leaving only the deep infiltrating part in relation of the internal capsule.

Postoperative Course

The patient did well, and 5 days after the operation he was on full diet. Clinically the result was satisfactory.

Discussion

The advantages of internal cooling, compared with surface cooling or extracorporeal blood cooling, have been discussed elsewhere (Khalil and Mac Keith 1954, Khalil 1957a, b).

An apparatus for application of internal cooling has been described (Barnard 1956), but the apparatus described here has several advantages:

Instead of pumping water into the stomach, the pump sucks the water from the balloon to the tank, the same volume of fresh cold water automatically passing from the water tank to the balloon. It is impossible to overfill the stomach.

The volume of the balloon can be adjusted at any moment to the required volume with greater ease.

A flow-meter is included in the circuit. By this means the rate of flow of water through the balloon can be controlled. This is particularly useful in the shift from cold to warm water, when the rate of flow should at first be slow in order not to damage the gastric mucosa.

Air-traps are included in the apparatus. This is considered essential for the smooth performance of the pump and to prevent air from getting to the balloon.

The action of the apparatus can be changed from cooling to rewarming at any moment. Accordingly:

(*a*) If, during the induction, serious cardiac arrhythmias appear, change to rewarming is possible.

(*b*) After the operation is completed, the patient can be rewarmed to 35–36°C; the blood-pressure will then rise, and any bleeding-points can be noted and ligated before the field of operation is closed.

(*c*) In cardiac operations the surgeon can perform the critical part of operation after rewarming has been begun by internal warming. The myocardium will then be colder than the blood supplying it, and will presumably get the oxygen it demands more easily than during the cooling period (Barcroft and King 1910). The heart-muscle will then probably be less irritable to touch and other surgical insults than it is where the heart is hypothermic from other techniques. Work is in progress in dogs to test the advantage of this procedure.

Hypothermia by internal cooling presents advantages, and it is hoped that the simplicity and safety of this method will lead to its being tried in other indications for hypothermia. Construction of the machine described here should be within the capacity of any good firm of engineers.

Summary

An apparatus for giving a continuous flow of cold or warm water through an intragastric balloon is described.

Two cases in which intracranial tumours were removed surgically under hypothermia by internal cooling are reported. The first patient was cooled to a rectal temperature of 29°C and the second to 32°C.

The method proved simple, easy to manage, and very effective—so much so that it was necessary to keep the intragastric balloon only half-filled to avoid too rapid cooling. Both patients had an uneventful postoperative course.

This method could be used in major neurosurgical and cardiac operations and in other indications for hypothermia.

I thank Prof. M. L. Dowidar, head of the department of surgery, Dr. B. Vlahovitch, and Dr. S. Boctor for permission and facilities to conduct this work in the department of surgery, Alexandria University; Dr. H. Nassar and Dr. W. Narshy for their help and cooperation and for conducting the anæsthesia; Prof. M. Naim for his encouragement and guidance; Mr. S. Mikhail for his valuable technical assistance; and Dr. R. C. Mac Keith for correcting the draft of the paper and for his help in many other ways.

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INFLUENCE OF LIGHT ON THE HYPERBILIRUBINÆMIA OF INFANTS

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In the first two weeks of life a raised serum-bilirubin level from any cause may lead to kernicterus. In those who have died, necropsy has shown staining by bilirubin of certain cells in the central nervous system, principally in the basal ganglia. The mechanism of this change is unknown, but there is evidence that it may be caused by an inhibitory action of excessive bilirubin on essential cellular respiratory activity.

Day (1954) showed that oxygen uptake of rat brain is significantly reduced in the presence of bilirubin 20 mg. per 100 ml., but that no such inhibition is found with biliverdin. Zetterström and Ernster (1956), working with liver mitochondria, showed that bilirubin at a concentration of 20 mg. or more per 100 ml. exerts a powerful uncoupling effect on oxidative phosphorylation. Lathe and Walker (1957) show that the livers of the newborn cannot conjugate bilirubin, which is unexcretable, to the glucuronides of bilirubin, which are excretable—the necessary enzymes being absent or deficient.

