at the time of discharge was smaller. The circumstances are the same with regard to urobilinuria, except that at discharge a slightly greater number of cases were positive in the M. series. Hay's test for bile acids showed a slight

TABLE II.—Results of Test for Bile Products and Their Derivatives in the Urine

Reaction	C. Series		M. Series	
	No. of Cases	No. of Weeks	No. of Cases	No. of Weeks
Hammarsten:				
Neg. whole time in hospital ..	31		42	
Pos. → neg. while in hospital ..	85	1.7	77	1.6
Pos. whole time in hospital ..	9		6	
Schlesinger:				
Neg. whole time in hospital ..	12		24	
Pos. → neg. while in hospital ..	71	2.6	53	2.3
Pos. whole time in hospital ..	42		48	
Hay:				
Neg. whole time in hospital ..	16		18	
Pos. → neg. while in hospital ..	99	1.9	91	2.0
Pos. whole time in hospital ..	10		16	

tendency to the contrary, with a somewhat longer positive reaction in the M. series. There were no significant statistical differences in the urine reactions.

The length of stay in hospital in the control cases was 27.5 ± 1.4 days and in the methionine cases 25.0 ± 1.4 days.

The essential facts obtained from these tests are that the cases treated with methionine tend to show a smaller increase in bile pigments in the blood and a quicker return to normal values, and consequently that the secretion of bile pigments and urobilin in the urine also ceases earlier. But, compared with the untreated cases, the difference is very small, and statistically is not significant. Definite effects cannot therefore be claimed for treatment by this method. If, however, methionine treatment had been given during the whole course of the illness the results might probably have been better; but this is problematical.

While these attempts to treat acute hepatitis with methionine have not been very encouraging, I certainly think that amino-acids should be used in the treatment of pre-comatose and comatose cases. Though I am unable to present a scientific basis for this opinion, our experience tends to show that a course of amino-acids given intravenously is of value in severe cases.

Summary

In experiments on animals several investigators have proved that the amino-acid methionine affords excellent protection to the liver against damage caused both by toxins and by lack of protein in the diet. Attempts to use methionine in the treatment of acute hepatitis have been made by several authors, with contradictory results.

Methionine treatment was given in 125 slight and semi-severe cases of acute hepatitis and an equal number served as control cases. The group treated with methionine showed fewer cases with increasing bilirubinaemia after admission to hospital, a slightly smaller increase in bilirubinaemia, and a somewhat quicker return to normal values, as well as an earlier cessation of secretion of bilirubin and urobilin in the urine as compared with the cases not receiving treatment. Thymol reaction and secretion of bile acids showed a more uncertain tendency. The prothrombin index decreased slightly more in the untreated cases. The differences, however, were small and were not proved statistically.

The investigation shows that a marked effect is scarcely to be expected from the use of methionine in the treatment of acute hepatitis of average severity. In more severe cases of hepatitis, however, clinical experience suggests that amino-acids may be of value when given intravenously.

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THE RATE OF EXCRETION OF A LARGE DOSE OF PENICILLIN

BY

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For some years past it has been a common practice in this country, although not elsewhere, to administer aqueous penicillin in only two daily intramuscular doses. The convenience of this system in private patients and hospital out-patients needs no emphasis, and the experience of many has been that it gives satisfactory therapeutic results, at least in certain conditions. In so far as it is likely to be superseded by the administration of slowly absorbed preparations containing procaine penicillin at even longer intervals, its effects will cease to be of interest. There is nevertheless some advantage in knowing how long a given large dose in water continues to exert an effect, and it seemed to us that in one important particular knowledge on this subject is incomplete. This is the rate of disappearance of penicillin from the blood after an intramuscular dose of 500,000 units, the largest dose commonly given at long intervals.

Many authors report the results of blood assays at intervals after various smaller doses, and it is well recognized that duration of effect is not directly proportional to the dose given. Reports of assays after a dose of 500,000 units are few and usually refer to control observations made in a small or unstated number of subjects during a study of some slowly absorbed preparation. May (1948) gave this dose to four subjects at rest in bed, and regards the results as indicating that it will be followed by a "therapeutic level" for 12 hours and "complete disappearance" in 16 hours; but this conclusion is based on only one positive titration after the ninth hour in each of three cases, while in the fourth no assay made after the third hour was positive, those intermediate between this and the twelfth hour having been omitted.

Miller and Boger (1948) gave 500,000 units at intervals of three hours and found the average blood content when the next dose was due to be 1.89 units per ml. Wayne *et al.* (1949) gave 600,000 units to three patients, and the blood level is shown as near zero at 10 hours. Loewe *et al.* (1949) state that 500,000 units in saline "gave no detectable blood levels at eight hours or thereafter," but in an accompanying table the level at eight hours is stated as 0.012 unit per ml. and *nil* at 12 and 16 hours.

