SYSTEMIC FACTORS INFLUENCING WOUND HEALING

BY

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Surgeons who were actively engaged in the treatment of the wounded in the war of 1914-18 may legitimately inquire how far and in what manner advance in the treatment of wounds has been made. It would appear that progress has been chiefly in the direction of the inhibition or reduction of infection by the universal recognition of the virtue of early incision, appropriate secondary suture, immobilization by closed-plaster or other technique, and the employment of a chemotherapeutic agent. Given the essential factor of the arrival of the patient at a surgical centre within the "contamination period" it may reasonably be expected that septic infection will be avoided in most cases. Unfortunately a time-lag in evacuation is sometimes inevitable, and established suppuration follows. Advance in the treatment of this condition seems to be almost imperceptible: neither local nor systemic employment of the newer chemotherapeutic substances seems of value. Still more disappointing is the relative ineffectiveness of the Winnett Orr technique as compared with its use in the suppurations of civil surgical practice. This may be due to rapid wasting of the tissues in high-explosive wounds which suppurate, with consequent failure of immobilization, recrudescence of infection, and further spread of sepsis. I suggest that the questions of tissue reactions to suppuration and the mechanisms of repair have not received enough attention in this country, and the discussion of some of these, with clinical inferences to be drawn from them, may be useful.

Exact knowledge of the physiological mechanisms of tissue repair now available originates from the systematic experiments in tissue culture of Carrel and his co-workers: the investigation of the biochemistry of local factors which may accelerate repair or by which differential inhibition of regenerating tissues may be effected is due to a number of research workers, among whom Hammett and Medawar may be cited. An excellent résumé of the subject by Riley (1940) deals exhaustively with this aspect of healing. My aim in this paper is to focus the attention of clinicians on the advances in our knowledge of certain systemic or constitutional factors which also have considerable influence on the repair process. These, too, have been the subject of intensive investigation in the United States and to some extent on the Continent, and the information gained from these researches has been translated into clinical practice in those countries (Whipple, 1940).

It is of the first importance that treatment should have a sound physiological as opposed to an empiric background. Two factors of supreme clinical importance may be considered: (1) the influence of vitamin content; and (2) the effect of controlled electrolyte and protein fluid balance.

Vitamin Content and Avitaminosis

High claims regarding a particular influence in repair have been made for the various vitamins, whether applied locally or given in the diet. Many of these are based on faulty premises or imperfect observation, and it may be stated categorically: (a) that no locally applied vitamin has been shown to influence tissue growth, whether the results are assessed scientifically by mensuration or by the effect on mitosis and cell proliferation as estimated either by photomicrography or by measurement of the nucleophosphorus

output; and (b) that only vitamins C and K taken in the diet have been shown to exert a direct effect on the mechanisms of repair: deficiency of vitamin C results in a fibroblastic aplasia, affecting the collagenation of the proliferated fibroblast cells and their maturation to formed fibrous tissue, and causing weak irregular scars; in vitamin K deficiency the production of prothrombin is inhibited, capillary clotting retarded, and the rhythm of vascular regeneration interrupted.

Several clinical inferences may be drawn from these facts. First, at the risk of appearing polemical, I would say that there is no scientific basis for the very popular use of cod-liver-oil or ointment dressings for the supposed virtue of their vitamin content. I regard their use as an example of pseudo-scientific mumbo-jumbo: any healing effect they may possess dwells, I believe, in their mechanically atraumatic character, and perhaps in the fact that a few hours after their application the wound surface will furnish a distinctly acid reaction (a large volume of research indicates clearly that the discharges of the healing wound have a consistently high hydrogen-ion content). Careful planimetric measurement in six cases treated by cod-liver-oil dressings showed no acceleration of healing, as plotted by the du Nouy formula.

Secondly, it is obvious that the diet of the patient in the surgical ward should contain foods of a high vitamin C content—e.g., fruit and green vegetables—and that care should be taken to ensure that the vitamin is not destroyed in cooking. The recovering patient should have a daily intake equivalent to 75 to 100 mg. of ascorbic acid. If this cannot be obtained from the diet it should be given in tablet form. The effect in the case which is slow to granulate is sometimes dramatic; but no effect on epithelization is to be expected. Thirdly, vitamin K is now available commercially, but by reason of expense its use should be reserved for cases in which recurrent bleeding from granulation tissue is encountered or minor secondary haemorrhage occurs.

Electrolyte Fluid and Protein Balance

This complex factor may be studied from two angles: (a) protein loss and protein replacement, and (b) the fluid balance and the occurrence of oedema.

