combined course over that represented by "C.D." for the induction of ovulation would appear to be demonstrated by the fact that ovulation was shown to have occurred after the "C.D." course in only two out of the nine cases in which it was used, whereas the "D.S.-I.E." course succeeded in one case where previously the "C.D." course had failed. Final conviction would seem to be provided by the occurrence of six pregnancies within 0 to 9 months of the completion of treatment, failure of ovulation having been the case prior to treatment in all of these patients.

A sobering note must, however, be struck by the conspicuous failure to produce ovulation in cases of long-standing secondary amenorrhoea as well as most cases of marked oligomenorrhoea.

It is tempting to speculate upon the mechanism whereby treatment with oestrogens and progestogen can lead to ovulation, but in the present lack of factual knowledge it would be unwise to proceed too far. That a direct action on the ovary could be implicated seems scarcely possible, so that one must invoke the anterior pituitary lobe as an intermediary, causing ovulation by the secretion of gonadotrophin. Unfortunately, although oestrogens can undoubtedly inhibit the pituitary, it is much less certain that they can have a stimulant action, and such an action is indeed strenuously denied by some. Be this as it may, it seems that the regular administration of oestrogens and progestogen, in the proper dosage, can so condition the pituitary gland as to secure its production of gonadotrophin in the manner necessary to cause ovulation.

Summary

A regime involving the oral administration of oestrogen and ethisterone for the treatment of menstrual irregularities has been described. Encouraging results have been obtained in cases of irregular prolonged and excessive uterine bleeding, using stilboestrol for the immediate control of bleeding and proceeding to treatment designed to regulate the cycles and re-establish ovulation. Moderate success was achieved in cases of oligomenorrhoea and regular anovular cycles; the treatment has had little value in cases of regular menorrhagia (for which the antimenorrhagic factor ("glanules," Armour) proved useful) and of long-standing secondary amenorrhoea.

The treatment appeared to be responsible for the re-establishment of ovulation in at least 15 out of 30 patients (not including cases of secondary amenorrhoea and menopausal menorrhagia) in whom failure of ovulation had been presumed or proved. Pregnancy occurred in six patients.

Intolerance to stilboestrol was encountered in only seven out of 46 patients to whom it was given.

[Restriction of space precludes publication of the details of all the cases in this study. However, for those interested, Tables II-V, listing these details in summary form, will be provided on application to the author.]

I wish to express gratitude to my colleagues in the Obstetric Hospital, University College Hospital, for their kind co-operation in this study, and to Messrs. Armour and Co., Ltd., for supplying some of the antimenorrhagic factor "glanules" used.

REFERENCE

Hamblen, E. C. (1945). *Endocrinology of Woman*. Thomas, Springfield, Ill.

The National Smoke Abatement Society has published as a booklet the proceedings of its conference held at Harrogate last autumn. The booklet includes the presidential address by Lord Simon of Wythenshawe on "A Survey of Domestic Smoke Abatement," and an address by Mr. Arthur Blenkinsop, M.P., Parliamentary Secretary to the Ministry of Health. It is obtainable for 4s. 6d. from the society at Chandos House, Buckingham Gate, London, S.W.1.

DEFICIENCY PATTERNS IN METALLIC POISONING

BY

WILLIAM HUGHES, M.D., M.R.C.P.

Resident Physician, Belmont Road Hospital, Liverpool

The account of the investigation which led finally to the discovery of 2:3-dimercaptopropanol (dimercaprol; British anti-lewisite—"BAL") (Carleton, Peters, *et al.*, 1946) makes one of the most fascinating chapters in the history of medical research. Peters (1936) gives as his starting-point the observation that the convulsions in thiamin deficiency could be traced to a biochemical lesion in which the pyruvate-oxidase system broke down through lack of thiamin. The enzyme was shown to consist of thiamin pyrophosphate linked with a sulphur-containing protein. The protein moiety of the system could be poisoned by iodoacetic acid, and thus the biochemical lesion could occur even in the presence of adequate thiamin. Iodoacetic acid is a mild vesicant—vesication is the outstanding effect produced on epithelial surfaces by lewisite. It was demonstrated that lewisite poisoned the pyruvate-oxidase system, and that its action was due to its avidity for the SH groups of proteins in the enzyme. The next step was to find a sulphur-containing compound which would compete with the protein for the available arsenic, and the dithiol, 2:3-dimercaptopropanol, was found to do this most effectively. Subsequent investigations have shown that dimercaprol is effective in other forms of metallic poisoning, including mercury (Longcope *et al.*, 1946) and gold (Burnett, 1947; Cohen *et al.*, 1947; Davison, 1947; Slot and McDonald, 1947).

