MALNUTRITION AND CHRONIC SEPSIS.¹

BY

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GENERAL RANKEN—LADIES AND GENTLEMEN,

I feel rather like Daniel in the Den of Lions—one Pathologist facing a score or more of surgeons. However, I feel so strongly on the subject of my talk to-day, that come what may, the lions must be bearded. What I have to say must seem somewhat undocumented, but in these days of difficulties in obtaining literature, I hope you will excuse me. Further, it is impossible to acknowledge all sources of information as these are culled from short abstracts made from papers, official circulars and so on, before they have to be passed on to other units.

The interest of myself and of my laboratory colleagues arose when we got tired of writing the cause of death in autopsies performed on cases dying of Chronic Sepsis, as the "Toxæmia of Chronic Sepsis," which is, by itself, a fairly meaningless phrase, unless the many underlying factors are analysed. An analysis was therefore carried out with the assistance of the Officer Commanding 128 I.B.G.H. and the Officer in Charge Surgical Division, to whom our grateful thanks are due.

Following our analysis, both ante-mortem and post-mortem, on these cases, of necessity not in any way exhaustive, we began to wonder if some of these cases were not dying unnecessarily. It is this aspect I wish to stress to-day.

On the diagram (p. 69) are set out some of the many interrelated factors involved, the sum total being a failure of the delicate cellular mechanism of the body, which is all important in sustaining life.

You are no doubt more interested in the clinical side of this question rather than in the elaborate biochemical processes involved and, for this reason, I ask you to accompany me in imagination to the bedside of a fairly typical case.

This, then, is the patient, a man aged 25 who has sustained a severe compound fracture, grossly infected, of the shaft of the right femur, from a gunshot wound at the Eastern front some two months ago. He has reached this hospital by a roundabout route and has had adequate surgical treatment by modern surgical tenets, that is to say, adequate drainage, immobilization and the administration of effective bacteriostatics, such as penicillin and sulphonamides, given correctly and in adequate doses for a sufficiently long time but, as you stand by the bed, you feel a sense of frustration and hopelessness at the lack of response.

However, let us analyse the case in detail. We see an emaciated, flushed

¹A lecture delivered at a conference of Southern Army Surgeons at a Base Area in India on September 11, 1944.
and febrile patient with a dry tongue and sunken eyes, with a low inter-ocular tension, and we become aware that dehydration ((I) on diagram) is rearing its ugly and dangerous head. Knowing that the adult male consists of at least 60 per cent water, we ask if the fluid intake is adequate. However, we find that the patient is taking only about two and a half pints of fluid in the twenty-four hours. We incidently note the far too frequent belief that the contents of a glass tumbler is equal to about one pint when in fact it is usually less than one-half. We point out the great importance of water, the fact that over half the weight of the body consists of water; that it is the universal solvent, and lubricant; that it plays a vital part in many chemico-physical reactions, and of course carries food and removes waste products from the remotest cells, as well as being intimately concerned with temperature control.

A young adult of say about 70 kg. in weight, in perfect health doing light work in a temperate climate, requires roughly 2,800 c.c. per day, less than half of which is obtainable in food. How much more, therefore, will be required for a febrile patient in a tropical climate?

A case in point arose the other day—a blood volume was done on a patient, because on arrival from an ambulance train at night the Medical Officer admitting the case stated that the patient appeared dehydrated. Six hours later at 9 a.m. when the patient was seen by me, the signs of dehydration were not very obvious. However, a blood volume was carried out and gave a surprisingly low result, and although not much attention was paid to it in view of the fair condition of the patient, he was put on high fluid intake and a measured urine output. During the first twenty-four hours he passed only a few c.c. of urine and it was only on the third day that his output reached 18 ounces. The dehydration was therefore masked and the importance of this hidden dehydration is emphasized when it is realized that the blood count which on the first day was 3,500,000 red blood cells per c.mm. had fallen without additional hemorrhage to just over 2,000,000 red blood cells per c.mm. on the third day. Therefore, what seemed to be a reasonable operative risk, was in fact a very bad one, although in this case sepsis may have aided the red cell reduction. Of course it is not only the red blood cells that are concentrated, but also other blood constituents such as plasma, proteins, etc. Plasma volume falls and with it the blood-pressure and results in impaired capillary circulation, anoxial endothelial damage and in loss of tissue constituents from the cells.

Salt metabolism is closely associated with that of water, and salt deficiency, as well as being responsible for the well-known muscle cramps, has far-reaching effects on the physiology of the animal.