HIGH PROTEIN INTAKE

Experimentally, observations of the measurement of healing wounds (Carrel, Fischer) confirmed by those on the tensile strength of wounds (Howes, Ellis, Cutler) have established the fact that a latent period of about four days before repair begins is constant for all clean wounds; this delay is reduced or eliminated by instituting a high protein diet from the start: high fat (ketogenic) diet, on the other hand, prolongs the lag period. Cuthbertson (1936) showed that the protein loss following fracture was very high, and the same is true in cases of prolonged suppuration. I made repeated estimations of the urea excreted in ten cases of prolonged bone or joint suppuration in my wards; this averaged 46 grammes daily: as the excretion of urinary chloride was not equally raised it may be assumed that the increased urea output is due to tissue destruction. In a case reported the nitrogen loss was 26 grammes daily—equal to nearly 2 lb. of muscle tissue.

The clinical significance of the hydrogen-ion content of wounds has received little attention in British surgery. From the work of Girgola (1924), Rohde (1926), and others it may be regarded as certain that the healing wound is acid in reaction, and that such acid tissues offer a resistance to invasion by organisms which diminishes as the pH

approaches the neutral or alkaline zones. An acid diet maintains this wound acidity, and may contribute to recovery in this way also.

Protein deficiency retards repair in another way. That the most powerful enemy of repair is the occurrence of oedema is a clinical fact with which we are all acquainted; it is well illustrated by cases of delayed union of fractures in which tissue support has been inadequate or gravitational oedema has been permitted. The protein molecule is of large size, and in hypoproteinaemia the missing large molecule is replaced by the smaller molecules of inorganic salts, especially the chlorides, and as a result salt action occurs in the tissues, followed by intercellular oedema.

From these physiological researches the important clinical lesson may be drawn that high protein intake should be arranged for at the earliest day after injury or operation and should be maintained during the whole course of healing. There is a persistent tendency to put a patient on light—that is, carbohydrate—diet in the early days, especially if the temperature is elevated. It will be seen that this is wrong: provided the digestion is competent the diet should include milk, grated cheese, egg albumen, and perhaps gelatin, followed by pounded fish, scraped meat, etc.; while fats, including butter, should be materially restricted. Protein-containing vegetables and cereals—e.g., peas and beans, oatmeal, and bran—may be useful as substitutes in the present shortage of animal proteins. Although cheese has a high fat content it is retained for the ready absorbability of its protein. For parenteral introduction blood plasma no doubt is the ideal, but the supply is limited; a solution containing the total amino-acids of casein, together with dextrose, is being employed in the United States, and the results so far are very hopeful. It is possible that a similar solution may become obtainable in this country.

LOCAL ELECTROLYTE FLUID BALANCE

It has been indicated that massive oedema is greatly inimical to repair: this is equally true of its occurrence locally. The importance of preventing it by maintaining adequate tissue support, by obviating gravitational fluid collections, and by maintaining functional movement so far as possible cannot be overstressed; for similar reasons care should be taken that tension sutures are not drawn so tight as to create areas of oedema between them. In addition some standard should be adopted for the administration of fluid: too often indiscriminate injection of dextrose-saline solution merely results in wrecking the fluid balance, sometimes to the extent of establishing a condition analogous to anasarca. Intake should bear relation to excretion and an endeavour be made to estimate the excretion of fluid as urine in each case where saline infusion is being resorted to. A good working rule is that no more than one and a half times the amount of fluid excreted as urine in twenty-four hours should be administered. Owing to rapid surface evaporation cases of burns can tolerate rather more, but even these wounds can be drowned in tissue dropsy.

These adjustments in the treatment of cases of wound suppuration have been in use for several months in cases under my care, and it is certain that improvement in the condition of these patients has resulted, as indicated by arrest of wasting, absence of oedema, acceleration of healing, and the maintenance of a normal blood pressure. I believe they form a distinct advance in our technique. It is difficult to ascertain the body weight of bed patients. In three cases, however, it was taken weekly; in these an average loss of 24 oz. a week was arrested on the institution of the acid diet, while a fortnight later the average gain was 30 oz.

Wartime High Protein Diet

Adequate supplies of carbohydrate are readily obtained, but the difficulty of maintaining a high protein diet under war conditions is patent. I must here express my indebtedness to Miss Gatenby, matron of the Memorial Hospital, Darlington, for her effort and ingenuity in this matter; at my request she has added the following notes.

In June, 1939, the full diet given in orthopaedic cases and wound infections possessed a moderately high protein content—approximately 110 to 120 grammes of protein a day. A cooked breakfast was supplied from the hospital kitchen to all patients (previously only tea and bread-and-butter were provided), and a better-balanced diet was maintained. The average daily diet was as follows—with as much variety and as little repetition as possible:

- 6 a.m.: Tea and milk, bread-and-butter (6.2 gm.).
- 8 a.m.: Milk 2 oz., oatmeal porridge 2 oz., kipper 3 oz., tea and milk, bread-and-butter (31 gm.).
- 12 noon: Rabbit stew 4 oz., potatoes 8 oz., chocolate pudding 4 oz., custard 4 oz. (42 gm.).
- 3.30 p.m.: Tea and milk, bread-and-butter, 1 egg (provided by patient) (16.5 gm.).
- 6.30 p.m.: Vegetable soup 8 oz., bread-and-butter, cocoa (15 gm.).
- 10 a.m. and 10 p.m.: 5 oz. milk, cocoa, etc. (10.9 gm.).

