St. Charles's, St. James', St. Mary's, St. Thomas's, University College, Whittington.

We are indebted to the staffs of the above-named hospitals for having allowed us to interview their patients and to have access to the hospital notes; also to the individual members of the staffs, both medical and lay, who notified the cases and collected the notes for examination. The work could not have been carried out without their co-operation. Sir Ernest Kennaway and Dr. Percy Stocks took part in a conference called by the Medical Research Council, at which this investigation was initiated, and we have been fortunate in having their helpful advice throughout its course. Professor W. D. Newcomb has advised us on individual problems of pathology. We are most grateful for this assistance. Finally, we wish to thank Miss Marna Buckatzsch, Miss Beryl Iago, Miss Keena Jones, and Miss Rosemary Thomson, who interviewed the patients and helped with the analysis of the results; and Dr. J. T. Boyd for assistance in the calculations.

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REGIME FOR TREATMENT OF SEVERE AND ACUTE LIVER DISEASE

BY

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In spite of increasing biochemical knowledge on the subject of liver necrosis, the high mortality rate of severe liver disease of acute onset remains a therapeutic challenge. Once coma has occurred a fatal outcome is probable; a recovery is always an event of note.

It is, however, a remarkable fact that even patients suffering from massive necrosis may linger on for a number of days. This is in marked contrast to the short period of survival of animals after hepatectomy. Moreover, in so-called "acute yellow atrophy" several of the liver's functions may remain apparently normal until death. Even the fasting blood-sugar level may remain within normal limits. This must surely mean that enough liver tissue survives to carry out certain highly important metabolic processes. There is also reason to believe that the histological picture of massive necrosis is not unrelated to post-mortem autolysis, and that much more liver tissue survives during life than is apparent after death (van Beek and Haex, 1943).

These facts are of great importance. If practically all the liver were necrotic during life, then treatment would obviously be useless. On the other hand, if large numbers of liver cells were diseased but not dead the possibility would remain that the process was reversible, and that a successful treatment might eventually be discovered. In the hope that the latter state of affairs actually occurs, I have been attempting over a number of years to treat these cases on biochemical principles.

Earlier Work

Some three years ago treatment was begun in a series of six patients in coma from acute liver disease (Latner and Mowbray—paper in preparation). By daily intravenous administration, each patient received 1 to 3 g. of cystine in addition to glucose and plasma. The importance of this amino-acid in the prevention of experimental necrosis had already been demonstrated (Glynn *et al.*, 1945). All these cases presented the clinical picture of "acute yellow atrophy" and all had a fatal outcome.

A gross amino-aciduria has been demonstrated in severe liver disease by paper chromatography (Dent, 1949). In view of the known increase in the amino-acid content of the blood, including the thioamino-acids, Dent has suggested that the necrotic liver cannot utilize them and they could not therefore be of much use in curative treatment.

There was some possibility that a reflex circulatory upset affecting the liver might prevent the cystine reaching the liver cells. With this possibility in view, tetraethyl-ammonium bromide was administered to our sixth case as soon as it became obvious that there was no response to cystine. The downhill progress of the patient was in no way affected.

These discouraging results made it obvious that we were thinking along incorrect lines. The diseased liver cell required cystine to prevent necrosis but could not utilize it adequately from external sources. The problem, therefore, was to render the cells less sensitive to cystine deficiency, so that they could utilize their own cystine until such time as recovery was complete enough to allow them to use the amino-acids of surrounding tissue fluid. From this point of view the role assigned to tocopherol in the production of experimental hepatic necrosis (Schwarz, 1944; György, 1947; Himsworth and Lindan, 1949) assumes great importance. This vitamin has therefore been included in the regime of treatment described below.

The intracellular oxidative processes of the liver and other organs also require other vitamins. In their absence toxic products accumulate which could easily be a factor in the final death of liver cells. The successful application of massive doses of the vitamin-B group in the cholaemia of cirrhosis has already been reported (Patek *et al.*, 1948). This form of therapy was therefore also included in the regime.

