changes were met with in Case III (post-operative exacerbation of the exophthalmos).

With regard to the pathogenic part played by the thyrotropic factor in this connexion, the following facts ought to be taken into consideration; the results of the animal experiments as described above seem conclusive. (The most suitable animals for these experiments are guinea-pigs, less so rabbits and rats.) In our opinion, however, it is very doubtful whether the results of experimental work may be applied to human pathology without any reservation. According to knowledge acquired thus far, no influence whatsoever of the thyrotropic factor on volume and water content of the extra-orbital muscles has been established. Another argument against the pathogenic part played by the thyrotropic hormone is the fact that exophthalmos is very rarely encountered in myxoedema, although the production of the thyrotropic hormone in this disease is abnormally increased. This may serve as additional evidence against the unreserved application of animal experiments to human pathology. On the other hand, the posterior lobe is known to produce an antidiuretic factor, and since this is passed straight into the liquor of the third ventricle, the possibility of its contributing to the production of ophthalmic manifestations through water retention might at least be taken into consideration. Marine assumes that in addition to the anterior pituitary the gonads play an important part in the production of exophthalmos. For example, castration of male rabbits caused an existing exophthalmos to regress; the administration of testosterone propionate to the same rabbits caused the exophthalmos to recur (Marine, 1938). As to the relation of androgens and water metabolism, the fact was pointed out by Mulvany that the capon's comb inflates in response to androgens, presumably owing to rise of its water content. The relation of oestrogens to water metabolism is well known and need not be gone into here (see Zondek, *Diseases of the Endocrine Glands*, 1944, p. 53). The fact that in certain cases the exophthalmos rapidly deteriorates after removal of the thyroid, so that finally malign exophthalmos develops, may be at least partly explained by the following hypothesis: thyroidin is known to have a dehydrating effect; thus after its elimination a factor causing water retention will obtain dominance.

In brief, it may be said that the cause of so-called thyrotropic exophthalmos in man is not yet definitely known. Our cases make it appear probable that this type of exophthalmos is part of a complex disturbance originating in the pituitary-diencephalic centres. It is still open to doubt whether in the individual case one or more diencephalic centres or one or more pituitary hormones respectively ought to be considered as the primary seat of the disorder. We therefore raise the question whether these cases would not be more properly covered by the name of "pituitary-diencephalic" exophthalmos so as not to anticipate any undue conclusion. It is worthy of note that Daniels (1938) also attributed the type of exophthalmos described in this paper to diencephalic disorders.

Therapeutically, all three patients received an average of 200 to 300 mg. of di-iodo-tyrosine a day for two weeks, at three-weeks intervals. Two additionally had irradiation to the pituitary. Di-iodo-tyrosine apparently had a beneficial effect, although it cannot be stated with certainty how great a part of it has to be attributed to the irradiation. Thyroidin administration, which would appear plausible in light of the above argument, was in fact recommended for post-operative exophthalmos by Gasteiger (1931) and Mulvany (1944). In any event, it is noteworthy that in Case I medicinal treatment alone brought any considerable regress of the exophthalmos. It should also be noted that in Case III dehydration through a mercurial diuretic resulted in at least subjective improvement of the eyes. In the same case relief of the intra-orbital pressure through partial removal of the orbital roof (Naffziger), which for quite a time appeared the only possible way to safeguard the eye, was rendered unnecessary by medicinal treatment and local protective measures.