In view of this paucity of information, it seemed worth while to follow the effect of this dose in an adequate number of subjects. It also seemed advisable to use as accurate an assay method as possible, and hence to work with volumes which could be more exactly measured than those of the various micro-methods in common use.

Method of Assay

Venous blood was used for all estimations, the serum being separated and the assay carried out within a maximum of four hours after its withdrawal. The medium used was beef-heart extract peptone broth containing 2% of inactivated Group O human blood pre-inoculated with approximately 1 part in 25,000 of a 24-hour broth culture of a Group A haemolytic streptococcus (strain "Brompton"). This was tubed in 1-ml. volumes, and 1 ml. of serum was added to the first tube and mixed; 1 ml. was then transferred to the second and so on, to give a series of doubled dilutions. After overnight incubation, the result could be read at a glance by the presence of haemolysis in tubes containing sub-inhibitory concentrations of penicillin. A control series was not run with each set of assays, but tests with serum containing a known amount of added penicillin were made several times during the investigation, and always showed the minimum concentration inhibiting growth to be 0.01 unit per ml., as in the following test, in which doubled dilutions were made from four different closely spaced initial concentrations:

Concentration of Penicillin in Units per ml.

No Growth				Growth	
0.1	0.05	0.025	0.0125	0.0062	
0.09	0.045	0.0225	0.0112	0.0056	
0.08	0.04	0.02	0.01	0.005	
	0.07	0.035	0.0175	0.0087	0.0043
	0.06	0.03	0.015	0.0075	0.0036

The minimum amount of penicillin detectable in the blood by this method is thus, as exactly as can be measured, 0.02 unit per ml.

Conduct of Tests and Results

Single intramuscular injections of 500,000 units of penicillin in 1 ml. of water were given to 31 adults believed to have normal renal function. Ten of these were patients in bed and 21 were ambulant volunteers. In two of the latter group amorphous yellow penicillin was used: all the remainder received crystalline penicillin G.

Venous blood was withdrawn at intervals after the injection of penicillin, and the penicillin content of these samples is shown in Fig. 1, in which each point represents a separate estimation. In three of the volunteers penicillin was still present in the last sample of blood examined—in one case at eight hours (0.04 unit per ml.) and in two at nine hours (each 0.02 unit per ml.). By extrapolation of the graphs of these cases it may be concluded that, in each, penicillin

FIG. 1

would have been below the titratable level at the tenth hour. Taking the midway point in time between the last positive and the first negative assay as the termination of an assayable blood level, its mean duration for the entire series is 7.79 hours.

The results expressed as the proportion of subjects in whom at successive hours the penicillin content of the blood had fallen below 0.02 unit per ml. are shown in Fig. 2. From this it is evident that the rate of elimination varied, no penicillin being detectable after six hours in eight subjects, and after seven hours in 21, although in a few others it persisted until the tenth hour. We cannot account for this variation, although it seems more likely to depend on the rate of absorption from the injection site than on the rate of renal elimination. Muscular movement might affect this, and the two positive assays at the tenth hour were both in bed patients; but the number of the latter is too small to permit conclusions to be drawn on this point.

FIG. 2

Discussion

From these results it seems that a detectable level of penicillin in the blood after an intramuscular dose of 500,000 units in water rarely persists for more than eight hours and may last for no more than six or seven hours.

It is now a common belief that the continuous maintenance of a therapeutic blood level is unnecessary in most cases. The best support for this belief is the recent work of Eagle and Musselman (1949), who have shown that when streptococci, staphylococci, or pneumococci have been exposed to penicillin for a limited period survivors require from one or two to over four hours (depending on species, length of exposure, and penicillin concentration) to resume growth. On this basis it is justifiable to add four hours to the period for which a large dose is deemed to act, and thus to conclude that in treating sensitive infections a dose of 500,000 units may be given at 12-hour intervals.

There is one ground on which a still longer interval may be considered permissible. As originally shown by Florey *et al.* (1946) in patients, and recently confirmed experimentally by Ungar (1950), penicillin can persist in an exudate for some time after it has disappeared from the blood. The effect of this factor will evidently depend on the volume of exudate formed while the blood level is high, and may consequently vary with the nature and stage of development of the lesion. The choice of a dosage system must depend on this and other considerations, but we venture to express the opinion that the administration of even large doses of sodium penicillin in water at longer intervals than 12 hours (e.g., 24 hours, which seems to have been a fairly common practice) is not fully justified by the information at our disposal, and may fail to exert full therapeutic effect.