Recent knowledge of the state of dynamic equilibrium of the body proteins also has a bearing on this problem. It seems likely that proteins are not only destroyed by wear and tear but are continuously being broken down and resynthesized at a remarkably rapid rate. This protein turnover can be demonstrated with radioactive tracers. One would not be far wrong in stating that every protein in the body was in a state of dynamic equilibrium with all other proteins (Whipple, 1948). The liver has been described as the master organ for protein metabolism. The diminution of the plasma proteins in severe disease of this organ could profoundly upset the normal equilibrium of the tissue proteins and so lead to metabolic upsets. The resulting toxic metabolites could act unfavourably on already damaged liver cells. It therefore becomes of great importance to administer plasma protein in severe liver disease, and for this reason it has been included in the regime.

Vitamins of the B group have been administered along with a dextrose solution in normal saline. The saline vehicle has been used because of the remarkable tendency for these patients to develop low plasma-chloride levels, probably related to vomiting and possibly to associated renal failure.

Large amounts of dextrose administered intravenously can lead to a dangerously low level of plasma potassium. This was in fact demonstrated in the one fatal case of this series. For this reason every pint (570 ml.) of dextrose in saline has also contained 0.5 g. of potassium chloride.

All patients in coma are very liable to develop aspiration pneumonia. This is well seen in liver necrosis; such patients seem to have a marked tendency to infection. For this reason penicillin has been administered daily. If this fails to control infection streptomycin may be used.

The Regime

The regime, as finally developed, is as follows.

Infusion 1.—To each pint of 10% dextrose in normal saline are added 50 mg. of thiamin hydrochloride, 150 mg. of nicotinamide, and 50 mg. of riboflavin as well as 0.5 g. of potassium chloride.

Infusion 2.—This consists of plasma to which the vitamins alone have been added in the same concentrations as in Infusion 1.

The patient's blood group is immediately determined and appropriate donors are contacted. Penicillin, 1,000,000 units, is administered daily for 10 days. During each 24 hours three separate pints of Infusion 1 are administered intravenously at six-hourly intervals and after a further six hours one pint of Infusion 2 is given. During this period 300 mg. of tocopherol is administered intramuscularly in three divided doses.

This treatment is continued until such time as fluids can be safely administered by mouth; usually two or three days. It is important to administer the tocopherol by mouth as soon as possible, as it is said to be much more effective by the oral route (Goettsch and Pappenheimer, 1941). As recovery sets in, the vitamin dosages are halved on consecutive days until they can be replaced by a reliable polyvitamin preparation, which is continued through convalescence.

As soon as the patient is able to take fluids by mouth, "hepovite" is administered in gradually increasing dosage until the patient is receiving 2 oz. (62 g.) daily in addition to the ordinary diet.

Unfortunately, in the early stages haemorrhagic incidents are common. In this series they have taken the form of epistaxis or melaena. It is of the greatest importance to be constantly on the alert for signs of severe haemorrhage. This must be treated by the immediate administration of appropriate amounts of fresh donor blood, to each pint of which the vitamins have been added in the same concentrations as in the infusions. It must be emphasized that for this purpose stored blood is useless, as the haemorrhage is due among other factors to prothrombin deficiency.

If an infection which is obviously not responding to penicillin develops, a course of streptomycin may be given. Sedatives are best avoided. However, these patients are liable to become very restless and extremely difficult to nurse, and on occasion it may be necessary to administer paraldehyde. Morphine should not be given.

The treatment has now been given in five instances, details of which follow. For the sake of brevity the regime is referred to as "the intravenous liver regime."

Case 1: Massive Necrosis Complicating Infective Hepatitis

A housewife aged 42 was jaundiced and stuporous on admission and soon lapsed into coma. One week previously she had felt unwell and had a temperature of 102.4° F. (39.1° C.). She suffered from anorexia and nausea, but drank quite copiously. Five days before admission she began to vomit a great

deal, and this continued for three days. She had not vomited since, but suffered from severe nausea. Her temperature became normal two days before admission. By the next day she had become drowsy, and gradually got worse until she was answering questions only when spoken to sharply. Jaundice now became evident.