While Peters's hypothesis hangs on the biochemical lesion of the pyruvate-oxidase system, it must not be forgotten that many other enzyme systems occur in which the coenzymes contain members of the B₂ complex, and that the specific proteins to which these are attached may also contain SH groups susceptible to poisoning by heavy metals. There is also the possibility that vitamins and factors outside the range of the B complex may form similar linkages with SH-containing proteins. Wherever such systems occur there is the possibility of interference with the protein by a heavy metal. We should expect to find, therefore, as a result of the "biochemical lesions" of metallic poisoning, many anatomical lesions, patterns of lesions, and syndromes which we are accustomed to associate with specific vitamin deficiencies. That these do occur is quite apparent from the accounts of cases in the literature of the subject. There are good examples in the comprehensive review by Carleton, Peters, *et al.* (1946), and in the paper by Longcope *et al.* (1946). In the following case the pattern of lesions was that which might have been expected in vitamin-K deficiency.

Case 1

A man aged 61 was admitted on September 18, 1948, for rheumatoid arthritis. The history went back 20 years, when the condition started in the small joints of the hands.

On admission there was severe involvement of all the peripheral joints of the limbs and also some involvement of the spine, leading to pronounced kyphosis. Psychologically he was difficult to treat and did not co-operate in the physical therapy prescribed. He was therefore put on a course of sodium aurothiomalate ("myocrisin"), starting with a dose of 10 mg. weekly, subsequently increased to 50 mg. weekly. By January 19, 1949, he had received a total of 0.68 g., and on

that day he had a severe epistaxis. The drug was discontinued. A blood count revealed: red cells, 4,500,000; haemoglobin, 10.5 g.%; white cells, 10,000 (polymorphs 74%, lymphocytes 19%, monocytes 6%, and eosinophils 1%). Platelets were much reduced in the films. Bleeding time was 12½ minutes, clotting time 5 minutes 40 seconds.

On January 20 he had further epistaxis and bleeding from the rectum. A petechial rash developed over the extensor surfaces of the limbs and on the face, neck, and half-way down the sternum. There were a few petechiae on the inside of the cheeks and on the side of the tongue. A tourniquet test brought up uncountable petechiae on the forearm. Haemoglobin had fallen to 6 g.%. Dimercaprol, 2 ml. of 10% solution twice daily, was injected for seven days beginning on January 20—a total of 28 ml. He was transfused with one pint (570 ml.) of whole blood on the 20th. Next day his general condition had already improved, and by the 24th the petechiae had obviously begun to fade. The rash cleared up in a week. His rheumatism, which had improved during the administration of aurothiomalate, showed further improvement with the onset of toxic symptoms. He was advised to take up physical therapy, and has continued to improve up to the time of writing.

Although rather spoilt by the blood transfusion the case still retains most of its academic value in that it demonstrates a picture of vitamin-K deficiency in a patient treated with gold. It was unfortunate that a blood transfusion had to be given, but we cannot always decide to give or withhold a line of treatment on purely academic considerations. Fortunately there are reports of similar cases in the literature in which the results were not obscured by blood transfusion. Cohen *et al.* (1947) report success in a case given vitamin K and dimercaprol, and Lockie, Norcross, and George (1947) report failure with vitamin K and success with dimercaprol. It is possible, therefore, that in such cases there is interference with the protein of a compound enzyme in which vitamin K is the prosthetic group.

The distribution of lesions in the next case corresponded exactly with what I have seen and described in many cases of riboflavin deficiency in the Tropics (Hughes, 1946). When riboflavin and B₂-complex therapy had failed to clear up the lesions, an exhaustive inquiry into the history revealed two courses of gold therapy—the last one completed 14 years previously.

Case 2

A woman aged 52 was admitted to Belmont Road Hospital on May 15, 1947, for advanced rheumatoid arthritis. The first lesion, arthritis of the left ankle, occurred 29 years previously. About 19 years ago she was admitted to a hospital—since bombed out and the records destroyed—and given “gold injections.” After a course of injections she developed a generalized “pimply rash.” Her arthritis was improved, and when the rash cleared up she was discharged. She was admitted to a second hospital in Liverpool on December 2, 1935, with advanced arthritis involving the peripheral small joints and both hip-joints. Her records from this hospital reveal sore, depapillated tongue and achlorhydria, but there is no mention of a rash. She was manipulated and given 9 0.2-g. doses of aurothiomalate during her stay. She was discharged in March, 1936.

