could not be criticized on any ground, and in addition received 2 c.cm. of liver extract every other week.

A possible interpretation of these findings is that the riboflavin requirements of certain individuals are unusually great, as the result either of abnormal utilization or of defective absorption, or both. The idea that synergistic reactions in respect of other vitamins condition the absorption and utilization of riboflavin must be taken into account in evaluating this possibility. Although the results of the present investigation may be taken to indicate the existence of at least two types of circumcorneal injection, only one of which is resolved by riboflavin therapy, an alternative interpretation would appear to be that the development of circumcorneal injection is conditioned by a number of limiting factors, only one of which is a relative deficiency of riboflavin in the diet. In the latter connexion it is of interest to recall the findings of Albanese and Buschke (1942), who observed the clinical manifestations of ariboflavinosis in rats occurring as the result of a lack of tryptophan in their diet. A relationship between the metabolism of protein and another vitamin of the B complex is indicated by the work of Banerji (1941), who found that the presence of a large amount of protein in the diet of rats prevented the bradycardia and loss of weight usually associated with thiamin deficiency, and also that the growth rates of rats on various graded levels of vitamin B₁ were better in each case with excess of protein than without it.

Summary and Conclusions

In a series of 204 unselected out-patients between the ages of 12 and 69 circumcorneal injection was observed in 70 cases (34.3%). In 63 of those aged 50 or over circumcorneal injection was found in 43 (68%).

The observations of Sydenstricker *et al.* on the occurrence of circumcorneal injection in ariboflavinosis have been confirmed, but a form of the condition exists even in subjects presenting evidence of frank vitamin deficiency disease which cannot be attributed to a deficiency of riboflavin, as it is not resolved by administration of the vitamin. The latter finding no doubt accounts for the relatively high incidence of circumcorneal injection observed.

Although circumcorneal injection may be an early stigma of ariboflavinosis it cannot be considered such unless supported by other clinical findings—cheilosis, glossitis, dermatosis, and ocular symptoms—or by slit-lamp examination of the cornea (Sydenstricker *et al.*). The result of a therapeutic test, however, probably still remains the best criterion.

Three cases of ariboflavinosis are described, and it is suggested that certain subjects manifest a requirement for riboflavin which, for reasons unknown, is unusually large.

ADDENDUM.—Since completing this paper we have had the opportunity of discussing the matter with Dr. Sydenstricker, who has seen with us several cases of ariboflavinosis confirmed by slit-lamp microscopy. It is evident that the circumcorneal injection which forms the basis of this communication differs in no material way, on purely clinical examination, from that described by Sydenstricker in frank ariboflavinosis.

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DOCTORS FROM OVER-SEAS: HOSPITALITY AT L.C.C. HOSPITALS

The London County Council is offering hospitality at its hospitals to Service doctors and nurses from the U.S.A., Canada, Australia, New Zealand, South Africa, etc. Details of the arrangements have been sent to the various authorities concerned. There may be, however, doctors and nurses who will not hear about it through official channels, and also there may be some from the countries mentioned who are serving with the British Forces. Any such who would like to visit L.C.C. hospitals or stay there during short leave should get into touch with the Medical Officer of Health, London County Council, County Hall, S.E.1 (telephone WATerloo 5000, extension 6425).

SULPHONAMIDES USED LOCALLY THEIR ABSORPTION FROM SEROUS CAVITIES AND WOUNDS IN MAN

BY

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The sulphonamides are the most satisfactory of the drugs at present available for use in preventing the development of infection in contaminated wounds. There is evidence to show that they are more effective when used locally in the wound than when they are given by mouth or parenterally, owing to the greater concentration at the site of potential infection. The local effects of these compounds depend on their individual bacteriostatic powers and their physical properties. To be of benefit the selected drug or mixture of drugs should be present in the wound fluids in sufficient concentration and for long enough for the infection to be wiped out or for the normal tissue reactions to obtain control of the situation. The rate of absorption of sulphonamides from wounds is therefore of importance, and the present study was undertaken to investigate this problem. As the work was interrupted by the change of appointment of one of the authors the results presented are unfortunately incomplete.

Methods.—Observations were made on patients undergoing operations, many of which were abdominal. Before the peritoneum was closed the sulphonamide was introduced in measured quantities. Powders were sprinkled or dumped into the cavity out of a small container and spread with the finger. Solutions and suspensions were inserted through a catheter, around which the peritoneum had been almost closed; in this way little or none of the drug was lost. The subsequent absorption was followed by taking blood samples at 6, 24, and 48 hours and by measuring the excretion in the urine.