On examination it was found that she could be roused with difficulty to say an occasional word. She reacted vigorously to painful stimuli. Her conjunctivae were yellow and her skin slightly jaundiced. Her abdomen was tender all over, especially in the right upper quadrant, with some guarding on deep palpation. The liver could not be palpated, but there was a reduction in the area of hepatic dullness. Some bruising was present over the right lower shin, and the plantar responses were flexor. Her temperature was 98° F. (36.7° C.), pulse rate 92 a minute, and blood pressure 160/95 mm. Hg.

A specimen of urine contained albumin and bile pigments but no casts. The white cell count was 7,800 per c.mm. The serum thymol turbidity and flocculation were respectively 21 units and + + + +. The plasma alkaline phosphatase and blood urea were respectively 18 units (Jenner and Kay) and 21 mg. per 100 ml.

Intravenous therapy was begun immediately. In this case the infusions contained no added potassium chloride, and tocopherol was given in much lower dosage than in the regime already described. The patient soon became extremely restless, and sedation was necessary. In spite of this, generalized twitchings of her muscles developed. On the second day of treatment she still remained comatose, with periods of extreme restlessness. By the afternoon of the next day she began to recover from her coma and was able to take fluids by mouth. The improvement continued, and by the fourth day of treatment she was speaking quite rationally and taking fluids well. On the fifth day she was much improved and talking quite rationally. She was feeling better but somewhat weak.

At this stage a cellulitis had begun in her right leg—the limb into which the intravenous drip was being administered. Her temperature was now 102° F. (38.9° C.). Sulphadimidine was given in an unsuccessful attempt to combat the infection. The temperature continued to rise, and by the next day it had reached 104° F. (40° C.), and she lapsed once more into coma. Her blood potassium was only 10.9 mg. per 100 ml. Her blood urea was 70 mg. per 100 ml. and the white cell count 23,000 per c.mm. In spite of the administration of 5 g. of potassium chloride by mouth and 2 g. intravenously she remained in coma and died next day.

One cannot escape the conclusion that the cellulitis played a large part in the causation of death, which may also have been contributed to by the lowered blood potassium. It was because of this case that potassium chloride was subsequently introduced into the routine intravenous therapy and the dosage of vitamin E was increased to 300 mg. daily. It is possible that the administration of streptomycin might have been a life-saving procedure.

Case 2: Infective Hepatitis with Massive Necrosis

A boy aged 9 was somewhat jaundiced on admission. He was delirious and had violent screaming bouts. He had first felt unwell five days previously and became delirious with severe epistaxis during the next 24 hours. The delirium continued up to the day of admission, when jaundice first appeared.

On examination he was seen to be very ill and somewhat dehydrated. A tinge of jaundice was present in the skin and conjunctivae, and purpuric spots were present on his back. His respirations were 45 a minute, his temperature was 99.4° F. (37.4° C.), and pulse rate 104. The liver seemed slightly enlarged. There was no neck rigidity and the plantar responses were flexor. Some moist sounds were present over both lungs. A specimen of urine contained albumin and bile pigments. Blood examination revealed a plasma bilirubin content of 4 mg. per 100 ml. and an alkaline phosphatase of 16.8 units (Jenner and Kay) per 100 ml. The thymol reactions were normal, but cephalin-cholesterol flocculation was + + + +.

At this stage he was given 1,000,000 units of penicillin daily, and this was continued for 12 days. Next day he was very ill indeed, with alternating coma and restlessness. He had become more deeply jaundiced and a morbilliform eruption appeared on his trunk. The diagnosis of acute yellow atrophy was made and the prognosis was regarded as extremely grave. Examination of the urine by paper chromatography revealed a gross amino-aciduria.