Summary

Three cases of exophthalmos are recorded which, according to the present classification, would have been designated as thyrotropic exophthalmos. The ophthalmic manifestations were of particularly severe degree in all these cases. Two of them presented marked decalcification of the skull bones and enlargement of the sella turcica; this finding points to involvement of the pituitary-diencephalic region. Both cases had diabetic glucose-tolerance curves. The abnormally high blood cholesterol level in two cases argues against hyperthyroidism. All three cases favourably responded to di-iodo-tyrosine. In one case (post-operative exacerbation of the exophthalmos) di-iodo-tyrosine, in combination with pituitary irradiation on two occasions, resulted in considerable improvement of the eyes (regress of proptosis, disappearance of chemosis and epiphora, etc.), and thus rendered surgical intervention unnecessary. In view of the fact that the part played by the thyrotropic hormone in the production of this type of exophthalmos is doubtful, while that of the pituitary-diencephalic system seems to be highly probable, the looser definition of "pituitary-diencephalic" exophthalmos is suggested.

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HEPATIC ENLARGEMENT WITH ASCITES IN CHILDREN

BY

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AND

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For many years cases of abdominal enlargement in coloured children in Jamaica, due to ascites and an enlarged liver, have attracted attention, but the aetiology of the condition remains uncertain. It closely resembles the disease among Indian children described by Sir Upendranath Brahmachari (1938), and called infantile hepatic cirrhosis. In our experience the fatal outcome is not so common, perhaps because the condition is not entirely the same or the cases seen by us are in an earlier stage. No cases of the acute type described by Sir Upendranath occurred in this series. The descriptions given by other observers known to us vary, but all are agreed that ascites and enlargement of the liver are present in every case. One member of the staff states that he observed five of these cases some years ago, and all were cured by a generous diet and improved living conditions; he followed them up for a period of over two years. Another member states that he has seen many of these cases, and that in his opinion the majority are fatal sooner or later.

Report on a Series of Cases

This paper is based on a series of 18 cases observed by us over a period of about a year; of these 15 have been followed up for six months or longer, and two patients were found to have died, apparently of this disease. There were 11 males and 7 females, but this series was too small to warrant conclusions as to the sex incidence. The illness is a chronic one, beginning between 1 and 10 years of age, usually in children who until then had been well. It lasts for months or years, and in our experience has ended in recovery in the majority of cases, though other observers have had contrary results. The history given is that the illness begins usually with fever, which may be intermittent, lasting for days or weeks, and is accompanied or followed by painless abdominal enlargement, of slight or moderate extent, which may progress slowly or rapidly, finally being greatly increased in size. Loss of appetite, nausea or vomiting, and irregularity of the bowels have been common, and in some cases paracentesis had been performed on one or more occasions, with temporary relief, but with reaccumulation of the fluid in a short time. Slight jaundice is not uncommon, and the skin is dry and scaly, sometimes shiny, but never wrinkled; there is no tendency to other skin diseases. Umbiblical hernia

occurs, probably because of the increased intra-abdominal pressure; oedema of the legs is rare. Shortness of breath frequently occurs, owing to mechanical interference by the enlarged abdomen. When first seen the tumid abdomen, wasted arms and legs, drawn facies, with bright but rather sunken eyes, the conjunctivae of which are sometimes stained a faint yellow colour, all give the child a striking appearance, which is easily remembered and readily recognized.

The disease is not familial, and probably not hereditary, as no history of its occurrence in any other member of the family or in the parents has been elicited; but the history beyond the immediate past is often undependable, and it is possible that some of the parents had suffered from the disease in infancy or childhood and had long forgotten.

The economic position of the majority of these patients is below the average, and investigation has shown that their diets not only are insufficient in quantity but are largely composed of carbohydrates and markedly deficient in meats, animal fats, and fresh fruits and vegetables. With one exception all the cases came from the poorer parts of the city of Kingston, and instances of this disease had not been noted by us in the rural parts of the island in which we worked for some years.