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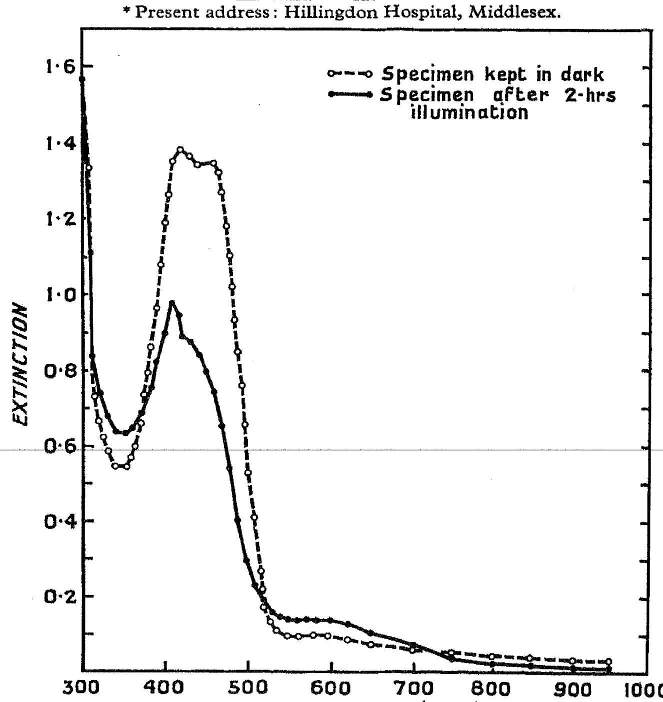

Fig. 1—Effect of light on absorption curve of icteric serum.

Mollison and Cutbush (1951) showed that the incidence of signs of kernicterus increases as the concentration of serum-bilirubin rises above 20 mg. per 100 ml., and that below this figure ill effects are rare. The prevention of a high level of serum-bilirubin, or the destruction of this substance, or its removal from the blood-stream, will prevent kernicterus. This has hitherto been achieved by replacement transfusion. Where experienced staff and good laboratory facilities exist, results are highly satisfactory (Norman 1957). However, such facilities are not universal, and an alternative approach seems desirable.

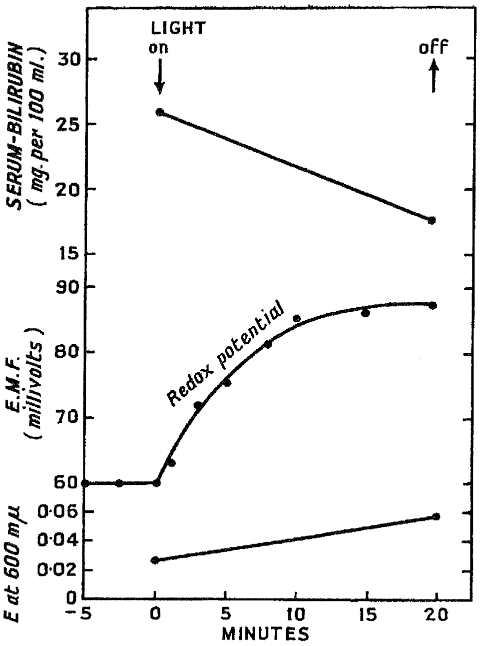

Fig. 2—Effect of light on icteric serum.

Effect of Light on Serum-bilirubin

During serial estimations of the serum-bilirubin in jaundiced infants we noticed that their serum-bilirubin is highly photosensitive in vitro (Cremer, Perryman, Richards, and Holbrook 1957). We have studied this sensitivity and tried to apply it therapeutically.

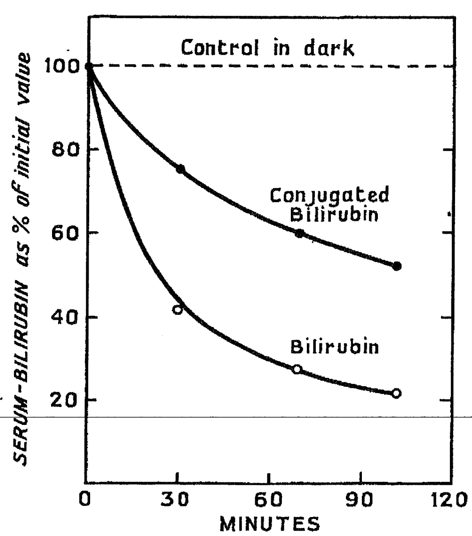

Fig. 3—Effect of sunlight on serum-bilirubin.