The intravenous liver regime was now begun. In this case, however, all the vitamins were administered by intramuscular injection. On the third day after admission the patient suffered a severe epistaxis and his haemoglobin was shown to be 50% of normal. He was therefore given a pint (570 ml.) of blood. Next day he was much improved, was rational, and was able to drink. The drip was discontinued. He made rapid progress and was discharged 18 days after admission. Leptospiral agglutinations were negative 18 days after the onset of illness.

He was readmitted 10 days later for a lung abscess which responded well to treatment. When last seen, a year later, he appeared to be in good health.

Case 3 : Massive Necrosis of the Puerperium

A housewife aged 25 was admitted in a confused and somewhat stuporous condition two days after the delivery of her first child. There was some jaundice of the skin and conjunctivae. She had begun vomiting a week before the birth of her child, and two days before delivery a slight jaundice was noted. It was hoped that delivery would result in improvement, which was apparent at first, but after 48 hours she relapsed into an almost comatose condition.

On examination liver dullness was markedly diminished: this was confirmed by a number of observers. She was somewhat confused, but could be made to answer questions more or less rationally. At this stage her urine contained bile but no albumin. Tyrosine and leucine crystals could not be demonstrated microscopically, but paper chromatography revealed a gross amino-aciduria. Blood examination disclosed a plasma bilirubin content of 3.36 mg. per 100 ml. The alkaline phosphatase and total serum protein were respectively 17.8 units (Jenner and Kay) and 4.2 g. per 100 ml. The plasma prothrombin was 61% of normal average and the serum thymol reactions were normal. The serum potassium level was only 12.3 mg. per 100 ml.

The patient was placed on the intravenous liver regime for three days and made a rapid recovery. One week later her serum protein had risen to 5.25 g. and her prothrombin was 88% of normal average. She was now shown to have a macrocytic anaemia, but marrow puncture revealed normoblastic erythropoiesis and no megaloblasts were seen. It is interesting to note that other cases in this series have developed a similar condition. The anaemia responded well to the administration of folic acid and a transfusion of the packed cells of two pints (1.14 l.) of blood. When last seen, six months later, she was in normal health.

Case 4 : Hepato-renal Syndrome Following Cholecystectomy

A housewife aged 36 was obviously gravely ill when I first saw her. She was deeply jaundiced, vomited copiously, and was in a stupor from which she could not be roused. Her eyes remained turned upwards. She had been admitted to hospital 11 days previously with a history of deepening jaundice of 16 days' duration, not associated with pain but accompanied by severe nausea and itching. There had, however, been intermittent attacks of biliary colic for about eight months.

On admission, laboratory examination revealed that each 100 ml. of her plasma contained 13 mg. of bilirubin and 10.8 units of alkaline phosphatase (Jenner and Kay). The plasma prothrombin was 92% of normal average and the serum thymol reactions showed a turbidity of 5 units and ++++ flocculation. In spite of this evidence of hepatocellular damage, it was decided to operate because of the previous history of biliary colic. Cholecystectomy was performed and a small stone removed from the common bile duct, into which a drain was

inserted. On the day after operation a transfusion of two pints of blood became necessary because of continual oozing from the wound. The patient was restless and vomiting, and her condition continued to deteriorate, with deepening jaundice. Because of continuous vomiting, intermittent gastric drainage was performed. She gradually became stuporous and developed oliguria.

Because of her abdominal incision, I was unable to carry out a complete clinical examination. This was made even more difficult by the presence of a large haematoma in the wound, which was still oozing blood. The spleen was not enlarged, and nothing abnormal was demonstrated in her chest. Her temperature was 99° F. (37.2° C.) and her pulse rate 100 a minute. A specimen of urine contained bile, and paper chromatography revealed a gross amino-aciduria. Her plasma bilirubin and blood urea were now respectively 32 mg. and 136 mg. per 100 ml.