About six months before admission to Belmont Road Hospital she first noticed elements of the rash described below. She was bedfast but well nourished, and when I first saw her in the hospital on October 15, 1947, the following epithelial lesions were noted. Tongue: smooth, normal colour, absence of papillae, no fissures. Angles of mouth fissured. “Seborrhoeic” dermatitis moist and weeping, with fissures in deep flexures, but otherwise dry and scaling on a cyanotic background at the following sites: hair margins and to a lesser extent in scalp; in internal and external canthi (with blepharitis) and behind pinnae; in naso-labial grooves; patch on neck with fissures; moist with fissures in axillae, under breasts, in umbilicus, and on extensive area involving perineum extending

above pubis in front and the groins and a large area of buttocks behind; on dorsal surfaces of fingers and toes involving roots of nails; and on dorsa of hands and interdigital clefts, extending on to palms (see Figs. 1 and 2).

FIG. 1.—Case 2. Appearance of rash in inframammary region after prolonged treatment with vitamin supplements but before treatment with dimercaprol.

FIG. 2.—Appearance of buttocks and thighs after prolonged treatment with vitamin supplements but before treatment with dimercaprol.

The patient was edentulous and disliked vegetables, but she consumed ½ pint (280 ml.) of milk daily and an occasional egg in addition to hospital rations.

Positive laboratory findings of note included occasional pus cells in the urine; stools negative for dysentery organisms during occasional bouts of diarrhoea; blood count on October 27—red cells, 3,800,000; haemoglobin, 9.8 g.%; leucocytes, 7,000, with normal distribution; W.R. negative on two occasions. Cultures from the skin lesions before treatment yielded *Proteus* organisms and coagulase-positive staphylococci.

Riboflavin deficiency was diagnosed and the patient was given large amounts of the vitamin orally and by injection for the next 14 months. Thus, in one period of intensive treatment she received in all 20 mg. of riboflavin by injection and 30 mg. by mouth daily and 2 ml. of “plexan” (crude liver extract) twice weekly. Later, in addition, penicillin was prescribed locally and by injection, and sulphonamides locally and orally. At first the lesions improved somewhat generally, and those on the neck, scalp, and umbilicus disappeared. The improvement coincided with the intensive penicillin and sulphonamide treatment, and progress seemed entirely uninfluenced thereafter by the vitamin supplements, which were continued until February, 1949. At this time the following

was the condition: sore tongue, papillae still absent; both angles of mouth excoriated; slight scaling in naso-labial grooves; large red weeping areas under both breasts; original lesions about pudenda still unchanged in area, weeping in centre, thick scales on a cyanotic background at periphery; slight desquamation still on dorsa of hands and feet.

The diagnosis was reviewed, and her history revealed the two courses of gold therapy mentioned above. Excretion of gold* in the urine in the 24 hours from 9 a.m. on February 2, 1949, amounted to 0.005 part per million—1,000 ml. excreted. After 6 ml. of dimercaprol 10% solution on February 7 and on February 9 excretion of gold in 24-hour specimen from 9 a.m. on the 9th was 0.11 part per million—720 ml. excreted. In the next month she received 26 injections of 2 ml. of 10% dimercaprol. Her lesions had almost disappeared by May 3, when a further three injections of 2 ml. were given (see Figs. 3 and 4).

FIG. 3.—Inframammary region after treatment with dimercaprol.

FIG. 4.—Buttocks and thighs after treatment with dimercaprol.

On May 23 she was got up in a chair and sat out in the sun for two days. Her face and hands became sunburned. She complained of photophobia and lacrimation. The tongue became raw and sore, fissures developed at the angles of the mouth, and within a week her skin lesions all relapsed to the state in which they were on October 15, 1947. Gold excretion in 24 hours on May 30–31 was *nil*—1,180 ml. excreted. She was given 6 ml. of 10% dimercaprol in the 24 hours on May 31–June 1 and her gold excretion was 0.008 part per million—1,530 ml. excreted. After 20 mg. of riboflavin daily by injection for a week the lesions improved rapidly, the tongue becoming normal in three days and the angular stomatitis clearing in four days. The weeping lesions under the breasts and pudenda were septic and took longer to heal, but the former had cleared up by June 28 and the latter by July 15. There has been no obvious change in the arthritic condition since admission.