When icteric serum of infants is illuminated by white light, and the temperature is kept constant at 20°C, the characteristic 420 mμ absorption peak decreases and the absorption at the red end of the spectrum, around 550–650 mμ, increases a little (fig. 1). At the same time the measured serum-bilirubin level is reduced and electromotive force (E.M.F.) measurements show a positive increase in the oxidation/reduction (redox) potential of the system (fig. 2). This indicates that, under the action of light, bilirubin undergoes photo-oxidation or dehydrogenation to biliverdin or some intermediate products. These substances are more polar, and therefore probably more easily excretable, than is bilirubin.

Bilirubin (van den Bergh indirect pigment), the type of pigment greatly predominating in icteric infants, is some two or three times as photosensitive as is conjugated bilirubin (van den Bergh direct pigment) (fig. 3).

These findings emphasise the need for special precaution in laboratories doing routine bilirubin estimations on jaundiced infants. We now make a practice of enclosing all our blood-specimen tubes in light-tight containers if immediate analysis is not feasible. We have found that specimens left in bright daylight may lose as much as 30% of their serum-bilirubin in an hour.

Fig. 4 shows the distribution of the photosensitivity effect over the visible spectrum.

Clinical Applications

The subjects chosen for this study were all infants in the premature babies unit of the hospital. The sister in charge of the unit had earlier reported the apparent fading away of the yellow pigmentation in the skin of jaundiced babies when they had been a short time in sunlight. It was decided, therefore, to expose jaundiced infants to sunlight and assess the results quantitatively by serial determinations of serum-bilirubin.

Before the exposure the general trend of the serum-bilirubin level was established by the micro-method devised for this

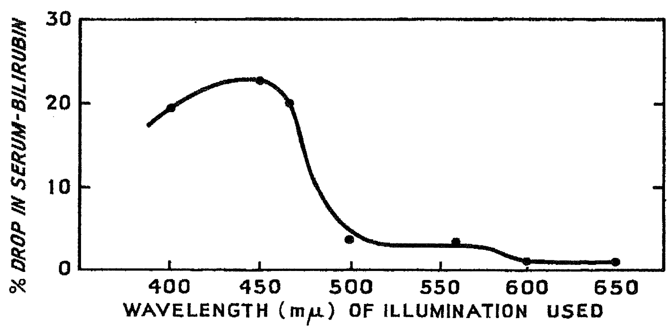

Fig. 4—Spectral distribution of the photodestruction of serum-bilirubin.

purpose (Perryman, Richards, and Holbrook 1957). To avoid overheating or excessive ultraviolet radiation, the babies were placed naked in direct sunlight for fifteen to twenty minutes (according to the sun's intensity) and then withdrawn for similar periods before again being exposed to the sunlight. During the exposure the infants' eyes were protected by a simple plastic shield.

Jaundice quickly disappeared from the exposed areas of skin but persisted in areas which remained in the shade.

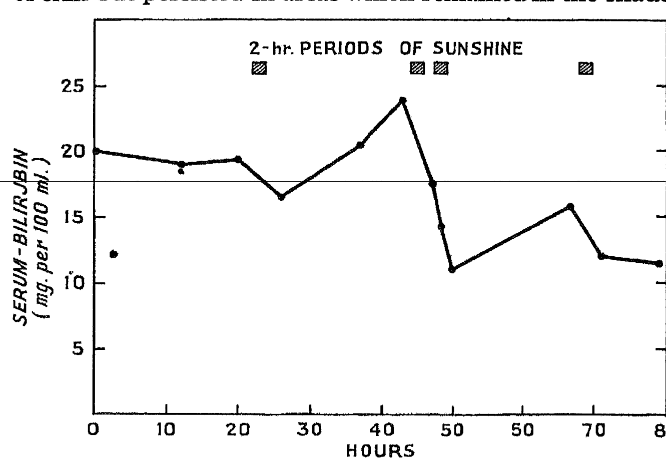

Fig. 5—Sunshine treatment of an icteric infant with jaundice of prematurity (case 6).