Clinical examination is essentially negative; only in the abdomen are positive signs discovered. The conjunctivae may be stained with bile, and the vessels may be pale owing to moderate anaemia; the teeth are usually good and the tongue remarkably clean. Enlarged and septic tonsils and adenoids, and cervical adenitis, are not more common in this group of children than in any other. Physical signs in the chest are usually normal; in a few cases a haemic murmur may be present or a few crepitations may be heard at the bases of the lungs. There are sometimes enlarged veins on the anterior abdominal wall; an umbilical hernia is not often present. The marked abdominal enlargement—due to free fluid and the enlarged liver, which were found in every case—made it impossible to decide which had preceded the other. The liver varied in size from one the edge of which was palpable only on deep inspiration to one which extended as far as or below the umbilicus. It was smooth and firm on palpation and not tender, and in several cases the left lobe appeared to be proportionately more enlarged than the right. The size of the liver varied, often rapidly, from time to time, but always remained palpable; the ascites varied in quantity with the size of the liver. In some cases the spleen was also enlarged, but as a rule only moderately. The quantity of fluid present varied, but was usually considerable, and as much as 100 oz. was removed at one tapping. The kidneys appeared to be unaffected, and there were no abnormal signs in the nervous system. The legs and arms were thin and weak, but all muscle groups seemed to share equally in the weakness and wasting.

In Table I the principal signs and symptoms are listed to show the frequency with which they were found in the present series of cases.

TABLE I

Sign or Symptom	Cases Examined	No. Found Positive
Abdominal enlargement	18	18
Hepatic enlargement	18	18
Ascites	18	18
Splenic enlargement	16	7
Jaundice	18	7
Fever	18	18
Dyspnoea	17	5
Umbilical hernia	16	2
Haematemesis	18	1

No cases of acute type were seen; all were subacute or chronic, and were observed for months without any marked deterioration in their condition becoming apparent, though periods of improvement and regression were common. The febrile attacks were usually short, lasting for a week or 10 days, and they occurred more often in the subacute type of case, in which a rise to 103° F. was seen and the child had the appearance of being seriously ill.

Chronic cases may be afebrile throughout their course, and usually after their acute onset pyrexia is not common unless an intercurrent disease supervenes. The chief feature of the illness is the painless and marked enlargement of the abdomen, which finally is so great that it brings discomfort and respiratory embarrassment, with an increased pulse rate; it may be the cause of the loss of appetite and vomiting. Paracentesis gives relief: at first it may be necessary every other day; later the child may be comfortable when tapped once or twice a week; and finally tapping becomes unnecessary. In fatal cases death is usually due to intercurrent disease, often a respiratory infection: one child died in hospital; the post-mortem findings of this case are given below.

Table II comprises a list of the special investigations made in order to throw light on the aetiology of the condition. In some cases it was not possible to carry out all investigations, because of the short time the patient was in hospital, the patient's condition or age, or unwillingness of the parents to consent.

TABLE II.—*Laboratory Investigations*

Pathological Findings	Number of Cases Examined	Number with the Finding	Number without the Finding
Moderate anaemia	18	13	5
,, leucocytosis	18	16	2
Low plasma proteins	10	9	1
Kahn negative	15	14	1
Urinalysis normal	15	15	0
Van den Bergh direct positive	13	3	10
,, indirect positive	13	8	5
Sedimentation rate increased	8	8	0
Fragility normal	12	12	0
Blood urea normal	7	7	0
Blood sugar normal	7	7	0

The findings of the single post-mortem examination were largely negative, as pathological changes were observed only in the lungs, liver, and spleen. Congestion and oedema were present in the lungs, but no areas of bronchopneumonia were found. In the liver there was a fine cirrhosis of pericellular type resembling Hanot's cirrhosis, with areas of subacute hepatitis, in which the liver cells showed cloudy swelling and degeneration. The spleen was somewhat fibrosed. In one case an exploratory laparotomy was performed, and it was found that the omentum had lost its fat and was made up of large blood vessels, chiefly veins, in a fine membrane of fibrous tissue. These vessels were adherent to the abdominal wall, and appeared to be acting as an alternative route for the return of blood from the abdominal viscera, in place of the partially occluded portal circulation.