The interpretation of this case is difficult. The original pattern of disease as seen on October 15, 1947, was similar

*The gold was co-precipitated with tellurium from the urine and estimated by titration with standard hydroquinone solution using *o*-dianisidine as indicator. The procedure followed was that of Jamieson and Watson's (1938) modification of Pollard's (1937) method.

to that which I have seen in many cases of "pellagroid" or pellagra sine pellagra in Malayan and Nigerian prisons and asylums. The pattern of ariboflavinosis can be identified in the tongue, lip, and genital lesions and in flexural "seborrhoea." The scaling on the dorsa of the hands and feet and the occasional bouts of diarrhoea combined with glossitis and buccal ulcers might suggest niacin deficiency. In addition, there was the complication of sepsis. That the condition was not due to a simple deficiency of either or both of these vitamins is suggested by the incomplete response to large doses of riboflavin and crude liver extract. It is considered that in February, 1949, the body reserves of B₂ complex were adequate, and that the residual pattern of deficiency was due to a "biochemical lesion" affecting chiefly the protein of the flavoprotein group of compound enzymes. This hypothesis is borne out by the fact that the gold excretion was accelerated and the lesions cleared up completely after a course of dimercaprol.

Relapse after exposure to sunlight ("photosensitivity") is a phenomenon which is often observed in pellagrins, and it may occur after the disease is apparently cured. It suggests that sunlight creates a demand for more compound enzyme than the body can supply quickly after the prolonged operation of a "biochemical lesion" due to hypovitaminosis. There are not enough data to decide whether the lingering "photosensitivity" in this patient is due to the prolonged action of gold or to hypovitaminosis. We can only note that the case behaves exactly as a pellagrin would in similar circumstances.

The most arresting feature of the "photosensitivity" was the fact that the relapse was complete. It began as sunburn on the face and dorsa of the hands, and the whole original pattern quickly evolved and lesions developed on the tongue, on the original site on the neck, in the axillae, under the breasts, in the umbilicus, and on the pudenda—all of which areas were not exposed to sunlight. We do not know what the factor is which integrates the pattern of lesions in deficiency disease, but it is very unlikely, as some authors suggest, that the lesions are due to casual traumata.

Arsenical Poisoning

Exfoliative dermatitis is common to both gold and arsenical—particularly arsphenamine—poisoning. Something approaching generalized exfoliative dermatitis is seen in severe infantile pellagra.

The treatment of syphilis with arsphenamine continues to provide many examples of exfoliative dermatitis. In the Tropics I saw numbers of these cases, but in this country, where the treatment of syphilis is confined to a few centres, such cases are seen only by practising dermatologists. Recently, through the courtesy of a colleague, I had an opportunity of seeing four cases of arsphenamine dermatitis. Only one need be described.

Case 3.—A woman aged 32 had gonorrhoea and secondary syphilis. From January 14 to February 3, 1949, she had 0.3 g. of neoarsphenamine and 0.1 g. of bismuth seven times. A rash appeared first on the extensor surfaces of both arms above and below the elbows on February 7. From February 7 to 21 she had 6 ml. of "calciostab" 13 times. The rash had extended to the body generally. Dimercaprol, 2 ml. of 10% solution, was injected daily from February 21 to 28.

On February 22 there was general erythema with puffiness of the face; desquamation was most severe in flexures—axillae, groins, popliteal spaces—but was also present about the elbows and on the dorsa of the hands and feet. The lips were red, and the angles of the mouth and canthi were slightly excoriated; the tongue was red and sore, with "strawberry" appearance at the tip; there were no haematological changes. Progress

under dimercaprol was rapid and uneventful, and the rash had cleared up by March 7.

These cases, from my personal experience and judged from the literature, run to a pattern, but the pattern as a whole does not conform to any one clinical syndrome of deficiency. The interpretation of the epithelial lesions in terms of deficiency patterns is difficult. Thus we might pick out the lesions on the face, neck, and dorsa of the hands and feet to represent a niacin-deficiency pattern and fit in the remaining flexural seborrhoea, glossitis, and cheilosis with ariboflavinosis. This would still leave a very characteristic lesion of the palms and soles to be accounted for. In any case, another observer with a different bias could insist that the exfoliative dermatitis as a whole mostly resembled the pattern of biotin deficiency. In such circumstances there is no room for strong views. It is going far enough to suggest that the exfoliation and glossitis could express the sum of several overlapping deficiency patterns.

