recovered from spray-dried eggs of American origin. Some of these types were found also in the mesenteric glands of pigs fed on spray-dried eggs condemned as unfit for human consumption. Other strains have been reported in recent years.

In addition to the salmonella and staphylococcal poisonings, severe outbreaks of bacillary dysentery have occurred, especially through the medium of milk. In such cases the infection can usually be traced to the human subject.

Many organisms other than salmonella and staphylococcus are recorded as probable causes of food poisoning. Some outbreaks have been related to the presence in food of *Streptococcus viridans*, *Proteus*, *Bacterium coli*, *Bacillus subtilis* and related organisms. Laboratory proof of the production of toxic substances by these organisms is lacking, and acceptance of these organisms as causative agents would almost lead one back to the original theory of 'ptomaine' poisoning.

An enormous amount of food is produced, especially in America, by the canning process and is consumed by people all over the world. It is a remarkable testimony to these products that food poisoning is so seldom reported. Sterility of the material is usually possible, or at any rate it can be heated sufficiently to destroy non-sporing bacteria. The only organism of importance, *Cl. botulinum*, whose spores may be exceptionally heat-resistant, has seldom been the cause of food poisoning in this country. Since the Loch Maree outbreak it has been encountered on only three occasions and has affected few people. The foods responsible were potted duck paste, vegetarian nut-brawn and home-made pies. Botulism has been reported much more frequently in America and on the Continent of Europe. It is associated most frequently with home-canned vegetables, not with the acid fruits. The toxin develops in the food before it is eaten; the organism itself does not grow in the affected subjects. The organism is present in soil, especially virgin soil, and its spores are sometimes extremely resistant to heating. Special conditions are necessary for the development of the spores: anaerobic environment; spores in sufficient numbers, possibly; insufficient cooking; and a suitable hydrogen-ion concentration. The foods which have produced cases of botulism in America are string beans, olives, spinach, maize, peas and salmon. In Europe sausages, ham, preserved meats, potted goose or duck, brawn and salted fish have been the vehicles of the disease. In many cases the appearance of the contents of the cans has been indicative of spoilage.

Vitamin C and Immunity

By G. H. Bourne, *London Hospital Medical College, Whitechapel, London, E. 1*

The term immunity means complete insusceptibility to infection, but we are not perhaps as much interested in this absolute condition as in relative immunity: in other words, a variable which may be anywhere between zero and infinity. The word immunity is better replaced by the word resistance, so that what I should talk about in this paper is whether vitamin C plays any part in improving the relative resistance of the body to infective agents.

The resistance of the body to infection depends upon a series of factors which are summarized by Wilson & Miles (1946) as follows:

(1) Innate immunity.
(2) Acquired immunity.
    (*a*) Active.
        (i) Naturally acquired.
        (ii) Artificially induced.
    (*b*) Passive.
        (i) Naturally acquired (congenital).
        (ii) Artificially induced.

It is not possible in this paper to deal with all the literature on the relationship of vitamin C to this problem and I propose to refer only to some aspects of it.

Relation of vitamin C to complement

One of the important factors in innate immunity is 'complement'. This is a non-specific, anti-bacterial activity which is present in all normal serums and is not increased by immunization. It is probably due to interaction of a number of separate components which, according to some authors, are four in number.