This diet yielded 121.6 grammes of protein and gave 3,047 calories.

In August, 1940, an endeavour was made to raise the protein content of the full diet to approximately 145 grammes daily, and emphasis was laid on the importance of persevering with a higher protein intake during the first few days until the patient was in a fit condition to partake of the fuller and more substantial forms of diet. The suggested daily diet for the first week was: 1 egg, 5 oz. milk (10.4 gm.), egg custard (5.9 gm.) (1 egg = 5 oz. of milk), 4 oz. minced chicken (29.6 gm.), 6 oz. pounded fish (37.8 gm.), milk jelly (8 gm.), extra milk fluids 5 oz. (4.5 gm.). Total, 96.2 grammes of protein. Balcony treatment, whenever possible, greatly improved the patients' general condition, appetite, and outlook.

To obtain 145 grammes of protein daily the following diet was given:

1. *Animal Protein*.—Breakfast: 4 oz. herring (21.6 gm.), 2 oz. milk (2 gm.), tea (milk) (1.8 gm.). Dinner: 4 oz. roast beef (30.4 gm.). Tea: 1 egg (5.9 gm.), tea (milk) (1.8 gm.). Supper: 2 oz. cheese (14.2 gm.). 10 a.m. and 10 p.m.: 5 oz. milk, cocoa, etc. (10.9 gm.). Approximately 88.6 grammes of protein.
2. *Vegetable Protein*.—Breakfast: 2 oz. oatmeal (7.6 gm.), 8 oz. bread-and-butter (8.8 gm.). Dinner: 4 oz. dried peas (8 gm.), 3 oz. jam tart (3 gm.), 8 oz. milk pudding (10.4 gm.). Tea: 4 oz. bread-and-butter (4.4 gm.). Supper: Vegetable soup (4.8 gm.), cocoa (5.8 gm.), bread-and-butter (4.4 gm.). Approximately 57.2 grammes of protein.

The pulses are among the cheaper foods, and in large quantity will raise the amount of vegetable protein, circumventing the deficiency of animal protein.

The following are valuable foods: Dried peas, butter beans, haricot beans, lentils: can be given as a vegetable or added to soup stock. Pea and bean flour: 1 heaped teaspoonful in each plateful of soup has a protein value equivalent to 1 oz. of meat; by making soup with milk the amount of protein is trebled. Macaroni, semolina, barley: Can be used as milk puddings or for thickening soups. Suet puddings, with milk or egg custard. Cheese: protein and fat content are nearly equal, and both are high. (It is possible to obtain a certain amount of cheese, and necessitous patients benefit.) Corned beef: high protein value, used as iron rations. Farex: added to milk puddings and porridge. Hovis bread: 3 lb. bread yields 100 grammes of protein (richest in nourishment of all breads). Peanuts: 1 oz. yields 8.5 grammes of protein. Bovril and oxo, made with milk: 1 teaspoonful of bovril equals 1/5 oz. meat.

Alternatives for Breakfast.—4 oz. fish cakes (13 gm.), 4 oz. sausage, 2 oz. sardines (11.6 gm.), 2 oz. bacon (13.8 gm.), 3 oz. haddock (18 gm.), 3 oz. herring (16.2 gm.), 3 oz. scrambled eggs (8.7 gm.).

Alternatives for Dinner.—2 oz. boiled mutton (14.6 gm.), 2 oz. fried liver (16.6 gm.), 2 oz. stewed beef (17.4 gm.), 4 oz. stewed tripe (20.4 gm.), 4 oz. fried cod (2.6 gm.).

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NEED FOR BIOLOGY IN EDUCATION

SIR WALTER LANGDON-BROWN'S ADDRESS

At the annual meeting of the British Social Hygiene Council, held at B.M.A. House on July 31, Sir WALTER LANGDON-BROWN delivered an address on "Biology and Health." He began with some remarks on the blight which has fallen upon European culture, the hapless conditions of university life on the Continent, and the subservience of scientific work to National Socialism. Incidentally he mentioned that the *Münchener Medizinische Wochenschrift*, formerly one of the leading medical journals of the world, had now become scientifically negligible, the happy hunting-ground of naturopaths and other cranks who hoped to catch the Fuehrer's eye. The fate of *Pflügers Archiv*, which was for more than seventy years the leading publication of physiological and biological research, was also significant. In 1932, the last pre-Hitlerian year, it ran to five volumes; in 1938 it appeared as one slim volume, the articles being mainly written by Russians and Japanese.

