sulphonamide and antibiotic treatment in controlling any tendency for the attacks to recur.

Admittedly, new measures in medical practice tend in the beginning to be misused, particularly overused. We have certainly seen this with urethral instrumentation and antiseptic urinary medication. In relation to the former, I had two women patients suffering from frequency, one coming from Bagdad and the other from New York. Each had been having urethral dilatations once a week for several months.

There were two other incidents which had a bearing on the same topic. (1) A prominent American urologist recently proclaimed at an important meeting the need to disregard all instrumental urethral treatment in cystitis and frequency cases, and to rely upon the latest medication; he did not relate any experience which would justify this attitude. (2) A prominent American woman, who gave a long history of recurring incidents of urinary infection, was advised by me to have a urethral polypus fulgurated. She said she hoped she would have no antibiotics while in hospital, because she had had them all and they made her very ill.

Bacteriological Consideration

This can be a big subject, but I shall be brief.

Because the physician does not have an opportunity of seeing for himself, the misconception that chronic urinary infection is not usually dependent on a continuing focus of infection somewhere in relation to the urinary tract itself will not easily be discarded. Cystoscopy and urethroscopy have both made it clear that the urine may fail to show signs of infection, while endoscopically these are manifest—in fact, often fitting in with the symptoms. Modern therapy can produce this situation.

The return at a later date of another acute attack should warn us of any undue complacency in making a good prognosis on a sterile urine.

It is not being too dogmatic to say that there is a solid reason for certainty why attacks recur in some cases, when treatment of urethral lesions is seen to lessen this tendency.

Summary

Reasons are given for the greater frequency of cystitis in women than in men.

An explanation is offered for differences in sex incidences of vegetative posterior urethritis in children.

The lull in disturbances of micturition in adolescence and the reappearance of these in early adult life are discussed.

Various aetiological groups of ascending cystitis in the male are summarized.

Different types of urethroscopes are criticized.

Prostatic obstruction is considered.

The fundamental principle of treatment is emphasized.

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HYPERBILIRUBINAEMIA AND KERNICTERUS IN PREMATURE AND FULL-TERM BANTU NEWBORN INFANTS

BY

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Kernicterus had, until recently, been observed in association with Rh incompatibility. It was not until Zuelzer and Mudgett (1950) and Aidin *et al.* (1950) drew attention to jaundiced premature infants suffering and dying from kernicterus, in the absence of Rh or any other blood-group incompatibility, that interest increased in the circulating serum bilirubin levels in these infants. Knowledge on this subject advanced when Hsia *et al.* (1952) showed a direct relationship between elevated serum bilirubin levels and kernicterus.

Claireaux *et al.* (1953) showed that indirect bilirubin was responsible for the bile-staining of the basal nuclei of the brain. This relationship between bilirubin and kernicterus was substantiated clinically by Crigler and Najjar (1952) when they described five cases of kernicterus occurring in a family with an inherent bilirubin excretion defect in the liver. These patients had high levels of indirect serum bilirubin, and this pointed to the liver as the organ responsible for the hyperbilirubinaemia and the kernicterus.

Rh iso-immunization is rare in the Bantu, and, to our knowledge, no case of kernicterus from this cause has been described in South Africa. This paper intends to draw attention to the frequent occurrence of hyperbilirubinaemia and kernicterus in premature Bantu infants and to a less extent in full-term infants.

Material and Methods

This investigation extended over a period of eight months, when 211 consecutive cases of neonatal jaundice were observed among 5,000 deliveries. This series comprises all infants found to be jaundiced during the first 36 hours of life, regardless of intensity, as well as those who developed severe jaundice between the second and seventh days of life. Four children with Rh incompatibility were excluded from this series.

The following data were noted about each child: birth weight, time of onset of jaundice, time of maximal development of jaundice, and clinical evidence of kernicterus such as failure to feed, vomiting, lethargy, cyanotic attacks, and irregular respiration. The neurological signs noted were divergent squint, oculogyric crises, head retraction, and changes in muscle tone.