Discussion

The condition is undoubtedly one in which the liver has been damaged. Its rapid enlargement and subsidence suggest an acute inflammatory or toxic condition—that is, a hepatitis—but the source of the toxic agent is not certain. That the disease is infective in nature is supported by the increased sedimentation rate and the fever, and by the recovery of most cases, presumably when the infection had come to an end. The occurrence of ascites only, without dropsy of the limbs, suggests obstruction of the return of blood through the liver, and the low protein content of the ascitic fluid is in favour of an obstruction and not of inflammatory changes in the peritoneal membrane itself. The enlargement of the left lobe of the liver suggests that the site of origin of the toxic agent, if one exists, is in the stomach or spleen—probably in the former, because splenic enlargement is not constant. The toxic agent is not known; it is suggested that the patient's diet, which has been deficient for a considerable time, has reduced the natural resistance of the gastric or duodenal mucous membrane, on which an infection has established itself, and from which toxins have been derived and have damaged the liver, causing its enlargement.

The evidence in favour of a dietary deficiency as the primary cause of the disease is: (1) It is known that the diets of the class from which the patients in this series are drawn are frequently inadequate and unbalanced, and mechanically irritating material is often given to infants or young children: these patients received an even more unsuitable diet than most persons of this class. (2) A balanced and generous diet, alone, produced an improvement which in some cases was marked. (3) The administration of glycocoll in one case appeared to bring marked improvement, which ceased when it was withdrawn. (4) Another member of the staff once observed that improvement in the diet and hygienic conditions brought about an apparent cure in five cases.

The syndrome may be produced by toxic damage of the liver cells, resulting in chronic hepatitis or cirrhosis, or the toxin may cause inflammation or thrombosis of the portal vein, resulting in narrowing or occlusion; the most likely position would be in the smaller radicles. The obstruction and possible damage to the portal vein may also be responsible for the low serum protein, through failure to absorb part of that ingested from a diet already protein-deficient.

Treatment

In three cases special treatment was tried: two were given a concentrated preparation of vitamin B_1 without success; one case appeared to improve remarkably during administration of glycocoll, but relapsed when the treatment was stopped. In all the others only general supportive treatment with rest and a full diet was tried, with some improvement in a few of them.

In a small number of cases seen after this series had been treated dried yeast was administered in doses of 6 or 8 dr. a day with striking results: all improved, and two cases were apparently cured in a few weeks. The explanation of this result is uncertain. It may have been due to the vitamin B complex, in which yeast is rich, or to replacement of protein, of which yeast contains over 40%.

Summary

Cases of hepatitis of unknown aetiology are described. It is possible that they are caused by a dietary deficiency, permitting easy damage of the gastric or duodenal mucous membrane, which becomes infected; the toxin absorbed from this focus damages liver cells or the portal vein, or both, resulting in phlebitis and finally cirrhosis, causing obstruction and partial failure to absorb a particular food constituent from a diet already deficient in that respect.

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DARK-ADAPTATION STUDIES IN PATIENTS WITH DISEASES OF THE SKIN

BY

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It is well known that an adequate supply of vitamin A is essential for the formation of normal epithelial structures. The basal cells are not apparently affected, and the keratinized epithelium resulting from deficiency of vitamin A is soon replaced by normal cells when the vitamin is given in sufficient quantity. Marked deficiency, whether occurring naturally or experimentally, produces characteristic changes in the skin, the earliest signs being roughness and dryness developing into phrynodermia and follicular hyperkeratosis. These changes are well known, and have been fully described (Bicknell and Prescott, 1942a; and many others). It is possible that slight or moderate deficiencies, though insufficient to produce observable changes in the skin, might render it more liable than usual to the development of dermatitis and infective and other disease conditions generally. It was considered interesting, therefore, to examine the correlation between vitamin A nutritional status and the incidence of skin diseases.