Summary

Penicillin was assayed in the blood by an accurate, and sensitive method at intervals of 6 to 11 hours after a single intramuscular dose of 500,000 units of sodium penicillin in water in 31 subjects. The mean duration of a blood level of 0.02 unit per ml. or more was found to be 7.79 hours, with individual variations covering a total range of four hours. Reasons are given for suggesting that the interval between doses of this size should preferably not exceed 12 hours.

We are indebted to a number of colleagues, technicians, and students for permitting themselves to be used as experimental subjects, and to Miss P. M. Waterworth and Miss M. Rhodes for technical assistance.

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HYPERTRICHOSIS: A REPORT OF THREE CASES

BY

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Hypertrichosis is a fairly common complaint, especially in women, and, like the secondary sex characters, usually appears after puberty; but it may occur at any time of life. It seldom remains the only symptom for long, and becomes linked with alterations in somatic growth, sex function, or general metabolism. In children it follows the pattern of iso- or hetero-sexual precocity, which may be due to hypothalamic tumour or to adrenocortical hyper-trophy or tumour. In virilism it may be pronounced, and mimic faithfully the male type. The hypertrichosis of Cushing's syndrome, whether of pituitary or of adrenal origin, is more downy. In anorexia nervosa the body is covered by fine down: amenorrhoea is invariably present and the hair disappears completely on recovery.

Hair in the male is of a much more stable character. The lack of it is generally associated with lesions of the testis. Profuse hair in men is occasionally seen in rare cases of adrenocortical carcinoma and in other men with tender nodules in the epididymides, or small testes, adiposity, and sexual disorders. It may be regarded as a type of feminism.

Danforth (1925) gives an interesting summary of some cases of hypertrichosis universalis in which the patients (either from birth or soon after) were covered with long fine silky hairs of the lanugo type. "The whole face, including the upper eyelids and nose, is covered with a thick coat of long soft hair. Likewise the pubic and axillary hairs are not present in the normal form, but replaced by the same 'exaggerated lanugo' that covers the rest of the body and limbs. These subjects are referred to as 'dog men' or 'ape men,' and several have been on exhibition. When the trait appears it is transmitted as a Mendelian dominant. The condition has been variously regarded as of 'arrested development' or 'atavism' or due to mutations. In some patients the teeth are deficient."

Danforth draws attention also to somewhat similar patients in whom the hair was coarser and "seems to represent an intermediate stage between a generalized covering of soft lanugo-like or transitional hair and localized hypertrichosis of the terminal hair."

The clinical histories only are recorded, and it would be interesting to subject patients of this type to detailed endocrine investigation. The various grades of hair run on closely similar lines to the various grades of intersexuality and their relation to prepubertal virilism. If we may regard the adrenal gland as an accessory sex organ, then clinically the emphasis is on hair in its hypertrichotic states, and on the lack of it in deficient states of the gonad.

Congenital Type: Case Report

This patient, a boy aged 9 months (Fig. 1), was born after a normal pregnancy, and is the youngest of five boys, the others being normal. So far as is known there is nothing abnormal in the family history. At birth he was covered with hair. The hair of his scalp extended down to his eyebrows; that on the limbs to his wrists and ankles; that on his trunk was abundant. His weight at birth was 6½ lb. (2.95 kg.), and he was breast-fed for three months. His lower incisors appeared at 7½ months, he could stand at 6 months, his epiphysal age corresponded to 2 to 3 years. He was precocious developmentally and also in behaviour. There were no other abnormal physical signs. His blood pressure was 130/70; his pituitary fossa was normal; his ketosteroid excretion was 1 mg. a day—normal for his age.

His head was covered by a mop of dark curly hair which reached to his eyebrows. The latter were heavy; the hairs of the inner half pointed upwards, and those at the outer canthus outwards and slightly downwards. The eyelashes were well formed and fanned outwards. The face, limbs, and body were smothered with fine downy hair of a lighter gingery colour, which was longer and denser in certain regions. On the back the hair converged upwards towards the occiput and towards the spine and then trickled caudally down the midline; over the sacrum it gathered and sloped downwards into a Pan-like tail. There were no whorls. In the region of the upper arms and shoulders the hairs converged in the form of a crest towards the line of contour, as if they had been combed both back and front in this direction.

In the mid-clavicular regions this crest passed across the back of the neck in a crescentic manner, like a necklace. This might have been due to the sweeping effect of the hairs from the back of the head. On the forearms the hairs swept towards the olecranon from the radial to the ulnar border. In front of the thighs they parted outwards and inwards, and behind the thighs they ran, obliquely downwards. The nose was broad and the mouth curiously pursed up by a narrow and prominent upper lip. The big toe lay apart from the others.

Sir Arthur Keith was interested in the

FIG. 1.—Child aged 9 months, showing atavistic hair tracts.