When it is realized that the sodium in the sodium chloride supplies 90 per cent of the metallic ions in tissue fluid, and the chloride 70 per cent of the acid electrolyte, its importance will be obvious and, further, there is practically no mobilizable store of sodium apart from that in the body fluids. There is therefore a disturbance of the acid-base balance with a resulting anorexia, which is of considerable importance in an already wasted patient. The
mechanism of osmotic control of the tissue fluids already profoundly disorganized by dehydration is further harassed, and tissue metabolism may give up the unequal struggle.

The next obvious facts about our patient are that he is both febrile and wasted (II) and (III) on diagram) and although these two symptoms are linked, let us first deal with the nutritional requirements of the febrile case. This patient is certainly not in a basal metabolic state, although he is in bed; he is restless and constantly moving as far as the plaster will allow him. He washes, shaves and has to feed himself, all of which actions call for a surprisingly large calorie output, also trauma itself seems to exert a specific catabolic effect. So let us say that this man will require some 2,000 calories in twenty-four hours if he were afebrile. Actually his temperature is 103°F and it is a well-known physiological fact that for each degree rise of temperature Fahrenheit the metabolic requirements are increased by 7 per cent. That is to say, in this man by 35 per cent, which is 700 calories in twenty-four hours. Further, it has been shown by Shaffer and Coleman that, if body wasting is to be prevented in a febrile case, the calculated calorie requirements must be exceeded by 50 to 100 per cent, and the diet must contain a large amount of proteins of high biological value. In fact this patient then requires about 3,500 calories in the twenty-four hours. Having realized what a large calorie intake is needed, let us go into detail. We find that, as the case is febrile, he has been placed on a "fever diet," consisting chiefly of milk and soda and, in fact, he is rapidly being starved to death. An average glassful of undiluted milk producing about 150 calories only.

I fear that the old teaching of light diets for fever cases dies hard; the Sister will, no doubt, point out that the patient will not eat. You may say this is so, and that the anorexia that accompanies fever cannot be so easily overcome. Then let me take you to a hospital in this area where a great deal of interest is taken in diet; there you will see patients who are febrile literally eating their way to health, taking 3,500 calories in the day, and asking for more. In fact chicken does not interest them, and they demand lightly cooked liver, etc. This desirable state of affairs was not achieved without a great deal of painstaking persuasion by all concerned. Firstly the Quartermaster had to be approached and a new "light" diet drawn up with his help. Then the nursing staff had to have their old-fashioned prejudices overcome and, finally, the patients had to be persuaded to eat. This was difficult at first but good nurses can achieve miracles if they are themselves converted.

I wonder just how many of you gentlemen can tell me how many calories your cases are actually taking in twenty-four hours. I feel it would be fair comment to say that this side of treatment is equally important with the best of surgical technique and it is far too often left to the nursing staff to carry out.

When, as I hope to point out later in this lecture, it is realized that it is not only calories, but protein, vitamins and other essential constituents that are not forthcoming in this man's diet, you will recall the old truism that "a good surgeon is a physician who sometimes uses a knife."

Wasting, which should be avoided especially in orthopaedic cases when
good muscle is essential to efficient recovery, will occur as long as the body is not in a state of nitrogen balance; that is to say just so long as the protein intake is insufficient to supply the body's needs, so will the protein tissues continue to be catabolized. There are sometimes difficulties in making a sick man take a high protein diet, but carbohydrate will act as a "protein sparer." However, in such a case at least 100 grammes of good proteins should be taken daily.

You may say that the patient will not digest and absorb this large amount of food, but we have practical evidence to show that the food is being absorbed. If, however, a sprue syndrome is present, possibly even induced by the starvation diet usually employed in such cases, the situation is admittedly more complicated, but a high protein, high vitamin, low fat diet will usually do the trick, and if necessary pre-digested protein can be administered as amino-acids by oral or parental routes. This will be discussed when we deal with liver failure.

The next important point that comes out of our study of this patient is that the laboratory reports that the plasma proteins are low and in fact may be at or below the oedema level ((IV) on diagram). This is due to a combination of factors: low protein intake, loss from hemorrhage, and loss from wounds in the sero-sanguineous discharge, liver damage, and possibly to plasmaphoresis through damaged capillary endothelium, the latter due to dehydration, local anoxia, etc.

You may ask what is the great importance of all this. Hypo-proteinæmia has been the subject of intensive work for some years, and the more obvious changes resulting are of course oedema inanition, failure of growth, anæmia and (to quote H. C. Hopps and J. Campbell, 1943) protein deficiency affects both qualitatively and quantitatively the regeneration of tissues. It predisposes the liver to injury by toxins and seriously interferes with antibody synthesis, and is an important cause of delayed wound healing and wound dehiscence. Further, experimental evidence has been brought to show that a low plasma protein greatly increases the risk of damage to the liver by toxic drugs such as chloroform and N.A.B.

The quantity of protein-containing serum that soaks into plasters is well known to you all, and so I expect are the difficulties that arise when massive oedema occurs under a plaster or at the stoma of a gastro-enterostomy.

