of persons on high purin diets *might* serve as some index of hepatic deficiency.

From the time of William Hunter of Charing Cross Hospital up to the present, a succession of dyes have been employed as tests of hepatic function. Although rather more sensitive than the simple van den Bergh, recent work with bromsulphalein and the older phenol-tetrachlorphthalein has failed to detect any but gross amounts of damage to the liver. Increase in the quantity of dye injected leads to toxic phenomena due to the dye itself. Such cases have not been unknown in the recent cholecystographic studies. It is unnecessary to discuss the extent to which cholecystography as a fairly reliable test of the function of the gall-bladder has been unwarrantedly confused with the question of function in the liver.

This apparently adverse criticism of the valuable laboratory aids to diagnosis in liver disease is designed to emphasize the importance of clinical signs and symptoms of hepatic disease. Jaundice and the general low level of metabolism ; the flatulence, nausea, and slowness of pulse ; the urine, the stools, the itchiness of the skin, the marked depression, the " jaundiced eye "—these are as reliable as some of the laboratory tests. It is permitted to quote that " laboratory guides are mostly artificial, are reliable in only some instances, and are the handiwork of man ; clinical symptoms are the natural, infallible, unalterable expressions of definite states, and are the ways of God."

The liver occupies a unique anatomical position for registering changes due to material ingested from the alimentary canal. All the blood from the digestive tract must pass through the liver. The extensive capillary bed of the liver is interwoven with the innumerable hepatic cells so that noxious substances entering the portal venous system from the gut may undergo immediate chemical transformation into innocuous substances, or even excretion via the hepatic cell into the bile canaliculi without entering the general circulation. Quite apart from the problems of the liver circulation which have been studied in the normal by Cameron and Mayes,[3] in cirrhosis by McIndoe,[4] and in the isolated perfused liver preparation by Dale,[5] there still remains the implication of the startling statement made by Starling that the liver may hold one-quarter of the total lymph of the body. If we accept the work dealing with the distribution of antibodies in the liver, such as that of Freund and Whitney,[6] there is still no fundamental anatomical or physiological study of the part played by the liver in the formation of lymph.

This brief note on the function of the liver has been prompted by the rapid accumulation of cases of jaundice, cirrhosis, or atrophy of the liver as a result of the administration of drugs of the cinchophen group. Many cases of non-fatal toxicity due to their use are probably unrecognized and unreported. It has yet to be proved that these cinchophen compounds have any beneficial effect other than an analgesic one. The analgesic effect of external application has not been quantitatively compared with that of internal administration. The analgesic effect of drugs of the cinchophen group has not been compared with that of the salicylate group. It might be possible to elucidate the peculiar properties of the benzene ring when in combination with the hydroxyl group in substances ranging from the toxic and analgesic carbolic acid on the one hand through salicylic acid to the toxic and analgesic substances which are peculiarly injurious to the liver.

The following list of cinchophen derivatives, among others published in a recent number of the *Proceedings of the Staff Meetings of the Mayo Clinic*, is reproduced in part so as to indicate to practitioners the particular drugs involved in the production of hepatic disease: Agotan, atochinol (atoquinol), atophan, atophanyl, biloptin (di-iodo-atophan), cinchophen (many brands), hexophan, neocinchophen, novatopan, phenylcinchoninic acid, phenoquam (phenoquin), quinophan, synthaline, tolysin.

The toxicity of chloroform, phosphorus, arsenic, and certain drugs of the salvarsan group is well recognized. The toxicity of the various preparations of cinchophen should be more extensively investigated. All cases presenting any clinical or laboratory signs of hepatic insufficiency should be analysed from the point of view of ingestion of toxic drugs and patent remedies.

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INTENSIVE VITAMIN THERAPY IN MEASLES

BY

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Recent research seems to have crystallized into the belief that vitamin A is concerned with raising the resistance of the animal body as a whole, and the epithelial cells in particular, to various bacterial invasions. The comparative scarcity of human investigations on this subject may perhaps be attributed to the fact that it is not easy to point to any clearly defined group of symptoms associated with a deficiency of this factor in man in any way analogous to the syndromes of rickets and scurvy. There is, however, good evidence for the belief that concentrates rich in vitamin A are valuable as prophylactics against infections.