The intravenous liver regime was immediately started and was continued for six days. For the first few days the patient remained exceedingly ill, with copious vomiting and well-marked oliguria. The wound haematoma increased in size but the jaundice diminished. On the last day of the regime the plasma bilirubin had fallen to 6.4 mg. per 100 ml. The blood urea, chloride (as Cl⁻), and potassium were respectively 200, 226, and 16.9 mg. per 100 ml. She was now able to take sips of fluid by mouth, and hepovite was administered. Oliguria still persisted, and in view of the low plasma chloride three pints (1.7 ml.) of 2.7% saline were administered intravenously over a period of 12 hours. This raised the plasma chloride to 311 mg. per 100 ml. (as Cl⁻), but the blood urea also rose to 440 mg. per 100 ml. A profuse diuresis now set in accompanied by much improvement in the patient's condition. In five days the blood urea had fallen to 110 mg. per 100 ml. The plasma chloride was now well within normal limits and the plasma bilirubin was 1.6 mg. per 100 ml. The red blood cell count was found to be only 2,800,000 per c.mm., the blood haemoglobin was 6.51 g. per 100 ml. A transfusion of two pints of blood was therefore given and folic acid administered.

On discharge, a fortnight later, all biochemical investigations were within normal limits. A high-protein diet supplemented by 2 oz. (62 g.) of hepovite daily was prescribed. When last seen five months after discharge she was fit and well and had obviously gained much weight. She had returned to normal housework.

Case 5 : Acute Massive Necrosis of the Puerperium

A housewife aged 25 was admitted in a desperately ill condition; she was jaundiced and comatose. At the thirtieth week of her second pregnancy she felt weak and breathless and suffered from headaches and swelling of the ankles. Six weeks later she first saw a doctor, who delivered her of a stillborn child. Within half an hour she collapsed, became delirious, and then sank into a state of coma, and was admitted to Preston Hospital, North Shields. There was now persistent hiccup, and a deepening jaundice became evident. She was obviously moribund, and in this condition was transferred to the Royal Victoria Infirmary for treatment.

On examination it was found that she could occasionally be roused to mumble a few incoherent words. She suffered from repeated hiccup, jerking movements, and muscular twitches. She was fairly deeply jaundiced and a well-marked fetor hepaticus was detected. Some spider naevi were present on her arms and face. There was also some palmar erythema. A number of bruises were present over the lower region of her back, particularly over the sacrum. In this position an early bed sore was evident. There was marked diminution of liver dullness and the uterus was enlarged to some 3 in. (7.6 cm.) above the symphysis. Crepitations and areas of diminished air entry were detected over both lung bases. The plantar responses were flexor. Her pulse rate was 100 a minute, blood pressure 70/40 mm. Hg, and temperature on admission 97.4° F. (36.3° C.).

A specimen of urine contained bile but no albumin, and a gross amino-aciduria was demonstrated by paper chromatography.

graphy. This latter finding was confirmed in subsequent specimens. Examination of the blood revealed a red cell count of 3,600,000 per c.mm. and a leucocytosis of 33,200 cells per c.mm. The blood haemoglobin content was 7.4 g. per 100 ml. Plasma bilirubin, alkaline phosphatase, and total serum protein were respectively 5.6 mg., 21.5 units (Jenner and Kay), and 4.95 g. per 100 ml. The thymol reactions and zinc sulphate flocculation were within normal limits. The blood urea was raised to 352 mg. per 100 ml.

The patient was immediately placed on the intravenous liver regime and the response was dramatic. Twenty-four hours after admission she was free from hiccup for short periods and was able to recognize her relatives. She could now take some fluids by mouth. Forty-eight hours after admission she developed a severe melaena, which continued for three days and necessitated the administration over this period of five pints (2.84 l.) of blood containing added vitamins. During this time it was thought unnecessary to administer any plasma. The hiccup vanished on the third day of treatment, and she was alert and smiling and taking her food. The drip was discontinued on the fifth day.

She now developed a temperature of 102.4° F. (39.1° C.). In spite of the penicillin therapy a cellulitis of her right leg had developed and the bed sore had increased in size. Physical signs were still present over both lung bases. The penicillin was discontinued and a 10-day course of streptomycin begun with a dosage of 0.5 g. twice daily. As a result of this therapy her temperature fell to normal and all signs of infection disappeared. The slow healing of the bed sore somewhat prolonged her stay in hospital. On the twelfth day of her illness the plasma prothrombin was 70% of normal average, and subsequent blood examination revealed normal plasma bilirubin, alkaline phosphatase, and blood urea. The flocculation tests were, however, now abnormal. Leptospiral agglutinations were negative.