A number of papers has been published on the relationship of vitamin C to complement. Simola & Brunius (1933) claimed that in vitamin C deficiency in guinea-pigs complement titre was reduced. This claim was supported by Marsh (1936). Other authors, however, e.g. Zilva (1936) and Chakraborty (1937), could find no significant alteration in the complement titre of scorbutic guinea-pigs. Ecker, Pillemer, Wertheimer & Gradis (1938) and Ecker & Pillemer (1939) claimed that if guinea-pigs on a scorbutic diet were given graded doses of vitamin C the larger doses of the vitamin were paralleled by increases in the complement titre. The apparent conclusiveness of these two papers was challenged by Chu & Chow (1938) and Maccolini (1939), who found that guinea-pig complement titre was not influenced by a scorbutogenic diet and that the addition of vitamin C to such a diet also had no effect on the complement titre. The observations of Crandon, Lund & Dill (1940) showed that in human scurvy the complement titre did not change, and Spink, Michelson & Agnew (1941) and Natvig (1941) came to a similar conclusion. Feller, Roberts, Ralli & Francis (1942) studied immunological phenomena in relation to intake of both vitamin C and vitamin A. They tested the capacity of nasal secretion to inactivate influenza virus, the titre in blood serum of neutralizing antibodies for influenza virus, the activity of lysozyme in the nasal secretion, the phagocytic activity of leucocytes and complement titre. None of these tests was significantly influenced by marked changes in the plasma levels of vitamin C induced by a period of severe vitamin C deficiency followed by a large excess of the vitamin. The authors argued that, because of the large number of factors involved in immunological reactions, it is difficult to generalize from their results, and it may be that the number of variables is responsible for the very diverse results that have been obtained in such studies. Kodicek & Traub (1943) tried to eliminate as many of these variables as possible but still found no significant change in complement in

guinea-pigs partly or completely deprived of vitamin C, and finally Deeny, Murdock & Rogan (1943) found that in eighty patients in Northern Ireland with acute infections there was no relation between the vitamin C level of the blood and complement titre.

It is difficult in the light of these contradictory results to say whether vitamin C does, in fact, play any part in maintaining the complement titre of the blood, although the weight of evidence seems to be against it.

Vitamin C and acquired immunity

Having dealt with one of the measures concerned in natural immunity, we may turn now to consider for a moment whether vitamin C is concerned with acquired immunity. Is it, for example, concerned with antibody production? Jusatz (1936 *a, b*) found that if 100 mg. of vitamin C were added to an immunizing dose of horse protein there was a 500 % increase in the specific precipitation reaction in rabbits. Jusatz's work was confirmed by Mutsuro (1939), Izutumi & Sowai (1939), Madison & Manwaring (1937–8) and Madison, Fish & Frick (1938). Cameron (1938) found that if guinea-pigs were injected with diphtheria toxoid, those receiving 3·6 mg. of vitamin C daily had more antitoxin in their serum that those receiving 0·9 mg. Here we seem to have something more definite. What still needs to be found out is at what level of vitamin C intake in animals and man maximum antibody production can be secured for selected organisms. At this point mention may perhaps be made of the work of Birkhaug (1939), who found that if he injected guinea-pigs with tubercle bacilli and administered 10 mg. of vitamin C a day to the animals, his controls receiving an adequate diet but no special supplement of the vitamin, there was a significant inhibition of the tuberculin reaction in the animals receiving extra vitamin C. The tuberculin reaction is of course an allergic reaction. Further, he found that the inhibition of the tuberculin reaction was definitely correlated with urinary excretion of the vitamin and the amount of vitamin C in the animal's adrenal glands. Unfortunately, Heise & Steenken (1939) were not able to confirm Birkhaug's work, but Steinbach & Klein (1941) found that the administration of vitamin C to tuberculous guinea-pigs increased the tolerance to repeated large doses of tuberculin. In chronic tuberculosis, fibrosis of infected areas in the lung occurred more rapidly and caseation was less well marked in guinea-pigs receiving the vitamin. In rabbits, which synthesize their own vitamin C, the administration of the vitamin, as might be expected, has no effect. This point is of interest in connexion with the work of Osborn & Gear (1940), who suggested that animals which are able to synthesize their own vitamin are naturally more resistant to the tubercle bacillus.

There is a large number of references in the literature concerning the clinical use of vitamin C in tuberculosis, but there is not time to consider them here. Since vitamin C is concerned with collagen production and the work of Abbasy, Harris & Ellman (1937) showed that excretion of vitamin C is reduced in tuberculosis, it seems that the vitamin might be beneficial in the clinical treatment of tuberculosis if only because it would facilitate the production of scar tissue.

Vitamin C and inactivation of toxins

There seems to be evidence that certain toxins are inactivated in vitro by vitamin C. For example, Jungeblut (1939) and Kligler, Guggenheim & Warburg (1938) showed that tetanus toxin can be neutralized in vitro by crystalline vitamin C. Souto & Lima (1938) and Catz (1939) claimed that vitamin C also neutralizes the toxin of *Clostridium oedematiens*, and Otani (1939) claimed that if vitamin C is added to the toxin of whooping cough bacteria (*Haemophilus pertussis*), its effect, when it is injected intra-cutaneously into rabbits or guinea-pigs, is much diminished. Toxicity is less as the quantity of the vitamin increases.