Sir Walter Langdon-Brown went on to say that, brought up as he had been, he found it hard to disbelieve in progress, though not necessarily as a law. Moreover, he thought the study of biology did impress the idea on the mind as the increasing complexity and adaptations of animal life came to be studied. If the study of biology had been pursued with the same intensity as that of chemistry and physics, it was possible that men might have become so interested in the wonderful processes of life that they would not be so keen on inflicting death. Here he mentioned the three main planks in the platform of the British Social Hygiene Council: (1) the study of biology as a subject of general education; (2) the education of the educator; and (3) general enlightenment on the principles of social hygiene. The general public would have no adequate grasp of the principles of social hygiene until they had some idea of biological principles. Recently an inspector of a certain examination of older students remarked to him on the relatively high percentage of failures in biology and the relatively low percentage of failures in physics and chemistry. Inquiry revealed that the teachers in many of the various institutions preparing the students had not been interested in biology and regarded it as a tiresome sideline of their work. If a teacher could not make biology interesting he should not teach at all. Perhaps it was the romanticizing tendency of the English which had made them unwilling in the past to face the uncomfortable fact that behind the divine mystery of the continuity of life lurked the shadows that were responsible for venereal diseases; but it was ignorance of biology rather than unwillingness to face facts which was responsible for failure to realize the natural law that whenever the continuity of life was threatened the impulse to create more life was increased.

Bearing in mind the shadow which accompanied this natural impulse, the work of the British Social Hygiene Council assumed a new significance. It was beside the point to say that there had been no sensational rise in venereal diseases in this war as in the last. It was like saying that the stirrup-pump had served so well when the last shower of incendiaries fell that it could now be discarded. In view of the fact that it was sometimes said that medical officers of health had little opinion of the usefulness of the work of the Council, fifty leading medical officers had been circularized, and the first thirty-three who had replied all said that they thought the Council served a useful purpose, though reservations were made by two. All replied in the affirmative on the question whether direct education on venereal disease was still necessary, and all except four (who were doubtful) were also in favour of a more general type of health education.

The Untrained Intruder

In view of the recent debate in the House of Commons on the Pharmacy and Medicines Bill, Sir Walter Langdon-Brown added a few remarks on the need for educating legislators. He said he was impressed by the curious bias shown in favour of the intruder into a sphere for which he was not trained, even though he was trained for some other. For example, the pharmaceutical chemist was to be safeguarded if he wished to take over the doctor's work of advising and prescribing, but when it came to his legitimate business for which he had been highly trained, sympathy was shown to the competing interests of the co-operative stores, the grocer, and the herbalist. The Minister of Health was very tender towards herbalists, pointing out that an expert committee had recommended that the collection of herbs for medicines and drugs should be encouraged as much as possible. But as he himself read the report of that committee, what it had in mind was the collection of herbs, not for their administration in a crude form, but to enable the extraction of their active principles in a pure state by skilled pharmacological chemists. The *Pharmacopoeia* would indeed be denuded if deprived of pure drugs of vegetable origin. In other words, the pharmacologist carried out the work of the herbalist in a much more scientific form to a higher pitch of accuracy. What struck him about the whole tone of that debate was the extraordinary *naïveté* with which the value of evidence in these matters was assessed. It might be said that ultimately some steps were taken in the right direction, but these would have been firmer and more speedy if the majority of the legislators had had a modicum of science imparted to them in their general education. There would not then have been so many who seemed willing to believe that an untrained man might intuitively discover a cure for a hitherto incurable disease which could only be brought to the notice of sufferers by advertisements in the lay press.

AWARD FOR GALLANTRY IN CIVIL DEFENCE

The award of the M.B.E. (Civil Division) to Dr. WILLIAM REMINGTON, medical officer, Mobile First Aid Unit, A.R.P. Casualty Service, Woolwich, is announced in a *Supplement* to the *London Gazette* dated August 1. The announcement reads as follows:

"During enemy air raids Dr. Remington has shown resource and a high sense of duty. A high-explosive bomb demolished dwelling houses. Dr. Remington was lowered through a hole in the top of the wreckage, which was in a very dangerous condition, to some casualties underneath. He gave them morphine and remained while the rescue party dug out the victims. On another occasion when a building was demolished and people were trapped, Dr. Remington, regardless of his own safety, stayed at the incident for three hours giving treatment to the casualties."

Walter Bauer and Joseph C. Aub (*J. clin. Invest.*, 1941, **20**, 295) state that patients with acromegaly have an abnormal calcium and phosphorus metabolism, characterized by an increased urinary secretion of these minerals. In one patient x-ray treatment of the pituitary caused a reduction in urinary excretion of calcium and phosphorus, in the metabolism of which, the authors conclude, the pituitary gland must be considered one of the controlling factors.