All cases in this series received, shortly after birth, 2.5 mg. of a vitamin-K analogue ("synkavit") by intramuscular injection. In addition, children treated by exchange transfusion received a daily injection of 300,000 units of procaine penicillin intramuscularly for three days. No child in this series received sulphonamides and there was no routine administration of antibiotics.

Laboratory investigations were carried out on samples of venous blood from mother and child. The maternal sample was examined for blood group, circulating haemolysins, and irregular antibodies. The blood of the infant was examined for blood group, red-cell sensitization (Coombs test), and bilirubin and haemoglobin levels. In five children bilirubin estimations were not carried out.

The haemoglobin was estimated in 150 cases as oxyhaemoglobin in a Klett-Summerson photoelectric colorimeter, and the bilirubin was determined by King's (1951) method, using 0.2–0.5 ml. of serum. In 109 of the 206 patients the serum bilirubin was fractionated into direct and indirect portions. The direct serum bilirubin levels were never above 1 mg. per 100 ml. of serum, and therefore only the total serum bilirubin was estimated in the remaining patients. For the same reason no further reference is made in this paper to "indirect bilirubin."

Results

Of the 211 patients, 148 weighed $5\frac{1}{2}$ lb. (2.5 kg.) or less at birth and were therefore classified as premature.

Time of Onset of Jaundice

The chart shows that the onset of jaundice varied with the weight of the child. Only 10% of children weighing 2–3 lb. (0.9–1.4 kg) developed jaundice within 36 hours of birth; in 26% jaundice became noticeable 36–48 hours after birth; in 31% 48–72 hours after birth; and

FIG. 1.—Relationship between four different birth-weight groups and the time of onset of jaundice in 211 newborn babies.

in 33% 72–120 hours after birth. On the other hand, in the full-term infants 60% became jaundiced within 36 hours of birth, 25% 36–48 hours after birth, 5% 48–72 hours after birth, and in 10% jaundice became apparent within 72–120 hours after birth. Those children weighing between 3 and $5\frac{1}{2}$ lb. (1.4 and 2.5 kg.) occupy an intermediate position, and developed jaundice 48–72 hours after birth.

Serum Bilirubin and Haemoglobin Levels

There was a close correlation between clinical impressions of the depth of jaundice and serum bilirubin levels. Of those who were judged to be highly jaundiced, 75% had serum bilirubin levels over 12 mg. per 100 ml. of serum.

In premature infants serum bilirubins rose to higher levels than in the infants weighing more than $5\frac{1}{2}$ lb. (2.5 kg.). Serum bilirubin levels of 206 infants are analysed in Table I. There were 107 patients with

TABLE I.—Maximum Serum Bilirubin Levels in 206 Premature and Full-term Infants

	Serum Bilirubin Levels in mg./100 ml.			
	<12.0	12.1–15.0	15.1–20	Over 20
Premature infants	27 (52%)	34 (77%)	49 (77%)	33 (69%)
Full-term "	24 (48%)	10 (23%)	14 (23%)	15 (31%)
Total	51 (100%)	44 (100%)	63 (100%)	48 (100%)

bilirubin levels between 12.1 and 20 mg. per 100 ml. of serum, of whom 83 (77%) were premature and 24 (23%) were full-term infants. Of the 48 patients with serum bilirubin levels higher than 20 mg. per 100 ml., 33 (69%) were premature infants, while only 15 (31%) were full-term babies.

High bilirubin levels are not necessarily associated with low haemoglobin levels. On the contrary, 93 of 150 patients had haemoglobin levels exceeding 15 g. per 100 ml. as well as bilirubin levels over 15 mg. per 100 ml., showing that the high serum bilirubin levels were not attributable to haemolysis alone.

Kernicterus

Kernicterus was encountered in 14 patients in this series; 12 were premature and 2 full-term. This disease was associated with physiological hyperbilirubinaemia in 12 and with ABO haemolytic disease in two patients.