The answer is of course that no military patients should ever be allowed to develop a low plasma protein, and if they do, a high protein diet, parental or oral amino-acids, with intravenous administration of plasma, are a vital necessity.

The next points to be considered are the liver changes ((V) on diagram) that take place in the type of case now under discussion.

The organ may be palpable during life but at post-mortem it stands out in the emaciated cadaver in a most dramatic manner. It is uniformly enlarged and on section cuts greasily and may actually show the waxy appearance of amyloid disease. But generally the organ is intensely fatty and microscopy shows large globules of fat pushing the nuclei of the liver cells to one side.
Malnutrition and Chronic Sepsis

giving the characteristic signet ring appearance of fatty degeneration. This condition, to quote Boyd's "Pathology of Internal Diseases," is induced by starvation, thus explaining in part the frequency with which it is found in hospital patients.

It has been shown that the sulphur-containing amino-acid methionine is of the greatest importance in the defence of the liver against toxic agents and that, by the mysterious process of transmethylation, methionine transfers its methyl group to enthanolamine with the formation of choline (Stretten). Choline is known to be a strong lipotrophic factor and greatly concerned with mobilization of fat in the liver. These essential elements are of course not readily available in a starvation diet although the fat that accumulates in the damaged liver cells is fat from outside that organ, i.e. alimentary or fat depot fat, and not, as was once thought, the actual product of the degenerating cells; the vital functions of the organ must be seriously impaired if the fat is present in vast amounts as indeed it is in the type of case under discussion.

To appreciate the importance of the above remarks your attention is drawn to the enormous lists of liver functions to be found in any modern physiology book; for example Best and Taylor give a list as follows: "Besides the secretory and excretory functions... the liver plays an important role in many other physiological processes... given below.

(a) Blood formation in the embryo; hematinic principle in the adults.
(b) Fibrinogen production.
(c) Prothrombin production.
(d) Heparin production.
(e) Iron and copper storage.
(f) Blood volume regulation.
(g) Reticulo-endothelial activity.
(h) Detoxication.
(i) Protein metabolism, deamination, amino-acid synthesis, urea and uric acid, hippuric acid synthesis.
(j) Carbohydrate metabolism.
(k) Fat metabolism.
(l) Heat production.
(m) Formation of vitamin A from carotine."

Besides the above may be added an important part of the antibody synthesis and possibly plasma protein control.

It should now be readily appreciated how desirable it is to prevent gross changes in the liver and realized that correct feeding will play a very great part in this prevention.

Therapy is not in my province but I would take this opportunity of drawing your attention to the large amount of work carried out in recent years by workers such as Ravdin on the feeding by parental or oral route of the essential amino-acids. The most useful is a casein hydrolysate as it is rich in methionine; however, we have used an acid pork digest with good effect and no reactions.

There is no reason why an ordinary military laboratory or indeed hospital kitchen should not be able to make a papain or peptic-tryptic digest for oral administration or feeding by duodenal tube. It has also been shown by
Ravdin that a loop of bowel will readily absorb such a digest and that high rectal feeding with digests of this nature has its uses.

Experiments have shown that in animals with experimental amyloid disease the feeding of raw liver will effect an absorption of amyloid. Raw liver being a rich source of protein of high biological value and containing many known and unknown factors will obviously be of the greatest importance in the treatment of cases of this nature especially if combined with the administration of vitamins now to be discussed ((VI) on diagram).

Continuing the clinical examination of our patient we refer back to the tongue and note that as well as being dry it may show the red raw beef appearance of a nicotinic acid deficiency or may be the magenta colour of riboflavin lack. Sordes and cracks may be noticed at the lip margins and angles and our ophthalmologist friends may point out an increasing limbal leash. The skin we notice is dry and harsh and pigmentation is present on the extensor surfaces, possibly the dermatitis of an early pellagra is seen and taken in conjunction with the mental changes previously called toxid delirium and the diarrhoea indicate a serious deficiency state. Bad wound healing with poor production of fibrous tissue, gum changes and a prolonged de-colorization time following the interdermal injection of 2-6 dichlorophenol indophenol (for what it is worth) and a refractory anæmia point to a vitamin C lack.

Quick tests may indicate a vitamin K lack and in general it may be stated that this type of patient will be suffering from a multiple vitamin deficiency syndrome and it is pointed out that when clinical manifestations of vitamin deficiencies present themselves the deficiency is extreme.

This is not the place to go into such a complicated subject as tissue respiration but it should be realized that at least three water-soluble vitamins are known to be very important parts of tissue oxidative catalysts—and are essential to the co-enzyme systems of the body without the proper functioning of which life itself cannot exist.