There is also evidence that vitamin C prevents the growth of some bacteria. Büsing (1939 *a*, *b*) found that it had this effect on cultures of pneumococci, streptococci and staphylococci. Otani (1939) found that a concentration of vitamin C of 2·5 mg./ml. in the media on which the bacillus of whooping cough was grown had a marked retarding action on its growth and that even concentrations of 1·2–1·8 mg./ml. greatly reduced the virulence of the bacilli.

One should note, however, that in normal human beings the blood plasma level of vitamin C is only 0·6–2·5 mg./100 ml. and that the concentration used by Otani in the medium in which he grew his bacteria was a hundred times as great. In such concentrations the reducing action of vitamin C might well be enough to exert a retarding effect on bacterial growth and to inactivate toxins; the amount used thus appears to be above physiological levels.

Since vitamin C appears to have these antitoxic and antibacterial effects, one would expect that blood having a high concentration of vitamin C would be relatively more bactericidal or at least bacteristatic than blood having a low concentration of vitamin C. However, Pfannenstiel & Dotzer (1940) found that the bactericidal titre of blood was independent of its vitamin C level. Further, Dotzer & Schuller (1942) and Spink, Agnew, Michelson & Dahl (1942) found that if vitamin C was given intravenously to human subjects with low vitamin C levels, it did not result in an increase in the bactericidal action of the blood against staphylococci, *Bacterium coli* and *Salmonella typhosum*. They then oxidized the vitamin C of human blood with copper and found no decrease of the bactericidal action against the same organisms or against *Shigella paradysenteriae* or *S. flexneri*.

A number of papers deal with the effect of vitamin C on *Corynebacterium diphtheriae* and diphtheria toxin. This toxin particularly affects the adrenal glands, causing loss of vitamin C (Bourne, 1935) and destruction of adrenal tissue. Jungeblut & Zwemer (1934–5) found that cortico-adrenal extracts had an inhibiting effect on diphtheria toxin. These observations are of interest in view of the idea that vitamin C may act as a side chain to corticosterones, making them water soluble, and suggest that the hormones of the adrenal and vitamin C may play an important part in the anti-infective processes of the body. It is known, for example, that one of the cortical hormones maintains the water and salt equilibrium of the body, which depends on the integrity and permeability of cell membranes. Some toxins affect the permeability of these membranes; hence there may be an antagonism between a toxin and the hormone.

The effective mobilization of the hormone presumably depends upon adequate vitamin C reserves, apart from the possible direct effect of the vitamin. In addition to this relation between vitamin C and diphtheria there is the more direct work of Jungeblut (1941), who found that diphtheria toxin is inactivated in vitro by vitamin C, particularly in the presence of cupric ions. Willison (1943) confirmed this and found that two minimum lethal doses of the toxin were inactivated by 1 mg. of vitamin C at body temperature.

Greenwald & Harde (1934–5) and others found that increased vitamin C intake reduced the severity of a diphtheria infection.

Against these positive results must be set the negative experiments of Zilva (1937), who found that when guinea-pigs were injected with vitamin C they had no more resistance to diphtheria toxin than guinea-pigs which were depleted of vitamin C, and of Torrance (1938), who found that diphtheria toxin was not inactivated by vitamin C and that there was no loss of vitamin C from the adrenals of test animals injected with diphtheria toxin. On the other hand, Willison (1943) claims that failure to demonstrate the inhibitory effect of the vitamin on diphtheria toxin could be due to the use of the wrong pH, to too short an incubation of the vitamin and toxin, or to an unfavourable ratio of the two. There appears, therefore, to be a sufficient number of variables to account for the disparity of some of the results.