Vitamin A and Infections

The work of Mellanby and his colleagues[1] on the prevention of puerperal sepsis by the use of such a concentrate appears convincing within the limitations imposed by the comparison of relatively small samples. There is, however, less evidence that a favourable influence can be exerted by such means on the course of a disease already in progress. The results achieved by Mellanby and Green[2] in the treatment (as opposed to prophylaxis) of puerperal infections await further confirmation. In Canada, Wright and his colleagues[3] failed to protect a small series of babies against the " common cold " by supplying them with large amounts of vitamin A, while those contracting the disease did not appear to escape more lightly than the controls. Nevertheless, we are not entirely without indications to guide us in the search for a profitable field for vitamin therapy. In his classical experiments on the deficiency xerophthalmia of rats in 1922, Mori[4] observed atrophy of the mucus-secreting cells in the salivary glands and in the mucous membrane of the larynx and trachea. If vitamin A was withheld for a further period, a local bacterial invasion of these tissues followed. Mori observed that most of his animals eventually died from bronchopneumonia. These findings were confirmed by Cramer and Kingsbury,[5] and similar observations have been made by Steenbock,[6] Mellanby,[7] and others.

Effect on Epithelium of Lack of Vitamin A

The changes which occur in epithelial cells following deprivation of vitamin A have been studied by Wolbach and Howe,[8] and later by Goldblatt and Benischek,[9] who were able to demonstrate metaplastic degeneration in columnar, cuboidal, and transitional epithelia, leading to the appearance of a squamous keratinizing type of cell. Mellanby and Green[10] have suggested that the desquamation of such cells may provide a favourable medium for bacterial growth. In any case it is clear that serious damage to the ciliated epithelium and mucus-secreting cells lining the upper respiratory tract must render the lung alveoli easily accessible to bacterial invasion. Therefore it is in diseases in which the patient's resistance to his own epithelial saprophytes is temporarily in abeyance that we might expect on *a priori* grounds to see benefit from the intensive exhibition of the factor which normally retains the defensive cells in good repair. But there is one considerable difficulty to be encountered in any human investigations on this subject. We cannot compare the condition of a man with that of his brother who has been totally deprived of his vitamin A factor. The point to be decided is whether an adult—or, *a fortiori*, a child—with a very liberal supply of vitamin A is better off in an emergency than one who has perhaps just enough for his normal occasions.

Epithelial Damage in Measles

Now a disease which attacks epithelial defences and whose incidence is greatest in those members of the community who are most likely to be suffering from various grades of vitamin deficiency will probably prove the best medium for testing the therapeutic properties of vitamin concentrates. Measles appears to me to fulfil these criteria. In measles the brunt of the attack falls on epithelial structures. The respiratory tract rarely escapes unscathed. Indeed, the condition of the lungs, trachea, and bronchi in a severe attack bears some resemblance to that which Mori observed in his devitaminized rats. The mucous cells are injured, the ciliated epithelium is shed, and a definite metaplasia is prone to occur in the stroma of the lungs.

Taking advantage of these opportunities, the normally harmless saprophytes, frequently headed by the bacillus of Pfeiffer, invade the lymphatics of the trachea and bronchi, producing in the lungs, through the irritation of their toxins, a further degree of hyperplasia of the inter-alveolar reticulum, easily recognized as the much dreaded "acute interstitial pneumonia" of measles.[11] At the same time the general immunity of the skin is lowered—hence the boils, styes, impetigos, eczemas, and other minor tribulations—or it may be lost completely, leading to the various forms of cutaneous gangrene which are among the major horrors of the disease. The whole alimentary tract is liable to serious catarrh, especially in the Tropics. The Eustachian tube, middle ear, and mastoid cells are liable to dangerous invasion.