The next observation we make on our patient is that there is a troublesome anæmia ((VII) on diagram) which may be either macrocytic, normocytic or microcytic, depending on various combinations of circumstances, and a low white cell count with a poor phægocytic capacity. The macrocytic type of anæmia is likely to be due to a combination of factors such as a poor absorption and intake of extrinsic factors coupled with liver damage and possibly chronic malaria associated with a toxic effect of the various circulating toxins on the bone-marrow. The normochromic normocytic anæmia may be due to recent blood loss or intravascular hæmolysis from circulating hæmolysins such as those produced by hæmolytic bacteria. Available iron and protein intake may be deficient or absorption poor and the actions of bacterial toxins on the marrow may even produce an aplastic type of anæmia. Vitamin and hormone deficiencies with parasites, such as those of malaria, hookworm and kala-azar, also play their part in generally depressing the hæmopoietic system.

The low white cell count is most troublesome and most feared by the
surgeon and unfortunately is little understood. This blood state has to be tackled from many angles both general and specific and a rational approach with a proper understanding of the physio-pathological principles underlying the condition is essential.

Your attention is now directed to a point (VIII on diagram) that may be overlooked—that is to say parasite infection of the body as an additional factor. Fever in septic cases is not always due to "pocketing of pus" and continual operative procedures naturally may interfere with local healing processes and may make general an infection in the process of being localized by natural defence mechanisms. The question of malaria and kala-azar should be constantly in the minds of surgeons working in those areas where these infections are likely to occur.

Hookworm may cause an iron deficiency anaemia resistant to treatment and amoebiasis may undermine months of hard work if not spotted and treated.

The next and last point on the diagram (IX) is "alteration in ductless glands" and it is regretted that this has not been gone into more deeply as it appears to be of some importance—the teaching that some cases of chronic sepsis have a lag type of glucose tolerance curve, was explained by the action of toxins on the liver and pancreas, but it did not strike one as important until at post-mortem on two of the cases of the type under discussion, I noticed the pancreas cut with a real creak and was extremely hard. Section showed quite an extensive cirrhosis of the organ. The pathology of the same possibly being damage by toxins and anoxæmia followed by fatty changes and subsequent attempt at repair by cirrhosis. We then examined the suprarenals which were found to show varying degrees of fatty degeneration. It is regretted that the other glands have not been examined in detail but it is hoped to do so in the future.

This, then, completes the rough general survey of our patient and points to some of the various combinations and permutations of side effects, all of enormous importance from the point of view of recovery, that must be taken into account in dealing with these cases.

It would be an impertinence for me to go into details of treatment of these various points but, to generalize, ensurance of good urinary output, good intake of well-balanced food, suitable replacement therapy with such specific treatment as may be indicated by a thorough summing up of an adequate clinical and laboratory examination, will go a long way to aid good surgical technique.

Please do not think this is an attack on our surgical colleagues; far from it. It is only due to their active co-operation that this survey was made and the point I stress is that the place for the pathologist is in the wards with his colleagues, the physicians and surgeons, and only by this co-operation at the bedside can we pathologists be truly your handmaids.

It is my belief that the future of Army pathology lies along these lines and, forsaking the bacteriological bench for the wards whenever possible, a cadre of clinical pathologists will be built up who, by their active bedside co-operation, especially in the tropics, may be of considerable value to their colleagues.
SOME OF THE MANY FACTORS INVOLVED IN MALNUTRITION IN CHRONIC SEPSIS.

- Endothelial damage
- MUSCLE WASTING
- Poor INTAKE
  - Poor absorption (sprue syndrome, etc.)
- Alteration in serum chemistry
- NITROGEN IMBALANCE
- Hæmoconcentration
- Loss of Serum FROM WOUNDS
- B.M.R. 7% each 1° F. rise in Temp.
- Low P.P.
- Fever
- DEHYDRATION
- MANY BIOCHEMICAL PROCESSES fail
  - ANTIBODY synthesis breaks down
  - Alterations in serum chemistry, A/G ratio altered, vitamins and haemopoietic factors fail, etc.
  - VITAMIN deficiencies
    - Especially B complex and C
    - Tissue respiration fails
    - Formative processes fail

- Parasites add their share
  - MALARIA, K.A. WORMS E.H.
  - Low W.B. Count

- Anæmia
  - 1. Macro
  - 2. Micro
  - 3. Normo

- Liver Disease
  - Fatty changes
  - Amyloid

- Alterations in ductless glands
  - Pancreas Cirrhotic
  - Suprarenals, fatty changes +

- Fever
  - (IX) Alterations in ductless glands
  - (a) Pancreas Cirrhotic
  - (b) Suprarenals, fatty changes +

- Parasites add their share
  - Malaria, K.A. Worms E.H.
  - Low W.B. Count