TABLE I—EFFECT OF SUNLIGHT ON ICTERIC INFANTS

Case no.	Birth-weight (lb.)	(oz.)	Day of life	Serum-bilirubin before treatment (mg. per 100 ml.)	Duration of exposure (hours)	Resulting decrease in serum-bilirubin (mg. per 100 ml.)
1	5	2	6	25	2	4
2	5	2	5	24	3	6
			7	16	2	4
3	4	5	5	21	2	7
4	3	4	4	20	2	6
5	8	2	5	20	4	7
6	5	0	3	24	4	12
			4	19	2	2
			5	16	2	4
7	5	9	5	19	3	4
			6	15	2	2
8	4	5	2	18	3	2
			4	16	3	2
9	3	3	5	16	2	4
10	5	3	5	19	3	4
			6	15	3	2
11	3	12	5	12	2	3
12	5	14	3	11	2	4
13	5	3	4	10	2	—2
			5	12	2	0

After this intermittent sunlight treatment, bilirubin levels were again measured.

Fig. 5 shows a typical result of this treatment. Table I records the initial level and drop in serum-bilirubin in 13 premature infants with twenty test exposures. These had the so-called "physiological jaundice" of prematurity, and in all (except case 13, where there was a rise) there was a definite drop in serum-bilirubin during the exposure. In general, we found that the higher the initial serum-bilirubin level and the longer the exposure-time, the greater the fall in serum-bilirubin.

In view of these results, we sought a source of artificial light instead of sunshine. Guided by our work on the spectral distribution of the photosensitivity (fig. 4), we examined various light sources. Finally the apparatus illustrated in fig. 6 was devised.

This consists of a hemicylindrical stainless-steel reflector suspended on a movable gantry and adjustable for height. Eight 24 in. light blue fluorescent 40-watt discharge tubes (G.E.C.), at 2 in. separation, are arranged around the curve of the reflector. The equipment is so made that a cot may be wheeled beneath the lights, and switch-gear provides that the illumination can be cut if less than the full power is desired. This equipment gives light of very high intensity in the region of 420–480 mμ without any dangerous ultraviolet or X-ray components. The height of the lamp from the infant is adjusted to make use of the small amount of radiant heat emitted for keeping the infant's body-temperature at 98–100°F.

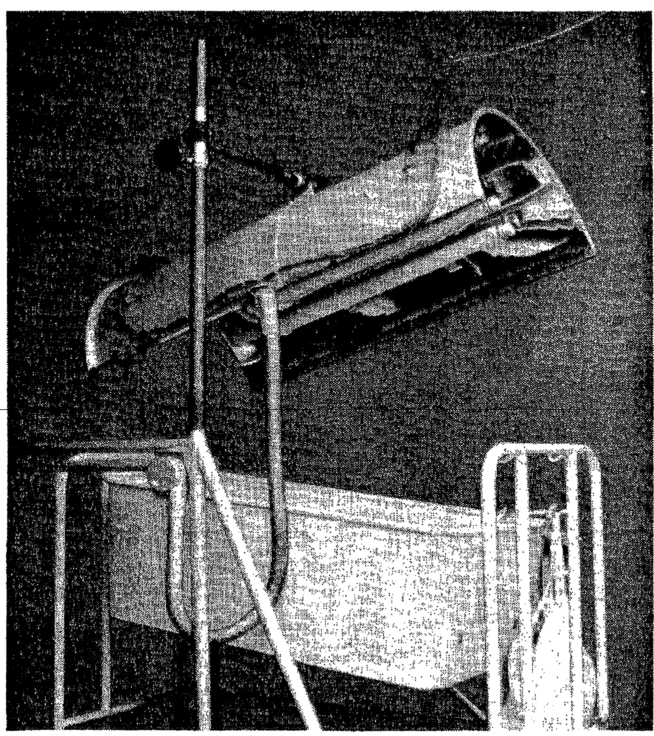

Fig. 6—Artificial-light apparatus for cradle illumination of infants.