Results

The results in 25 cases are shown in the accompanying table. These include 8 cases observed by Prof. R. S. Pilcher. Nearly 60 other cases were observed clinically, but they have been omitted from this table as the records are incomplete in some particular or other. The first group consists of 11 patients who received 5 g. of sulphanilamide powder. This group comprised 6 abdominal operations, 3 thoracoplasties (2 on children), 1 nephrectomy, and 1 wound of the forearm. The blood and urine figures varied somewhat irregularly, without particular reference to the nature of the operation; for conciseness they are given as an average. Three other cases received 7.5 to 10 g. and a fourth case 15 g., and the concentrations in the blood and urine were somewhat higher. It is seen that when 5 to 10 g. of sulphanilamide is placed in the peritoneal cavity most of the urinary excretion occurs during the first two days. An effective blood concentration was maintained for 24 hours, the maximum reading (at 6 hours) corresponding in this series to about 0.5 to 1 mg. per 100 c.cm. for each gramme of sulphanilamide inserted.

Three patients received 5 to 7.5 g. of "hypoloid sulphanilamide L.S.F." intraperitoneally. This is a Burroughs Wellcome preparation consisting of 15% sulphanilamide in solution as sulphanilamide lactoside sodium formaldehyde sulphoxylate, and it is intended for intramuscular injection. As seen from the table, most of the urinary excretion occurs during the first twelve hours, and probably bacteriostatic activity in the peritoneum is too brief for the optimum results to be obtained.

In 2 cases a wound was packed with gauze and an oil-in-water emulsion, Preparation C, made by the British Drug Houses Ltd. (sulphanilamide 30, beeswax 0.7, cod-liver oil 49, oleic acid 3.6, sodium hydroxide 0.5, water to 100 parts—Fuller, Hawking, and Partridge, 1942). In animals it has been

found that the presence of the oil delays absorption, provided that the surface is small compared with the volume, as in the present instance. In these two cases the results are rather irregular, but after 5 to 6 days the dressing still contained considerable quantities of sulphanilamide. In a third case a small deep wound was packed with gauze plus a preparation consisting of sulphanilamide 30%, cod-liver oil 60%, and beeswax 10%, about 4 g. of sulphanilamide being inserted; the blood concentration at 24 hours was free 1.1, total 1.7 mg. per 100 c.cm., and during the next 5 days the daily excretion of sulphanilamide in the urine was about 0.2 to 0.4 g.; when the dressing was removed on the fifth day it contained about 0.2 g. of the compound. It should be noted that further histological study of experimental wounds has led us to the conclusion that all types of oil which may become embedded in a wound lead to undesirable tissue reactions and that cod-liver oil is particularly deleterious in this respect (Hawking, 1942).

Six patients received sulphadiazine inserted as a micro-crystalline suspension (Chambers *et al.*, 1942), and the results with 4 of them are shown in the table. The blood concentrations in these cases were high, but the urinary excretion was less prolonged than animal experiments had led us to expect. The effect of this treatment on the clinical condition seemed to be good, allowing for the grave nature of these cases. Two

pyridine administered prophylactically by mouth from the time of operation onwards. As regards abdominal operations, the cases recorded in the table showed uniformly satisfactory results so far as concerned the prevention of local infection, in spite of the fact that in many instances the peritoneum was heavily soiled. In one case a peptic ulcer re-perforated 4 days after the original operation for closure of the opening, and a second closure combined with gastro-enterostomy had to be done, yet no peritonitis developed. In other cases existing infection was suppressed. An appendix abscess was evacuated and packed with about 15 g. of sulphanilamide powder; a corrugated rubber drain was inserted and removed 24 hours later; the wound then healed by first intention. Ten weeks later the appendix was removed. No trace of the powder remained, the only sign of the abscess being a few light adhesions.

(B) *General Toxic Effects*.—The quantity of drug inserted rarely exceeded 10 g., and no general toxic effects of any significance were observed. The method is considered perfectly safe. If systemic administration was combined with local insertion, due allowance was made for the amount which had been inserted.

(C) *Local Effects other than Counteracting Infection*.—In muscle and fascial layers the sulphonamides appear to delay healing by their chemical effects on cell-proliferation and by

Table showing Amount of Various Sulphonamide Compounds in Urine and Blood following Insertion into Abdominal or Other Wounds