Observations on the Vitamin Treatment of Measles

In this country the disease afflicts most heavily the children of the poorest classes, among whom the greatest mortality is observed during the first eighteen months after weaning. Since most of them are suffering from a lack of suitable fats in the diet, it is natural to suppose that they are insufficiently furnished with vitamins A and D. In the present investigation an attempt has been made to decide whether a liberal supply of these two factors at an early stage is able to exercise a favourable influence on the course of the disease. Observations were made on 600 cases of measles in children under 5 years of age, admitted to the Grove Hospital between October, 1931, and April, 1932. These were divided into two equal groups. One received an accurately measured quantity of a rich concentrate of vitamins A and D from the first day of admission. The other received the normal diet supplied in measles. Naturally vitamins were not withheld from them, but they received no liver oils during the febrile stage, though the usual dose of cod-liver oil was supplied during convalescence. Thus the treated cases received a relatively enormous dose of vitamins A and D for a limited period, while the controls received the usual amounts administered to sick children.

Each of the treated cases received 20 minims daily of "adexolin," a cod-liver oil concentrate at present on the market, either in liquid form or in capsules containing an equivalent amount of the vitamins. According to the manufacturers' statement (Glaxo Laboratories) the daily quantity administered amounted to 300 units (Carr and Price) of vitamin A, and 2,000 international units of D—that is to say, approximately the amount contained in one ounce of high-grade cod-liver oil. This dose was continued irrespective of age for a minimum period of seven days in mild cases and for a maximum period of three weeks in those developing complications.

Statistical Data

It is essential before attempting to draw conclusions from such a relatively small sample of the total measles population to show that the two groups were strictly comparable in all respects. In order to secure a perfectly random distribution of cases between the two groups all the cases admitted to certain wards between October, 1931, and April, 1932, received the concentrate, while all cases admitted to the remaining measles wards served as controls. It was necessary to ensure absolute congruence of the two groups in point of time, since it would be clearly unsound to compare cases treated in February with controls selected in June. It was also necessary to obtain a similar age distribution in both groups, because the age of the patient is the most important single factor affecting the prognosis of measles in London.

The age distribution and corresponding death rates in the two groups are shown in the following table:

Table I

	Controls			Treated Cases		
Age	Number	Deaths	Rate per cent.	Number	Deaths	Rate per cent.
0-1	32	4	12.5	31	1	3.2
1-2	90	16	17.8	101	8	8.0
2-3	60	4	6.7	55	1	1.8
3-4	61	2	3.3	61	1	1.6
4-5	57	0	0	52	0	0
Total ...	300	26	8.7	300	11	3.7

These figures require more careful analysis before we can attribute the lower death rates observed in the vitamin-treated cases to the effect of the concentrate. The observed difference of 5 per cent. in the total death rates is approximately 2.5 times the "standard error," or 3.7 times the "probable error" of simple sampling. The most that can safely be said is that in two random samples of 300 cases such a distribution is not likely to occur purely by chance.

A comparison of these figures with those obtained in the previous epidemic appears to increase their significance.

Table II.—*Acute Fever Hospitals, October, 1929, to July, 1930 (L.C.C. Special Report, July, 1931)*

Age	Number of Admissions	Deaths	Rate per cent.
0-1	488	78	15.9
1-2	1,453	201	13.8
2-3	1,110	70	6.3
3-4	1,041	34	3.2
4-5	886	19	2.1
Total	4,978	402	8.1

It will be seen that there is a fairly close correspondence between the death rates of the large group of just under five thousand cases and the controls in the present investigation. A somewhat higher mortality was to be expected in my series, because mild cases occurring towards the end of the epidemic in May, June, and July were excluded. This comparison shows that the expected death rate at these ages lies somewhere between 8 and 9 per cent. ; hence the rate of 3.7 observed in the treated cases appears unusually low.

Effect of Treatment on Pneumonia

These facts are made clearer by a consideration of the following table, which shows the number of cases admitted to hospital either already suffering from pneumonia or developing the complication after admission.

Table III

	Controls		Vitamin Cases	
Age	Cases of Pneumonia	Deaths	Cases with Pneumonia	Deaths
0-1	4	4	4	1
1 2	20	13	13	7
2-3	8	4	8	1
3-4	2	2	6	1
4-5	0	0	1	0
Totals	34 (5)	23 (5)	32 (2)	10 (2)

(Note.—The figures in brackets indicate the number of cases in which pneumonia developed after admission to hospital.)