Acute encephalopathy is a complication of intensive arsphenamine medication. Lydon (1944) and Sexton and Gowdey (1947) have described cases, and have drawn attention to the close connexion between such cases and cases of Wernicke's encephalopathy. The association of the latter with deficiencies of the B complex, particularly of thiamin, is fairly well recognized. Sexton and Gowdey have tabulated the points of resemblance between arsenical encephalopathy and thiamin deficiency and bring out coincidences in all the characteristic clinical and pathological findings in both diseases. Furthermore, they found raised blood pyruvate content in their patient undergoing intensive drip therapy with oxophenarsine. This, they note, points very definitely to a breakdown of decarboxylation, which, of course, could be due either to an attack on the specific protein of carboxylase or to lack of thiamin.

The chronic arsenical poisoning which follows the prolonged administration of small quantities of arsenic by mouth presents a different picture. This picture bears so close a resemblance to chronic or dry beriberi as to be almost indistinguishable in many cases. It would seem, therefore, that all the recognized forms of arsenical poisoning are characterized by patterns of deficiency.

Mercurial Poisoning

It has often been suggested that infantile acrodynia (pink disease) is a vitamin-deficiency disease closely allied to the tropical infantile pellagra (kwashiorkor). It cannot be said, however, that treatment with vitamin supplements has yielded spectacular results. In any case, the epidemiology of pink disease hardly suggests malnutrition, the condition being much more common among the well-fed children of the temperate zones than among undernourished children in the Tropics. In the circumstances the report of Warkany and Hubbard (1948) that children with pink disease excrete comparatively large amounts of mercury is of special interest. Bivings and Lewis (1948) have reported that dimercaprol accelerated recovery in a case of acrodynia. In this hospital our standard treatment for congestive cardiac failure includes a low sodium intake and frequent mercurial injections. In a paper describing our results we have already mentioned two cases which developed a rash (Reid and Hughes, 1949). In one case only a transient erythema occurred, which subsided in a few days, but the other merits a more detailed description.

Case 4.—A man aged 75 was admitted on May 31, 1948, with residual right hemiplegia and congestive cardiac failure. His blood pressure was 220/135 and he had gross oedema. The oedema responded well in the beginning to mersalyl B.P. 2 ml. on alternate days for seven injections. On June 13 a morbilli-

form rash was noted chiefly on the face, arms, and legs. Mercury was discontinued. He had conjunctivitis, and small buccal ulcers were noted chiefly on the gums. The rash became more generalized, and the patient looked very ill and felt very wretched. He received two 2-ml. doses of 10% dimercaprol on June 29 and 30 and July 9. By the last date the rash had begun to fade, but the morbilliform appearance was still evident up to July 12, and his conjunctivitis had not healed on that date. After this desquamation occurred in fine powdery scales and his conjunctivitis began to clear up. He developed bronchopneumonia and died on July 26. A post-mortem examination revealed some enlargement of the left ventricle, bronchopneumonia, and granular kidneys. Histologically, no trace of any acute degenerative changes in the kidneys was found.

Before comparing the symptoms in this case with those of pink disease it is as well to point out that deficiency diseases vary in their manifestations according to the age of the patient. The most striking example of such a difference is seen in the laryngeal palsy which is characteristic of infantile beriberi but is not encountered in adult beriberi. The difference between adult and infantile scurvy and between rickets and osteomalacia is too well known to need comment. Those who look for elements of deficiency in the case quoted will note the symmetrical distribution of the rash and desquamation—two important characteristics of a pellagraderm and also of pink disease. The conjunctivitis is also a link with pink disease, and so is the irritability. On this evidence, however, it is premature to state that mercurial poisoning causes a deficiency syndrome, and we must await further reports from observers in pink disease and mercurial poisoning.

Thallium Therapy

Through the courtesy of a colleague I have recently been able to observe 12 cases of ringworm in children undergoing thallium treatment. It so happened that two of the children developed thallium intoxication—fortunately a rare occurrence—and were transferred to another hospital, where they died. Two things impressed me about these cases. First, other observers as well as myself (Hughes, 1946) have recorded the fact that the hair in kwashiorkor can be drawn out painlessly in large bunches. If the child survives for a while the scalp becomes completely bald. Secondly, I have emphasized the fact that lethargy going on to coma is a characteristic symptom of kwashiorkor. Epilation and lethargy are the outstanding symptoms of thallium intoxication. Apart from the epilation, I did not notice any epithelial pattern of deficiency in any of these children treated with thallium.

A mild degree of epilation is seen in rickets and in wasting diseases, especially those associated with diarrhoea, such as typhoid fever. In such diseases epilation is only one minor lesion in a complicated pattern. The inference is that epilation is the result of one "biochemical lesion"—possibly the only one that occurs in thallium therapy, but one of many which occur in kwashiorkor. In thallium poisoning presumably the protein of the compound enzyme is affected, while in kwashiorkor the prosthetic group of the compound enzyme—probably a vitamin of the B₂ complex—is deficient.