Preparation and Dose	Daily Excretion in Urine (g.)					Total Excretion (g.)	Concentration in Blood, free/total (mg. per 100 c.cm.)			Remarks
	1st	2nd	3rd	4th	5th		6 hrs.	24 hrs.	48 hrs.	
Sulphanilamide:										
5 g.	1.08	1.10	0.35	0.21	0.02	2.5	3.2/4.2	2.7/3.8	1.0/1.5	Av. of 11 miscellaneous cases Av. of 3 cases (thoracoplasty, thoracotomy, gastrectomy) Excision of loop of colon
7.5-10 g.	2.0	2.7	0.85	0.48	—	6.0	6.3/8.1	4.2/6.4	1.2/2.2	
15 g.	anuria	0.76	0.90	0.76	0.26+	2.7+	—	12/13	2.3/3.8	Av. of 3 cases (perforated D.U. (2), appendice tomy)
Sulphanilamide L.S.F. 5-7.5 g.	($\frac{1}{2}$) 2.0	1 $\frac{1}{2}$ 0.8 0.4 0.6	2 0	3 days)	—	3.3	1.5/1.9	0.5/1.0	—	
Preparation C:							(12 hrs.)			
9 g. sulph.	1.0	0.84	0.04	0.09	0	2.0	2.4/3.7	1.4/2.4	0.0.7	Wound of thigh. After 6 days 1.5 g. sulph. remained Excision of rectum. After 5 days 19 g. sulph. remained
30 g. sulph.	1.48	0.31	—	—	—	1.8+	2.3/3.1	8.1/9.5	2.3/2.9	
Sulphadiazine:										
3.7 g.	0.09	3.1	0.38	0.12	0.27	3.9	10/10.5	8.1/9.7	2.3/2.3	Perforated D.U. No drug excreted during 6th to 10th days Perforated D.U. 72 hours Perforated D.U. Died 8th day. Blood conc. at 72 hours, 2.6/3.8 mg. Pelvic peritonitis. Blood conc. at 72 hours, 0.6/0.7 mg.
3.4 g.	—	1.5	0.72	0.24	—	2.4	7.5/9.0	2.4/3.3	1.4/1.3	
4.0 g.	anuria	0.96	0.87	—	—	—	—	7.2/18	5.0/5.8	
4.8 g.	2.8+	0.71	0.30	0.07	0.07	4.0+	—	2.9/4.2	2.2/2.6	
Sulphathiazole:										
5 g.	0.44	0.68	0.36	0.08	0.02	1.7	(18 hrs.) 1.9/3.0	—	—	Nephrectomy with drainage, 0.5 g. escaped on to dressing Resection, carcinoma of colon. Drained
5 g.	anuria	2.6	trace	trace	—	2.6	(12 hrs.) 1.0/1.0	0.0	0.0	

of the patients died, on the eighth and tenth days respectively, and small cakes of solid sulphadiazine were found in the rectovesical fossa, surrounded by adhesions and lymph; histologically, there was little evidence of irritation specifically due to these lumps. It is concluded that the absorption of sulphadiazine is incomplete and that it is not the best compound for intraperitoneal use. Further investigations were planned but could not be carried out.

Clinical Conclusions

In only a few cases was it possible to estimate the absorption and excretion of sulphonamides with accuracy, but clinical conclusions have been based on a series of more than 60 cases, many of which were air-raid casualties.

(A) *Local compared with General Administration*.—Local administration was found beneficial in every case. In 20 severe cases of lacerated wounds, including many multiple dirty bomb wounds, no case of gas gangrene or spreading wound infection developed. On the other hand, a clean through-and-through bomb wound of the leg, not involving bone, developed a virulent gas-gangrene infection two days after operation in spite of radical surgical excision, with drainage, and full doses of sulpha-

their presence as foreign material. Their use should be reserved for contaminated or potentially contaminated wounds. Serous cavities showed no surface reactions of an inflammatory nature. As noted above, caked sulphadiazine was walled off by adhesions and a deposit of lymph, and it is considered that it was too insoluble to be entirely suitable. By packing sulphanilamide at one end of a nephrectomy wound and placing a tubular cigarette drain at the other, it was shown that the drug diffused throughout both the wound and the drain within 48 hours. This observation indicates that although most careful distribution over the whole wound is desirable, sulphanilamide will spread beyond the exact area into which it has been introduced.

Discussion

Many papers dealing with the intraperitoneal application of sulphonamides have now been published, the majority by American authors. Besides the workers mentioned in a recent review (*Lancet*, 1942, 1, 235), experiments with animals have been described by Schmidt *et al.* (1941); Stevens, Taliaferro, and Haag (1941); Rosenburg and Wall (1941); Epps, Ley, and Howard (1942); Harvey, Meloney, and Rennie (1942); and Pearl and Rickles (1942). Some of these authors described

results in human patients. Clinical observations have also been described by Burford and Graham (1941), Kinney (1941), Anderson (1942), and Hudson and Smith (1942). Ryan, Bauman, and Mulholland (1942) inserted sulphadiazine intraperitoneally during 6 operations, with satisfactory results.