This table accounts for all the deaths except four—three of the controls and one of the treated cases. These deaths were attributed to acute gastro-enteritis. The pneumonia attack rate of 10.8 per cent. for the total of 600 cases is lower than that usually recorded in measles during the same period of time. This is attributable to the fact that only those cases are included in which no possible doubt could exist concerning the presence of definite pneumonic areas after the disappearance of the rash. A number of doubtful cases have been excluded from both groups.

The distribution shown in Table III is somewhat unfavourable to the controls, though it is noteworthy that the number of cases presenting signs of pneumonia on admission to hospital was greater by one in the treated group than in the controls. It is, however, obvious that the numbers are too small to permit any very fine analysis.

Otitis Media and Skin Lesions

An attempt was also made to determine whether any protection of the middle ear could be obtained with the concentrate. Only cases free from ear discharge on admission and with no history of such discharge in the past were included in the observations. The results are shown in Table IV.

Table IV

Age	Controls	Vitamin Cases
0 - 1	2	2
1 - 2	15	12
2 - 3	4	6
3 - 4	6	6
4 - 5	1	3
Totals	28 (1)	29 (1)

(Figures in brackets indicate cases requiring operation.)

It will be seen that no benefit whatever was obtained from the concentrate in preventing otitis media ; nor was there any perceptible difference in the length of time required for the otorrhoea to cease in the two groups. A negative result has also to be recorded as regards the various skin complications. The figures are too small to be worth recording *in extenso*, but it was quite clear that the vitamin cases did not escape any more lightly than the controls.

General Observations

The dose of the concentrate administered in this experiment was quite arbitrary. It may have been greater than necessary, but it is not possible to state to what extent the vitamins were absorbed and assimilated. Contrary to expectation, enteritis did not prove any drawback to the treatment ; actually this complication proved less troublesome among the treated cases than in the controls. In the only case which proved fatal from acute gastro-enteritis in the vitamin group the complication did not develop until a fortnight after the withdrawal of the concentrate.

The youngest cases were carefully watched for any signs of hypervitaminosis, but this was never detected. In a preliminary experiment I have observed definite signs of intolerance in a marasmic baby who had received 6,000 international units of vitamin D daily for ten days. The symptoms were diarrhoea, anorexia, and marked irritability. Rapid improvement occurred on withholding the vitamin. From a study of recorded cases it appears unusual for clinical evidence of hypervitaminosis to develop in such a short space of time, but it is possible that this child had been receiving vitamin D in some form before admission to hospital. There is no reason to fear that 2,000 units given daily to a baby for two or three weeks will produce any undesirable effects. Vitamin A seems to be perfectly innocuous even in huge doses.

There are no grounds for supposing that the vitamin D in the concentrate exerted any specific beneficial effect on the course of the pneumonias. The work of Goldblatt and Benischek[9] has demonstrated that only vitamin A can claim to possess any protective value against respiratory infections in animals, while recent clinical observations of Friedlaender[12] have shown that the presence of rickets does not seem to affect unfavourably the prognosis in bronchopneumonia. Nevertheless it is possible that some adjuvant effect was obtained from the co-operation of the two factors, since the concentrate " adexolin " is stated to contain them in the natural proportions in which they occur in cod-liver oil.

Conclusions

Although the evidence submitted in this experiment scarcely amounts to a demonstration of the value of intensive vitamin therapy in measles, it is difficult to resist the conclusion that some protective effect was

obtained in the treated cases which tended to limit the severity of the pulmonary complications. The use of a concentrate rich in vitamin A as a prophylactic against secondary infections in a population of young children known to have been exposed to measles might well repay further study. Obviously too much cannot be expected in the way of rescuing cases already desperately ill with bronchopneumonia, since it is almost inconceivable that a sufficiently rapid effect can be obtained by such means.

The total failure to reduce the otological and cutaneous complications is disappointing, but here again it is reasonable to suppose that better results might have been achieved had it been possible to start the treatment during the incubation period, though it is unlikely that the problem will be solved by these means alone. In presenting the results of this experiment I am fully conscious of the dangers of founding arguments on the comparison of relatively small samples.

In a statistical investigation of this nature it is probably wisest to set down an impartial record of what was observed, leaving the reader to draw his own conclusions regarding the significance of the figures obtained.

Summary

1. Three hundred cases of measles received a concentrate of vitamins A and D during the acute stage of the disease: eleven deaths occurred in the series. In a control series of 300 cases having a similar age distribution twenty-six deaths occurred.