Discussion

In certain instances of metallic poisoning, and particularly in the case of gold and arsenic, quite definite epithelial patterns of deficiency can be recognized. There are cases, however, in which the pattern is indistinct or does not emerge clearly from the background of the general exanthem. There is a temptation in such cases to read

more into the exanthem than is legitimate. All the same, the fact that deficiency patterns can be recognized in some instances carries greater weight than the fact that they cannot be distinguished in others. The pattern may be there, but it can be obscured by the presence of other patterns and the incidental lesions of sepsis.

Occasionally we get an exact correspondence between the deficiency syndrome and the metallic-poisoning syndrome. A good example of this is the correspondence between the purpura of gold poisoning and that of vitamin-K deficiency. What happens more often, however, is that we can identify a single lesion such as alopecia or a set of lesions such as flexural seborrhoea in cases of nutritional deficiency on the one hand and metallic poisoning on the other.

Cohen *et al.* (1947) have noted the following toxic reactions as common in their experience of gold poisoning: pruritus, seborrhoeic dermatitis, stomatitis, thrombopenic purpura, gastro-enteritis, and conjunctivitis. They quote other observers who give, in addition, peripheral neuritis, dizziness, nausea and vomiting, nephritis, and acute yellow atrophy.

In the complete list there is not one of these reactions which has not been recognized in the various patterns of deficiency disease. One or two may need elaboration. Jaundice, for example, is rare in deficiency disease, but there is increasing support for the view that the jaundice of gold and arsenical "toxic" reactions is really infective in origin. Advanced fatty infiltration of the liver is a common post-mortem finding in pellagra. Nephritis has not been definitely ascribed to any deficiency, but oedema is a common finding, especially in vitamin-B-complex deficiencies. Gastro-enteritis might be ascribed to the irritant effect of the metal or it might also be a label for the diarrhoea, which would correspond to that which occurs in niacin deficiency.

In the accompanying table I have listed some of the commoner anatomical lesions of deficiency and tried to correlate each with its appropriate biochemical lesion,

Anatomical Lesion of Metallic Poisoning	Biochemical Lesion		Clinical Syndrome
	Enzyme Poison	Vitamin or Factor Deficiency	
Flexural seborrhoea	Arsphenamine, arsenic, gold	Riboflavin	Pellagra, kwashiorkor, pellagra sine pellagra, pink disease, exfoliative dermatitis
Glossitis, stomatitis	Gold, arsphenamine, iron, mercury	Riboflavin, niacin, iron, vitamin B ₁₂	The pellagras, sprue, pernicious and aplastic anaemias; gold, arsenic, and mercury poisoning
Encephalopathy (haemorrhagic encephalitis)	Arsphenamine, lead, thallium	Thiamin	Wernicke's encephalopathy, wet beriberi, lead encephalopathy, thallium poisoning
"Peripheral neuritis" (mixed lesion)	Arsenic	Thiamin	Dry beriberi, chronic arsenical poisoning
"Peripheral neuritis" (motor lesion)	Lead	Unknown	Lead poisoning
Hypoproteinaemia	Gold	Vitamin K	Neonatal jaundice, purpura of jaundice, purpura of gold poisoning
Alopecia	Thallium	? unidentified member of B ₂ complex	Thallium therapy of ringworm, kwashiorkor, rickets

whether due to protein poisoning or to factor deficiency. In the last column is given the deficiency and metallic-poisoning syndromes in which the anatomical lesion can be identified. Unintentionally, the table illustrates the confusion caused by the overlapping of various patterns of lesions. It would seem that, with the outstanding exception of lead palsy, all the commoner expressions of metallic poisoning have some counterpart in deficiency diseases.

Theoretically, a "biochemical lesion" can be traced to four possible causes: (1) a nutritional vitamin deficiency; (2) an anti-vitamin effect; (3) a specific anti-protein effect; and (4) a specific protein deficiency conditioned, perhaps, by lack of an essential amino-acid or a breakdown of protein synthesis. Although there is apparently no clear-cut instance of the fourth cause it seems reasonable to claim that in the case of vitamin K the other three possible causes have been realized—a deficiency as in certain cases of neonatal haemorrhage, an anti-vitamin effect as in salicylate therapy and dicoumarol poisoning, and an anti-protein effect as in gold poisoning.

