Penicillin	3,951	3,194	80.84	545	13.79	212	5.37	94.63
Others	481	301	62.57	106	22.04	74	15.39	84.61

The wounds were assessed on a uniform standard:

Grade I (Success).—Wound healed and completely dry at the end of 14 days. This period was selected as sutures were often performed under some tension and then the stitches were not removed until the eleventh or twelfth day.

Grade II (Partial Success).—Wound incompletely healed at the end of 14 days (slight moistness, small gaps, mild stitch suppuration, etc.), but healed and completely dry at the end of 21 days.

Grade III (Failure).—Wound incompletely healed at the end of 21 days.

Anyone with experience would regard Grades I and II as successes for the delayed suture of war wounds, so both were included when computing the percentages in the final column. As originally planned the investigation should have provided results in almost equal groups of cases. In fact, they were unequal, and the reason was simple. Most surgeons became so impressed at a relatively early stage by the superiority of penicillin that, for the sake of the wounded, they abandoned the use of contrast agents. Despite this a clear answer was obtained to the problem under investigation. In this large series of cases treated by many different surgeons penicillin proved itself superior to all other agents tested. This result is more evident if the highest standard (Grade I) is regarded as the criterion of success, and the superiority of penicillin over the other agents becomes less evident if the standard is lowered and both Grades I and II are regarded as successes.

The results in the group of patients whose wounds were sutured without any adjuvant agent are interesting, but they cannot be compared strictly with the others as this group contained only minor cases. It represents what can be accomplished by unaided surgery in small clean wounds; and it must be remembered that the wounds were clean when the patients reached hospital, because the men had probably received prophylactic penicillin in some forward surgical unit. On the other hand, the penicillin groups—and particularly those treated with parenteral penicillin—contained almost all the major wounds, yet these showed the highest standard of success. In the light of this knowledge the penicillin results appear to be still better.

Analyses of other features connected with these cases supplied the same answer—that penicillin had no serious rival—and, if time and space permitted, figures could be quoted relating to other injuries and diseases which all support the belief that penicillin is of supreme value. Time and space, however, are finite in medical if not in mathematical affairs, and perhaps the facts and figures I have given, together with those already known to you, will strengthen your belief that Fleming, by an inspired vision, discovered what had seemed until then a biological impossibility—the almost perfect antiseptic.

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A REVIEW OF THE DIETETIC FACTORS IN LIVER DISEASE

BY

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II.—THE APPLICATION OF NUTRITIONAL PRINCIPLES IN TREATMENT*

Acute Necrosis of the Liver

Acute necrosis of the liver is an anatomical diagnosis which cannot be made with certainty without biopsy or necropsy. Usually, however, we must rely on the indirect evidence of acute hepatic insufficiency. Jaundice is intense and the serum bilirubin rises to 20 mg. per 100 ml. or higher. The patient is critically ill with delirium, stupor, coma, and up-going toes. There are ascites, oedema, purpura, and occult blood in the stools. If we confine the terms "acute necrosis" and "acute hepatic insufficiency" to such cases—and I believe we shall make no therapeutic advance until we establish rigid criteria—we shall find ourselves dealing with a hepatic disorder which is uncommon and which has a mortality of 50 to 100%. From a sample analysis of death certificates carried out for the Jaundice Committee of the Medical Research Council by Dr. W. H. Bradley and Dr. Percy Stocks in 1944 (unpublished report), it appeared that there were approximately 400 deaths a year from acute hepatic insufficiency, of which only about 8% were toxic jaundice, whereas the greater part were probably due to the viruses of infective hepatitis, homologous serum jaundice, and post-arsphenamine jaundice. The average number of deaths from notifiable toxic jaundice during the years 1940–4 was fewer than six a year. I stress the rarity of fatal toxic jaundice in man in view of the fact that so much of our present information has been derived from toxic jaundice in animals.