Table II shows that the manifestations of kernicterus appeared on the second day of life in one case, on the fourth day in five cases, on the fifth day in four cases,

TABLE II.—Kernicterus—14 Cases

Birth Weight		Maximum Serum Bilirubin mg./100 ml.	Time of Onset of Jaundice	Result	Post-mortem	Day of Life of Onset of Symptoms
lb. oz.	g.					
2 6	1,080		12 hours	Died	+	4
3 5	1,500	35.0	48 "	Alive	—	5
3 5	1,500	21.0	32 "	Died	+	6
3 7	1,560	15.1	72 "	"	+	5
3 9	1,615	17.1	48 "	"	+	5
4 0	1,815	22.0	48 "	"	+	4
4 1	1,845	33.0	26 "	"	+	4
4 1	1,845		48 "	"	+	2
4 2	1,870	16.5	72 "	"	+	6
4 9	2,070	26.0		"	—	?
4 9	2,070			"	—	5
4 10	2,100	30.0	72 "	Alive	—	4
5 11	2,580	20.5	72 "	Died	—	4
6 12	3,060	35.0	12 "	Alive	—	6

and on the sixth day in three cases. A further patient showed signs of kernicterus on arrival in hospital, and it was not possible to ascertain exactly when symptoms began.

All the patients suffering from kernicterus had serum bilirubin levels above 15 mg. per 100 ml. In three of the smaller babies, who weighed 3 lb. 7 oz., 4 lb. 2 oz., and 3 lb. 9 oz., kernicterus appeared when the bilirubin levels reached 15.1, 16.5, and 17.1 mg. per 100 ml. respectively. The two full-term infants with kernicterus had bilirubin levels of 20.5 and 35 mg. per 100 ml. The first of these children died, and the second developed signs of kernicterus the day after exchange transfusion. At the time of writing this child was still alive but showed signs of kernicterus.

Role of Diarrhoea

Diarrhoea developed in six of the jaundiced premature babies between the second and sixth days of life. In

five of these a rapid rise in the serum bilirubin was associated with dehydration. In fact, the highest serum bilirubin observed during the course of this study—that is, 41 mg. per 100 ml.—occurred in one of these infants. The sixth child with diarrhoea died of kernicterus on the third day of life before blood studies could be carried out.

Discussion

Rh incompatibility is rare in the Bantu races of South Africa. In 1951 Shapiro showed that the incidence of Rh negativity in the Bantu races was 5.15% as compared with 15% in European races (Whitby and Britton, 1946). During this series only four babies were found to be suffering from Rh incompatibility and associated jaundice. On the other hand, 211 of 5,000 deliveries, or approximately 1 in 25 of children born at this hospital, had early or severe "physiological" jaundice. The incidence of prematurity is greater in the African than in the European (Kahn *et al.*, 1958), and, as 70% of these children with physiological hyperbilirubinaemia were premature, the problem of kernicterus of prematurity in the Bantu and its management is greater than kernicterus associated with haemolytic disease. The reverse is true for the European races (Franklin, 1958).

This survey has confirmed the marked predisposition of the premature baby to severe jaundice. The evidence strongly points to the fact that kernicterus results from very high levels of indirect bilirubin in the serum and that this pigment is toxic to nerve tissue, especially in the immature child. It is therefore not surprising that 12 of the 14 babies developing kernicterus were, prematurely born. Of the two full-term children who developed the disease, one weighed only 5 lb. 11 oz. (2,580 g.) and had an associated ABO incompatibility, while the other had an excessively high serum bilirubin level (35 mg. per 100 ml.).

The time of onset of kernicterus occurred with amazing consistency between the fourth and sixth days of life (with one exception on the second day). This agrees with the findings of Aidin *et al.* (1950), Crosse *et al.* (1955), and Meyer (1956). This critical period during which neurological complications appear corresponds with the peak levels of bilirubin in the serum (Brown and Zuelzer, 1957).

One severely jaundiced child, who died on the second day of life, showed early kernicteric staining of the basal ganglia of the brain at necropsy. This is an unusual finding, which may have its explanation in the intercurrent diarrhoea and dehydration, which in turn may have greatly concentrated the serum bilirubin in this patient.