Right from the earliest days in the study of pellagra clinicians have isolated cases with the characteristic epithelial lesions but without the cachexia which goes to make up the complete syndrome of true pellagra. Such cases were given the paradoxical label "pellagra sine pellagra." Sebrell and Butler's (1938) later identification of the syndrome of ariboflavinosis accounted for the vast majority of these cases. Peters's hypothesis should go a long way to account for the rest. It does at least demonstrate the circumstances in which a pattern of deficiency can be manifest in well-nourished patients.

A practical question which arises is whether the "biochemical lesion" is the only toxic effect which we are to expect from current therapeutic preparations of a metal such as gold. Cohen *et al.* (1947), after their successful experience with dimercaprol, have suggested that the use of gold in rheumatoid arthritis can be extended with impunity. It is generally conceded that in the treatment of rheumatism with gold "toxic" cases do best. I have previously suggested (Hughes, 1942) that all agents which are known to be curative in rheumatism have in common a debilitating factor, whether it is a major surgical operation, trauma such as parathyroidectomy or fracture of a long bone, mock operation such as bone forage or mock parathyroidectomy, a debilitating condition such as jaundice (hepatitis), or pregnancy, etc.

The way certainly seems open for higher dosage in chrysotherapy, and it might even seem desirable to aim at a toxic effect. Unfortunately, when the debility is terminated in such cases the rheumatic symptoms recur. The "cure" during pregnancy persists throughout lactation, for example, but it terminates with the onset of the menses (Hench, 1933). A few cases of cure coincident with gold intoxication have already been reported in which relapse followed successful treatment with dimercaprol therapy (Ragan and Boots, 1947; Cohen *et al.*, 1947). Even so, with dimercaprol to fall back upon in an emergency it might be possible to develop a technique in chrysotherapy which would depress the resistance below the level at which the chronic rheumatic lesion can develop.

Summary

Peters's hypothesis of a "biochemical lesion" in metallic poisoning would lead us to expect lesions and patterns of lesions indistinguishable from those which characterize vitamin deficiencies.

The clinical findings in cases of gold, arsenic, mercury, and thallium poisoning are analysed, revealing lesions and patterns of lesions characteristic of vitamin and factor deficiencies.

It is suggested that the hypothesis of a "biochemical lesion" might be stretched to include the possibility of lesions by heavy metals in systems other than the pyruvate-oxidase system.

In the case of "pellagra sine pellagra" and other epithelial patterns of deficiency not associated with obvious malnutrition it is worth while keeping in mind the possibility of metallic poisoning.

The uninterrupted reports of success with dimercaprol in cases of metallic poisoning may encourage the use of higher dosage of gold in the treatment of chronic rheumatism.

I am indebted to many colleagues for help with the preparation of this paper; particularly to Miss M. Roberts, assistant city analyst, Liverpool, for the gold estimations in Case 2. I am grateful to Dr. C. McGibbon, Dr. R. B. Nelson, and Dr. C. D. Alergant, of the dermatological and V.D. departments of this hospital, for allowing me to see their cases, and to Dr. C. O. Stallybrass and Professor R. A. Morton, Liverpool University, for helpful criticism.

REFERENCES

- Bivings, L., and Lewis, G. (1948). *J. Pediat.*, **32**, 63.
 Burnett, J. A. (1947). *British Medical Journal*, **2**, 670.
 Carleton, A. B., Peters, R. A., Stocken, L. A., Thompson, R. H. S., and Williams, D. I. (1946). *J. clin. Invest.*, **25**, 497.
 Cohen, A., Goldman, J., and Dubbs, A. W. (1947). *J. Amer. med. Ass.*, **133**, 749.
 Davison, R. (1947). *Stanford med. Bull.*, **5**, 37.
 Hench, P. S. (1933). *Proc. Mayo Clin.*, **8**, 430.
 Hughes, W. (1942). *Ann. rheum. Dis.*, **3**, 89.
 — (1946). *Trans. R. Soc. trop. Med. Hyg.*, **39**, 437.
 Jamieson, A. R., and Watson, R. S. (1938). *Analyst*, **63**, 702.
 Lockie, L. M., Norcross, B. M., and George, C. W. (1947). *J. Amer. med. Ass.*, **133**, 754.
 Longcope, W. T., Leutscher, J. A., jun., Wintrobe, M. M., and Jäger, V. (1946). *J. clin. Invest.*, **25**, 528.
 Lydon, F. L. (1944). *Brit. J. vener. Dis.*, **20**, 87.
 Peters, R. A. (1936). *Nature*, **138**, 327.
 Pollard, W. B. (1937). *Analyst*, **62**, 597.
 Ragan, C., and Boots, R. H. (1947). *J. Amer. med. Ass.*, **133**, 752.
 Reid, H. A., and Hughes, W. (1949). *Lancet*, **1**, 593.
 Sebrell, W. H., and Butler, R. E. (1938). *Publ. Hlth Rep., Wash.*, **53**, 2282.
 Sexton, G. B., and Gowdey, C. W. (1947). *Arch. Derm. Syph., Chicago*, **56**, 634.
 Slot, G., and McDonald, A. D. (1947). *British Medical Journal*, **2**, 773.
 Warkany, J., and Hubbard, D. M. (1948). *Lancet*, **1**, 829.