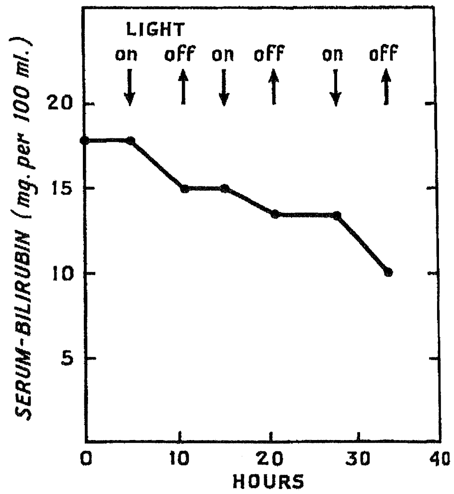

Fig. 7—Effect of artificial-light treatment on a jaundiced premature infant (case 16).

Fig. 7 shows the effect of this source of artificial light on an icteric premature infant; the coincidence of the drop in serum-bilirubin with the period of illumination is noteworthy.

TABLE II summarises the results of twelve light-exposure tests in 9 jaundiced premature infants. These all show small but significant drops in serum-bilirubin. At first continuous illumination was used, but in the light of experience a routine of six hours in the lights followed by two hours out seems to give better results. 2 infants with severe jaundice due to Rh incompatibility are not included in table II. These failed to respond to the light treatment and exchange transfusion was necessary.

TABLE II—EFFECT OF ARTIFICIAL LIGHT ON ICTERIC INFANTS

Case no.	Birth-weight (lb.)	(oz.)	Day of life	Serum-bilirubin before treatment (mg. per 100 ml.)	Duration of exposure (hours)	Resulting decrease in serum-bilirubin (mg. per 100 ml.)
14	7	1	11	22	24	8
			12	14	20	3
			13	12	20	3
15	3	12	5	18	6	3
			6	14	6	3
16	4	12	5	19	36*	8
17	6	8	1	10	12*	5
18	6	14	1	13	24*	6
19	5	0	6	15	18*	6
20	5	3	8	14	18*	4
21	5	10	5	10	12*	2
22	6	7	4	12	24*	2

* Intermittent illumination: 6 hours on, followed by 2 hours off.

Discussion

Our results so far are insufficient for a complete statistical appraisal, but they encourage further work. From our biochemical studies, it has become clear that a complex series of chemical changes is involved.

Under the action of light, bilirubin seems to be dehydrogenated, and the role of hydrogen acceptors and photocatalysts is being investigated. Several compounds accelerate the photodestruction of serum-bilirubin in vitro—e.g., methylene-blue at a concentration of 10 μg. per ml. of serum; similarly toluidine-blue and cresyl-blue, though they are less effective, and riboflavine. We suggest that the difference in degree of response to light treatment between one jaundiced infant and another and also the complete failure of some to respond may be related to lack of essential hydrogen acceptors or other factors in the circulating plasma. We have found that in the first few days of life cœruloplasmin is absent from the blood-serum, which may have a bearing on this problem.

No prospect can be entertained that this light treatment will prove a substitute for exchange transfusion in the erythroblastotic infant with active hæmolysis, but the method may be turned to clinical advantage in controlling the level of serum-bilirubin in cases of jaundice of prematurity.

Summary

In some cases of neonatal jaundice the serum-bilirubin level is reduced by sunlight or by suitable artificial-light treatment.

We should like to thank Dr. R. H. Dobbs, consultant pædiatrician to this group, for his interest and encouragement, and Prof. G. H. Lathe, of Leeds. We are indebted to the group engineering department of the Southend Hospitals for the design and manufacture of the cradle illumination machine.