Vitamin C and inactivation of viruses

Vitamin C is also said to inactivate some viruses. Klein (1945) has claimed this for influenza virus and Jungeblut (1939) for poliomyelitis virus. In experiments in vivo they found that in rhesus monkeys vitamin C had a protective effect if the animals were treated with minimum infective doses of the virus. Post-mortem investigation showed fewer pathological changes in animals that had received vitamin C than in those without the vitamin. Sabin (1939), however, was not able to confirm this work. Lyman, Schultze & King (1937) state that when vitamin C oxidizes in air, hydrogen peroxide is formed and that it is the peroxide that inactivates viruses when the vitamin is applied directly to them. This may also explain the effect of the vitamin on bacterial toxins.

Vitamin C deficiency affects phagocytosis of bacteria by leucocytes (Cottingham & Mills, 1943) and delays leucocytic migration (Bourne, 1948). Leucocytes are known to absorb large amounts of vitamin C particularly when they migrate into an injured (Bourne, 1944) or infected (Tonutti & Matzner, 1938) area. A scorbutic diet also causes a fall in white blood-cells (Crandon *et al.* 1940) and subsequent administration of vitamin C causes leucocytosis.

Vitamin C requirements

In this paper I have not attempted to discuss clinical experiments to test the value of vitamin C in infections. In acute infections, metabolism is increased and presumably the demand for all vitamins is increased, possibly much above normal. There seems to be a good case there for increasing total vitamin intake. Whether the vitamin C level

in the tissues and blood of the normal person affects his susceptibility to infection or the virulence of an attack, has yet, I think, to be satisfactorily answered. Man's nearest zoological relations are the great apes. The gorilla weighs more than man and its average energy requirement is probably something like 4000 or 5000 Cal. daily. The chief food of these creatures in the wild is grass or leaves, which have a low energy value. In fact, to obtain 4000 Cal. it would be necessary for a gorilla to eat at least 20 lb. of greenstuff a day. Twenty pounds of such green feed would provide about 4·5 g. of vitamin C daily. Before the development of agriculture and the large-scale growing of cereals which made the development of civilization possible, it is likely that man existed largely on greenstuff supplemented with what meat on the hoof he could catch. It may be possible, therefore, that when we are arguing whether 7 or 30 mg. of vitamin C a day is an adequate intake we may be very wide of the mark. Perhaps we should be arguing whether 1 or 2 g. a day is the correct amount. Perhaps it is normal for our blood and tissues always to be saturated with the vitamin and for large quantities to be flushing constantly through our urinary system and excreted in our sweat. We may find that continuous doses of vitamin C at this level over a considerable period of time may have a pronounced and unequivocal anti-infective action.

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Diet and Disease of the Liver

By L. E. GLYNN

Canadian Red Cross Memorial Hospital, Taplow, Maidenhead, Berks

The nutritional approach to the study of disease has proved extremely fruitful, especially in the case of diseases of the liver. By the use of experimental diets, not only is a series of specific nutritional deficiency diseases produced, but valuable clues are obtained to the mechanism which underlies the development of many well recognized diseases whose aetiology has hitherto been quite obscure and not obviously nutritional. I refer in particular to liver cirrhosis and acute yellow atrophy. By carefully chosen diets one can deprive the experimental animal of remarkably specific food factors, and the results of such deprivation may be equally remarkable and specific. An insight is thus obtained into the normal function and structure, and an equally important insight into derangements of function and structure which constitute disease. Thus we are not only led to the elucidation of nutritional deficiency diseases as such, but to the elucidation of many diseases not hitherto so considered. For deficiency of some essential metabolite may well arise apart from its absolute deficiency in the diet. Deficiency is a relative state and may equally well arise from increased demand, from increased excretion or from some interfering metabolites, as from diminished intake, and it is gradually becoming apparent that many so-called idiopathic diseases, i.e. diseases of obscure aetiology, are the result of such a conditioned nutritional deficiency.

Nutritional factors necessary for maintaining the normal state of the liver

It has been recognized for many years that the appearance of the liver depends on the nutritional state of the individual. Starvation causes a rapid reduction in the weight of the liver, depletion of its glycogen, the loss of a considerable amount of its protein (Kosterlitz & Campbell, 1945) and some accumulation of fat. The increased susceptibility of the liver in this state to injury by chloroform has also been known for many years (Opie & Alford, 1915).