HOSPITAL AND DOMICILIARY CONTROL OF RESPIRATORY TUBERCULOSIS*

BY

HARLEY STEVENS, M.R.C.P.

Physician Superintendent, Peppard Sanatorium,
Henley-on-Thames

HOSPITAL TREATMENT

The Problem

In certain places visited significant statistical evidence was available of changes in the rates of infection, morbidity, and mortality associated with active anti-tuberculosis programmes. Graphic records of these statistics show a progressive shift of the maximum incidence of infection to the right, or to older age groups. The same is true of active disease and of deaths from tuberculosis. A population which is being infected, which is suffering definite symptoms and succumbing to the disease at a greater age than previously, and in whom this age change is progressive, affords hope for the ultimate elimination of tuberculosis from the community by methods already in use or by factors already operating.

Similar statistical evidence of progress in the United Kingdom during recent years is less reassuring. In some areas, in spite of the general downward trend which is common to many lands, there seems to be a disturbing shift to the left, or to younger age groups, in the mortality figures. Elsewhere a definite increase in the death rate

*Extracted from a report to the Nuffield Provincial Hospitals Trust, to whom I am indebted for travel facilities during the spring and summer of 1948.

per 100,000 of population has occurred, and the morbidity in some age groups is on the increase in certain localities.

These figures indicate that an intensification of the present measures for controlling the disease is needed and that elimination will require even greater efforts.

Common Measures Employed Against Tuberculosis

A Pure Milk Supply.—Among measures of public health the necessity for an uninfected milk supply is generally accepted. Myers, in Minneapolis, presenting the features of an exceptionally successful control scheme, is emphatic regarding a great fall in the incidence of tuberculin reactions within the general population which accompanied the development of tubercle-free herds in the State of Minnesota.

Apart from general public health reforms, the main features of the anti-tuberculosis campaigns are alike in Scandinavia, the U.S.A., and the Canadian provinces I was privileged to visit. They are:

1. Segregation in sanatoria or tuberculosis hospitals of all persons known to excrete tubercle bacilli in their sputum.
2. Treatment of all cases of active respiratory tuberculosis to the stage of sputum conversion and stability of the disease.
3. Restoration therapy, or "rehabilitation," designed to keep the treated patients in good health.
4. Case-finding by miniature chest x-ray surveys.
5. Protection of non-immunes in exposed groups with B.C.G. vaccine.
6. Domiciliary supervision.
7. An economic and social evolution outpacing similar reforms for the general population.

The emphasis on these measures is not uniform and the factors bringing one or other into prominence will be discussed.

1. Segregation of Infectious Cases of Tuberculosis

A sanatorium bed ratio of 2.5 per annual death from respiratory tuberculosis is widely accepted as a minimum in Canada and the U.S.A. Mark, in Minneapolis, claims (personal communication) to make full use of the 4.5 beds per annual death which the reduced incidence of the disease now makes possible. A recent claim for 10 beds per annual death has been advanced by Bogen (1949) as the appropriate measure for elimination of the disease. Scandinavian countries favour a ratio of 3 to 1. The more extreme ratios represent individual views unlikely to be the basis of national policy.

Public Health Law 725 in the U.S.A. laid down that the number of beds required to provide adequate hospital services for tuberculous patients should not exceed, for the purpose of grants-in-aid, two and half times the average annual deaths from tuberculosis in any State over the five-year period 1940-4. Canada and the other countries mentioned intend that beds shall be available, without waiting, for every case of tuberculosis requiring admission, and that indefinite segregation for infectious cases shall be provided.

In the U.S.A. there seems to be considerable evidence of an agreement in policy existing between the major interests in tuberculosis control. The National Tuberculosis Association, the Trudeau Society, and the Tuberculosis Control Division of the U.S. Public Health Service are united in a policy of hospital treatment, to which the allocation of Federal funds has given a great stimulus.

State and city authorities are naturally influenced by the prospects of grants-in-aid for sanatorium construction.