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ACTION OF CITRATE AND OXALACETATE ON DIETARY AND DIABETIC KETOSIS

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THE effect of ketosis on the administration of Krebs-cycle metabolites has been extensively studied as a tentative approach to knowledge of this pathological condition. It may be assumed, in fact, that ketosis develops whenever acetyl radicals are inadequately metabolised via the Krebs cycle, owing to a deficient availability of oxalacetate. This pathogenic mechanism has also been postulated for diabetic ketosis (Thompson and King 1957); but Beatty and West (1955) did not detect any effect of the administration of succinic acid and malic acid on the ketonuria of alloxan-diabetic rats fed on Wesson oil; consequently they suggest that a deficiency of oxalacetic acid is not the cause of diabetic ketosis.

To provide further evidence on this question the action of citrate and oxalacetate on experimental dietary and diabetic ketosis has been examined.

Material

The rat and the dog were chosen for experimenting on because there is evidence that, in both species, the pathogenic mechanism of dietary ketosis (Crandall 1941, Deuel 1957) and alloxan-diabetic ketosis (Lukens 1948, Hoet and Young 1954) is essentially the same as in man. However, because of the difficulty of obtaining stable ketosis of exclusively diabetic origin in the rat (Beatty and West 1955) and dietary ketosis in the dog (Crandall 1941) each type of ketosis was investigated in only one of these animal species. Nevertheless a comparison between the results seems legitimate because, as mentioned above, the pathogenic mechanisms are essentially the same in the two species.

TABLE I—EFFECT OF CITRIC ACID AND OXALACETIC ACID ON DIETARY KETOSIS

Treatment	No. of experiments	Ketone bodies (mg. per 100 g. of body-weight in 24 hr.)
Fasted 24 hr.	8	1·0±0·5
Butyric acid	5	6·9±2·6
Butyric acid + 4·5 mM of oxalacetate	4	2·3±0·7
Butyric acid +4·5 mM of citrate	4	1·6±0·7
Butyric acid +6·0 mM of oxalacetate	4	0·6±0·3
Butyric acid +6·0 mM of citrate	4	0·7±0·4

TABLE II—TYPICAL EXAMPLE OF EFFECT OF CITRATE AND OXALACETATE ON BLOOD-SUGAR AND KETONE-BODY LEVELS OF ALLOXAN-DIABETIC DOG FASTED FOR 6 HR.

Administration of	Substance	Blood-level (mg. per 100 ml.)		
		Before administration	90 min. after administration	180 min. after administration
Citrate Na salt	Sugar	380·0	470·0	380·0
	Ketone bodies	16·7	16·5	15·0
Oxalacetate Na salt	Sugar	310	380·0	330·0
	Ketone bodies	25·3	23·3	22·3

Dietary ketosis was induced by feeding butyrate to female albino rats; the 24-hr. urinary excretion of ketone bodies was determined by the method described by Greenberg and Lester (1944) with and without administration of citrate and oxalacetate (table I). A 10% solution of butyric acid adjusted to pH 6·0 was administered in the dose of 2 ml. per 100 g. of body-weight by stomach-tube to rats fasted 15 hr. The millimols of the test substances injected intraperitoneously denote the dosage per kg. of body-weight for 24 hr. Oxalacetate was prepared according to the method described by Heidelberger (1953).

Experimental details and results are reported in table I.

Diabetic ketosis was studied in alloxan-diabetic dogs; blood-sugar and ketone-bodies levels were determined before and after intravenous injection of citrate and oxalacetate (table II). Blood-sugar levels were determined by the method described by Somogyi (1945), and ketone bodies, expressed as acetone by that of Greenberg and Lester (1944). Citrate and oxalacetate were administered intravenously in a single dose of 3 mM per kg. of body-weight. The time intervals between the administration and the determinations were chosen on the basis of Crandall's (1941) results and are reported with other experimental details and data in table II.

Results

The results show that dietary ketonuria is practically abolished by intraperitoneal injection of either citrate or oxalacetate.

Diabetic ketosis, on the other hand, is not significantly influenced either by citrate or by oxalacetate injected intravenously.

The discrepancy between the results obtained in diabetic and in dietary ketosis suggests that the pathogenic mechanisms responsible for these two conditions are fundamentally different.

Diabetic ketosis may not be attributable, as dietary ketosis is, to a deficiency of oxalacetate or of citrate but rather, according to Beatty and West (1955), to a disturbance in the Krebs cycle.

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