Diarrhoea is a serious complication in a jaundiced newborn baby. In all probability the resultant dehydration concentrates the serum and the tissue bilirubin and therefore makes kernicterus a likely complication. If a newborn infant develops diarrhoea, frequent serum bilirubin estimations should be carried out, and an exchange transfusion is indicated if such levels are dangerously high.

Other factors which might predispose to the development of kernicterus are sepsis (Zimmerman and Yannet, 1933; Biemond and van Creveld, 1937) and anoxia (Claireaux, 1950; Govan and Scott, 1953). Certain agents such as sulphafurazole (sulphisoxazole, "gantrisin") (Silverman *et al.*, 1956) and large doses of vitamin-K analogue (Laurance, 1955; Bound and Telfer,

1956; Meyer and Angus 1956) have been shown to increase the serum bilirubin levels and thus to predispose to kernicterus.

So far as could be determined, sepsis, chemotherapeutic agents, and antibiotics played no part in the pathogenesis of jaundice or kernicterus in any of our cases.

The absence of any correlation between the serum bilirubin and haemoglobin levels indicates that "physiological" hyperbilirubinaemia is not purely haemolytic in origin. Furthermore, jaundice occurring within the first 36 hours of life is not necessarily due to haemolytic disease (Gellis and Hsia, 1955; Brown and Zuelzer, 1957). In fact, only 12 of the 52 patients who became jaundiced during the first 36 hours were suffering from ABO haemolytic disease. One must therefore conclude that liver dysfunction plays the major part in the production of "physiological" jaundice, and that haemoglobin estimations give no indication of the severity of the jaundice. The necessity for exchange transfusion can be gauged only by the bilirubin level, which should be determined daily, if necessary.

There is no agreement on the critical level of serum bilirubin at which exchange transfusion should be carried out. This investigation has shown that this level is inversely proportional to the weight of the infant. In three of our patients kernicterus supervened at serum bilirubin levels below 17.1 mg. per 100 ml. There are case reports in the literature of kernicterus occurring with serum bilirubin levels varying between 15 and 20 mg. per 100 ml. (Maclean *et al.*, 1955; Crosse *et al.*, 1955; Brown and Zuelzer, 1957), and in order to avoid neurological sequelae the following serum bilirubin values are suggested as indications for exchange transfusion:

15 mg./100 ml. for birth weight of	3-3½ lb. (1.4-1.6 kg.)
16 mg. " " " " " "	3½-4½ lb. (1.6-2.1 kg.)
18 mg. " " " " " "	4½-5½ lb. (2.1-2.5 kg.)
20 mg. " " " " " "	5½ lb. + (2.5 kg. +)

A relapse of intense jaundice may follow blood exchange and may necessitate repeating the procedure (Brown *et al.*, 1957). It is therefore necessary to continue daily serum bilirubin estimations after treatment, until it is certain that the levels remain below the above-mentioned values.

Billing and Lathe (1956) and Schmid (1956) showed that insoluble indirect bilirubin is converted by the liver to soluble direct bilirubin by conjugation with glucuronic acid. This knowledge has led to the use of glucuronic acid in the jaundiced premature infant by Danoff *et al.* (1958), who succeeded in causing a fall in the serum bilirubin levels in a number of cases. This therapy, if successful, would be a more rational approach to the prevention of kernicterus than blood exchange.

Summary

In a series of 211 consecutive Bantu newborn infants with early or marked jaundice, 70% (148) were premature. "Physiological" hyperbilirubinaemia was the most common finding (90% of cases), then ABO haemolytic disease, and in only four cases (excluded from this series) was Rh iso-immunization the cause of the jaundice.

It was shown that the onset of jaundice is related to the birth weight and that it occurs earlier in the full-term infant and later in the premature infant.

Kernicterus was observed in 14 patients, of whom 12 were premature infants. It occurred between the fourth

and sixth days of life and coincided with the peak bilirubin levels in the serum.

Diarrhoea may aggravate the jaundice.