2. Evidence is brought forward in support of the view that the pulmonary complications were less severe in the treated cases than in the controls.

3. No difference was detected between the two groups regarding the number of cases developing otological or cutaneous complications.

My acknowledgements are due to Dr. J. H. Whitaker, medical superintendent of the Grove Hospital, for permission to make use of the clinical material at the hospital, and also to the director of the Glaxo Laboratories for a liberal supply of the concentrate "adexolin."

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Memoranda

MEDICAL, SURGICAL, OBSTETRICAL

TWO CASES OF TRAUMATIC ANEURYSM

Nowadays traumatic aneurysms in hospital practice are comparatively rare, so that the occasion of two cases occurring within the space of three months is my excuse for reporting them.

Case I

A butcher boy came up to the West London Hospital in May last year stating that he had cut his left forearm in the following manner: he had, whilst steadying a carcass with his left hand, thrust a knife into it. He had been holding the knife in his right hand, dagger-like, and had obviously misjudged the thrust. This was followed by a spurt of blood about 2 feet high, which he had stopped with digital pressure.

On examination he had a small punctured wound on his left lower forearm about 2 inches above the wrist-joint, in the line of his radial artery, with some deep haematoma. As it seemed that ligature of the radial artery was likely to be necessary, the tourniquet was left on until the patient was taken to the theatre. On its removal, however, no further haemorrhage took place, and one found it difficult to believe his story of the "two-feet-high jet." The skin wound was cleaned and sutured, primary union taking place.

From the day of the operation he was given a wrist strap to prevent the possible formation of any aneurysm in connexion with the injured artery. The patient came up to the hospital two months later, complaining of a swelling which was obviously an aneurysm of his radial artery; this, he stated, was getting larger. Mr. Wood Walker also saw the case and advised operation.

At the operation the radial artery was ligatured proximally and distally to the aneurysmal sac, which was excised, the venae comites tied off, and the wound closed. The subsequent course of events was of an unexpected nature. The next day the hand became very swollen and blue, but as this was thought to be a transient condition he was ordered to soak the hand in hot baths and to keep the arm elevated in a sling. During the next few days the condition became worse, the wound gaped, and it looked as though a mild degree of gangrene would set in. Electric baths and radiant heat were ordered, and for the next week the condition remained stationary. However, within a fortnight of the original operation the trophic condition of the hand greatly improved, healing took place, and movements were again permitted.

There appear to me several possible explanations of this sequence of events, which obviously followed the ligation of the radial vessels. First, that the ulnar artery was either absent or that it was too small to act as an anastomatic channel to maintain the nourishment of the limb, which it should have been capable of if it was of normal size and not diseased. The other explanation, which in the case of the hand surely could not have been a factor, was the ligation of the radial veins. When seen three months after the operation the circulation of the hand was perfect.

Case II

A man, aged 23, fell from his motor bicycle, and appeared when first seen to have merely abrasions on his forehead and temple. Two days later he came up because two pulsating swellings had appeared on his right temple. These proved to be two aneurysms, each about one inch long and three-quarters of an inch wide, arising from the two anterior branches of his superficial temporal artery. In this case, after evacuating the contents of the sac by digital pressure, the vessels above and below were ligatured through small incisions, whilst the sacs were kept compressed. This treatment proved satisfactory, and a week later it was impossible to see any bulging, though the sacs could just be felt after careful palpation.

Pathology

The specimen of the aneurysmal sac in the first case is interesting, as in most cases of aneurysms of the traumatic type the sac is either that of the false type formed by the condensation of the surrounding tissues with a deposition of blood clot, which after a time forms a fibrous internal layer, or else the vessel wall is merely damaged and not actually perforated, when an aneurysm of the sacular type may be expected. But the arrangement in the first case described was a combination of both sacular and dissecting types, the sacular part being the expanded external coat, whilst the dissecting part consisted of a stripping of the external from the middle coats, thus allowing an intramural extravasation of blood up and down the vessel for nearly an inch.

Microscopical section of the external coat shows much fibrous tissue, probably mainly protective reaction to the stretching of the muscle fibres, but also evidence that the external coat had been perforated at the original injury.