The difficulties of carrying out therapeutic trials on a disease which is uncommon and hard to diagnose are great. Much of the literature on the subject is worthless, recording isolated successes, changes of fashion, and the surprising capacity of the organism, even in sickness, to withstand onslaughts on its integrity. This state of things should improve as a result of the careful collection and study of morbidity and mortality statistics which is occurring in several parts of this country. More is to be hoped from animal experiments, which are still curiously incomplete in the matter of treatment. The drawbacks to animal experiment are the dissimilarity of animals and man, and the failure to transmit infective hepatitis to animals. Another possibility, which it is to be hoped we shall be spared, is the occurrence of epidemics of infective hepatitis with a mortality of the order of 15%, such as have lately appeared in Denmark and Switzerland.

It will be simplest to begin by discussing orthodox therapy with glucose. The untreated hepatectomized animal always dies of hypoglycaemia, and life may be prolonged for many hours by the administration of glucose. Dextrose therapy in diseases of the liver in man has been reviewed by Althausen (1933), but perhaps the most convincing data are those of Chester Jones (1936). He collected 56 cases of acute hepatic insufficiency from the records of the Massachusetts General Hospital and showed that the mortality had fallen from 95 to 63% over a period during which glucose therapy had been made more intensive. In the final period an attempt had been made to give the patient 450 to 500 g. of carbohydrate by mouth, usually combined with intravenous therapy, with solutions of glucose ranging from 5 to 25%.

There is no magic in glucose, whether it is given by mouth or intravenously, but there are, nevertheless, circumstances in which the intravenous injection of glucose may be of special value. There is normally a careful adjustment between the level of blood sugar and the release of sugar into the circulation by the liver. When the liver is damaged it may require a much higher concentration of blood sugar than normal to inhibit the formation of hepatic sugar. Such levels may not be attainable by oral feeding, and the intravenous infusion of dextrose may be essential. The fact that the hyperglycaemia so produced may lead to glycosuria is of no moment, and insulin should not be used as a rule or it will defeat the very purpose for which the glucose was given (Soskin and Hyman, 1939). A small number of human cases of acute hepatitis was treated by Minot and Cutler (1929) on a meat-free diet rich in carbohydrate, accompanied by oral administration of calcium lactate, but the work does not seem to have gone very far. Nevertheless, it has become standard practice in acute hepatic insufficiency to administer calcium intravenously, usually in the form of 10 ml. of 10% calcium gluconate, though few who carry out this procedure have read Lamson's (1930) advice on the need for extreme care and slowness.

The remarkable success of a high intake of certain proteins and protein derivatives in the prevention of acute necrosis in animals and in the treatment of cirrhosis in man has naturally given rise to the hope that these substances might be of value in acute hepatic insufficiency. Many theoretical objections can be raised against this new heterodoxy. The metabolism of proteins and amino-acids demands work from the liver, and it is a cardinal principle of therapeutics to rest a damaged organ. There is abundant evidence that meat and meat extracts may be positively harmful to animals with acute or repeated damage to the liver from carbon tetrachloride. The patient with acute hepatic insufficiency is liable to extrarenal azotaemia and uraemia, though opinion is divided whether this should indicate or contraindicate the administration of protein (Leitis, 1946; Zondek, 1946). In some cases of severe damage to the liver a state of acute renal failure develops which is known as the hepato-renal syndrome and which has been attributed to toxic derivatives of protein (Helwig and Schutz, 1932; Reich, 1941; Trueta *et al.*, 1946).

In this atmosphere of dubiety the ordinary clinician will do well, in the treatment of acute hepatic insufficiency, to concentrate on the relief of shock and the restoration of the normal internal milieu of the organism by fluids and glucose. Milk protein appears to be harmless, and milk should therefore form part of the fluid intake, though it is unlikely that more than 30 to 40 g. of protein will be supplied in this way. The therapeutic value and application of nitrogenous materials such as choline, amino-acids, protein hydrolysates, and plasma still await demonstration in

* The second of two University of London Lectures in Medicine given at the Westminster Hospital Medical School on Oct. 29, 1946. The first lecture appeared in last week's issue.