There is no correlation between serum bilirubin and haemoglobin levels, and this suggests that "physiological" hyperbilirubinaemia is not attributable to haemolysis alone. This series provides confirmatory evidence that jaundice occurring during the first 36 hours of life is not necessarily haemolytic in origin. Hepatic immaturity and dysfunction are major factors in the production of high circulating levels of "indirect" serum bilirubin.

It is shown that serum bilirubin levels can be used as an indication for exchange transfusion only if taken in conjunction with the birth weight. A recurrence of hyperbilirubinaemia may occur after blood exchange. This "rebound" phenomenon may necessitate repeat exchange transfusions.

We thank Dr. I. Frack, superintendent of Baragwanath Hospital, for permission to publish this paper, and Drs. D. Lavery and W. Evans, of the obstetrics department, for referring the patients to us. We are indebted to Dr. R. Cassel, Dr. J. Metz, and their laboratory staff for the biochemical investigations; to the registrars of the paediatric department for technical assistance; to Dr. I. Simson for performing the necropsies; and to Dr. M. Shapiro and Dr. B. Ellis, of the South African Blood Transfusion Service, for carrying out the exchange transfusions, the blood grouping, and the serology. Last, but by no means least, we thank Dr. E. Kahn, senior paediatrician, for his encouragement, help, and criticism in the preparation of this paper.

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Infrared Absorption Spectra of Steroids: An Atlas, Volume II, by G. Roberts, B. S. Gallagher, and R. N. Jones, contains 98 pages of text matter and 452 charts of absorption spectra. Volume I (1953) dealt with 308 steroids, and the indexes included in Volume II cover both volumes. The book is published by Interscience Publishers Ltd., New York and London, price \$20.

PERIPHERAL EFFECTS OF "VASCULIT"

BY

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The search for an answer to the problem of degenerative arterial diseases has in recent years produced a bewildering variety of drugs with more or less of a vasodilator activity. Unfortunately, only a small proportion are found to have any clinical application, for, despite extensive animal studies, most are issued with insufficient appraisal of their effect on the human beings for whom they are intended. It is of considerable interest that slight alterations in the structure of substances chemically and pharmacologically related to noradrenaline may lead to a reversal of the vasoconstrictor effect. One of these, the butyl derivative of the para-oxy homologue of phenylephrine, was synthesized in the Boehringer Laboratories before the war, and has been used in Germany under the trade name of "vasculat" ("vasculit" in U.K.) in the treatment of peripheral ischaemic disorders (Becker and Kaiser, 1951; Beiglböck and Odenthal, 1954). The following is a report of some studies of the vascular effects of intra-arterial vasculit in a group of hospital patients of various ages and conditions.

Subjects and Methods

Patients of both sexes between the ages of 24 and 67 were studied during their convalescence from acute and chronic respiratory infections, pneumonia, or peptic ulcer, and one subject was suffering from malignant hypertension. None of them had clinical evidence of ischaemic disturbances of the extremities. Throughout each experiment the blood flow in both hands was measured plethysmographically under controlled conditions, while a continuous saline (0.9% w.v. NaCl) solution was infused into the right brachial artery (Duff, 1952). At regular intervals known amounts of the laevorotatory isomers of adrenaline and noradrenaline, and of vasculit, separately or in combination, were added to one of the infusion syringes for periods of four or six minutes. From the differences in blood flow between the two hands, the effect of each dose (of drug or hormone) on the volume of blood flowing through the infused right hand was calculated by a method that made due allowance for incidental fluctuations unrelated to the infusion (Ginsburg and Duff, 1956). The results provide a quantitative estimate of the net effect of each on the vascular bed (the hand) supplied by the right brachial artery.

The general procedure was to give a series of separate infusions of one or more doses of adrenaline and noradrenaline (0.125 µg./min. and 0.5 µg./min. for four minutes), each preceded by a saline control period of at least four minutes. Then vasculit was given during a four- or six-minute period, after the completion of which the adrenaline and noradrenaline infusions were repeated. In another series vasculit was instead given *along with* the second adrenaline and noradrenaline infusions. To begin with, pilot experiments were done to find a suitable concentration