There appear to be only two methods which are likely to yield the required information: blood vitamin A estimations and dark-adaptation measurements. The former of these methods was used by Cornbleet, Popper, and Steigmann (1944), who estimated the plasma vitamin A and carotenoids in 55 dermatological cases and compared the levels with those found in controls. Vitamin A was above the lower normal limit in all, but low levels were present in one case of pityriasis rubra pilaris and two of disseminated lupus erythematosus.

The information obtainable from blood vitamin A and carotenoid estimations is at present limited by the technique employed. Such estimations as are usually carried out provide little evidence beyond the subject's ability to absorb vitamin A and carotenoids from the intestine, and a development in technique (e.g., serial estimations during a test period on a deficient diet) is clearly required if information is to be obtained regarding liver storage capacity. A refinement in technique is also required (e.g., estimations to be made in relation to time and content of a controlled diet) if the present so-called "normal" range of values is to be reduced to useful limits. Such development and refinement in technique would seem to be of importance, since clearly some reduction below a normal blood vitamin A level would be necessary before vitamin A nutrition of the tissues can suffer—unless, of course, the defect is one of tissue utilization.

A combination of blood vitamin A estimations and dark-adaptation measurements has useful possibilities, but first a correlation must be established between the two methods. At the moment Yudkin (1941a) considers estimations of blood vitamin A valueless for diagnosing mild deficiencies.

Dark-adaptation measurements have been used successfully to evaluate the vitamin A nutritional status of groups of people (e.g., Kohn, Milligan, and Wilkinson, 1943), it being usual for the diagnosis of A deficiency to rest upon a significant change in adaptation following the administration of the vitamin. Moreover, the changes in dark-adaptation are regarded by the majority of workers to be the earliest observable sign of a deficiency (see Bicknell and Prescott, 1942b). In the absence of a therapeutic test the results are clearly less reliable, since the causes of impaired dark-adaptation are many (Godding, 1945).

It was not possible to complete the therapeutic tests in the present investigation, but as there was no significant difference between the two groups in respect of age, ametropia, and social status, and as certain other known causes of poor dark-adaptation had been eliminated from both groups, it was thought highly probable that any discrepancy between the dark-adaptation measurements in the two groups would reveal mainly differences in metabolic and nutritional status, vitamin A being included as probably the main factor concerned.

The Investigation

A group of skin cases was provided by the out-patient department of St. John's Skin Hospital and a control group by friends of patients attending the near-by Royal Dental Hospital. Approximately 100 subjects were tested in each group. The skin condition required was a lesion not associated with parasitic infections—e.g., scabies; otherwise, the cases were taken as they appeared. The 103 cases tested were made up as follows: acne (var.) 7, alopecia 7, boils 1, cheiropompholyx 1, Darier's disease 1, dermatitis (var.) 44, eczema (var.) 16, Fox-Fordyce disease 1, impetigo 1, keratosis folliculosis acneformis 2, leuconychia 1, lichen (var.) 3, lupus erythematosus 1, mycosis pedis 1, pityriasis rubra pilaris 1, plantar wart 2, psoriasis 5, pust. bacteride 1, urticaria 3, varicose ulcer 1, seborrhoea 1, sycosis barbae 2. It will be observed that dermatitis accounts for nearly 50% of the cases.

From both groups the following were excluded: subjects under 16 and over 45, subjects with uncorrected refractive errors of less than 6/24 either eye, obvious muscular defects (e.g., squint), opacities of the media and ocular disease condi-

TABLE I.—*Comparison of the Test and Control Groups*

	Total	Sex		Age			Average Age	No. Wearing Glasses	No. with Uncorrected Vision less than 6/6 (R. or L.)
		M.	F.	15–25	26–35	36–45			
Skin cases	103	49	54	27	45	31	29·8	13	22
Controls	101	34	67	50	33	18	26·9	14	15

tions generally, subjects with a history of general disease conditions, particularly gastritis, gastric and duodenal ulcer, liver