She was discharged from hospital six weeks after admission, and when last seen, six weeks later, was feeling perfectly well, had gained weight, and had returned to all her household duties. Nothing abnormal could be demonstrated by physical examination. Serum flocculation tests were markedly abnormal; the thymol and zinc sulphate turbidities were respectively 7 and 16 units, and the thymol and cephalin flocculations were each + + + +.

Discussion

In five consecutive cases of severe liver disease there has thus been only one death. The expected mortality was much higher. Even the patient that died recovered from her coma. Her eventual death was in some measure due to a superadded infection and possibly to the fact that she did not receive the full regime.

Those patients who recovered have been observed for periods of up to one year. The most remarkable fact has been the degree of recovery they apparently achieved. After a preliminary period of weakness, lasting about a month and associated with fairly easy fatigue and swelling of the ankles, there has been a gradual return to apparently normal health. Three of the patients have remarked spontaneously on the great subjective improvement that occurred during the first few days of treatment. One now claims she feels better than she has done for years.

It is interesting to note that three of the patients developed a macrocytic anaemia during their stay in hospital. In one instance (Case 5) normoblasts were found in the peripheral blood.

It is felt that no apology need be made for the polytherapy. The liver is, after all, a highly complex organ, and it would be presumptuous to assume that any single substance could bring about its recovery from severe disease.

It might well be suggested that those cases that recovered would have done so spontaneously. Most medical men of some experience will remember having seen or heard of at

least one case of severe liver disease which did not have the expected fatal outcome. It is extremely unlikely, however, that the recovery of four out of five consecutive cases would be unrelated to treatment. In this connexion it has already been mentioned that death occurred in each of six similar cases seen by me. In fact, this latter group may be regarded as a control series, as similar diagnostic criteria were used. It must be emphasized that all the cases that recovered showed at some stage the clinical picture of so-called "acute yellow atrophy." They all had gross amino-aciduria, which is known to be associated with a very grave prognosis (Dent, 1949).

Liver disease of acute onset and of great severity is fortunately relatively uncommon in this country. The cases herein reported have been seen over a period of three years. This work was done in a hospital which serves an extensive area and so a relatively large number of cases were seen in that time. The absolute number is, however, somewhat small, and for this reason it would perhaps be wise to restrain one's enthusiasm. The results of therapy have proved so remarkable that it is hoped that others will adopt the same regime in similar cases and so help to arrive at a final assessment of its value.

In conclusion, it should be pointed out that this form of therapy may also be used prophylactically after surgical operations on patients with severe liver impairment. These are notoriously bad surgical risks. The regime has already been successfully applied in two such cases.

Summary

A regime for the treatment of severe liver disease of acute onset is described.

Five cases have been treated, with only one death.

In contrast, six cases treated with cystine intravenously showed 100% mortality.

Two further cases have been successfully treated prophylactically after surgical intervention.

I am much indebted to various colleagues on the staff of the Royal Victoria Infirmary, Newcastle-upon-Tyne, for giving me such free access to their patients.

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The Ministry of Supply has recently given details of a new product from the Harwell atom pile which may take the place of radium in the treatment of some skin diseases. This is Ir¹⁹², an isotope of the metal iridium. To make Ir¹⁹², iridium is "cooked" inside the atom pile for three months. It is then ready for clinical use, although after a month it must be returned for further treatment inside the pile. The new isotope is not only cheaper and more plentiful than radium—it costs £12 to hire one dose for four weeks—but, because the radiation it emits is less powerful than that of radium, it can be used for treating skin disorders without danger of harming the bone structure underneath the skin. For the same reason very much less lead screening is required to shield the operator, and the equipment which houses the isotope is simpler and less expensive than radium appliances.