Harild (1942), working with the Finnish Army, reports the intraperitoneal insertion of sulphathiazole into 8 cases of abdominal wounds, and recommends further trial. A detailed discussion during a meeting of American surgeons is given by Mueller and Thompson (1942), and Jackson and Collier (1942). General opinion is in favour of using sulphanilamide in doses of 5 to 10 g. per patient, in cases in which the peritoneum has been contaminated by bacteria; the suitability of sulphathiazole for this purpose is still under consideration. Several writers have stated that the insertion of sulphanilamide into clean wounds of the abdominal wall may cause sero-sanguineous effusions and therefore its application at this site should be restricted to infected cases. The researches described in the present paper were designed to compare the suitability of the various sulphonamide compounds for this purpose and to amplify results obtained in animal experiments (Fuller, Hawking, and Partridge, 1942). Although they are incomplete they support the use of these compounds in cases in which contamination of the peritoneal cavity has occurred. Sulphadiazine appears to be too slowly absorbed, and "hypoloid sulphanilamide L.S.F." to be too rapidly absorbed, for the optimal results to be obtained. A mixture of sulphanilamide and sulphathiazole might be the most satisfactory preparation.

Before leaving the subject, however, it is necessary to draw attention to the need for sterilizing compounds before their insertion into wounds: this has been emphasized by the recent case of tetanus which followed the intra-abdominal insertion of sulphapyridine during an abdominal operation (*Journal*, 1942, 2, 134).

Summary

Sulphonamide compounds were placed in all types of wounds, including the peritoneal cavities of patients undergoing certain abdominal operations. The absorption was studied by estimating the subsequent concentrations in the blood and urine. The effects of this treatment seemed beneficial.

When sulphanilamide powder (5 to 10 g.) was inserted most of the absorption and excretion occurred in the first two days. When "hypoloid sulphanilamide L.S.F." (5 to 7.5 g.) was inserted most of the excretion occurred in the first 12 hours; when microcrystalline sulphadiazine was inserted some of it was still present in the peritoneal cavity 8 to 10 days later. It is considered that the absorption of "hypoloid sulphanilamide L.S.F." from the peritoneal cavity is too rapid, and that of sulphadiazine too slow, for the optimal therapeutic effect to be obtained.

We express our thanks to Prof. R. S. Pilcher for allowing us to make use of his 8 cases; and to many members of the junior surgical staff and of the nursing staff of St. Bartholomew's Hospital for their assistance at the operations and in the collection of the specimens of blood and urine.

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A red pigment described as actinomycin A has been isolated in a pure crystalline organism, *Actinomyces antibioticus* (S. A. Waksman and M. Tishler, *J. biol. Chem.*, 1942, **142**, 519). Actinomycin is actively bacteriostatic and bactericidal in concentrations of 1 in 1,000,000 against certain Gram-positive bacteria. It is highly toxic to animals.

SPONTANEOUS ANNULAR DETACHMENT OF THE CERVIX DURING LABOUR

BY

M. DAVIES WESTERMAN, M.R.C.S.

This accident appears to be a rare complication of labour. DeCosta (1933) reported that there were only 32 recorded cases between 1820 and 1933, and the spontaneous nature of some of these was debatable. The following case can, however, be definitely included under the title given above. The last case published in the *Journal* was by Burt-White (1938).

Case History

The patient, a primipara aged 27, was a short, fat, flabby Jewess of excitable temperament who had attended the antenatal clinic regularly. She was always "full of woe," with multiple complaints but no abnormal physical signs, apart from oral sepsis. On routine vaginal examination (July 8, 1941) she was found to have a flat type of pelvis. The sacral promontory was felt. The foetal head remained high as she approached term, and she was booked for a trial labour in Shardeloes Emergency Maternity Hospital, Amersham. The expected date of delivery was Feb. 10, 1942.

First Stage of Labour.—The patient was admitted to hospital on Feb. 25, complaining of generalized abdominal pains and diarrhoea for 24 hours; there were no signs of labour having started. The head was two-thirds above the brim and freely movable; presentation V.R.O.P. The blood pressure was 150/100. At 10.15 p.m. on Feb. 26 her membranes ruptured, and she began having short pains every 5 to 10 minutes. After 10 hours the head was in the pelvis, and on vaginal examination the cervix was two-fingers dilated. The first stage continued normally, apart from difficulties arising out of her very unco-operative behaviour, until the evening of Feb. 27, when the pulse rate began to rise gradually from 88 to 110. Morphine 1/4 grain was given, and despite a good night the pulse had risen to 130 by the morning of the 28th. This rate was maintained till after delivery. The rhythm was always regular and the volume good, except for a short period (3 to 8 minutes) during the afternoon of the 28th, when it became irregular and thready. No cause for this rise could be found. Her general condition was good, and she was more co-operative. She was having fair pains every 5 to 10 minutes. There was no bleeding, the head was deeply engaged, and the uterus was relaxing well. The following treatment was given during the first stage:

- Feb. 26: Routine ol. ric.; bath; enema.
 Feb. 27: 2.45 a.m., morphine gr. 1/4; 2 p.m., syrup. chloral gr. 30, pot. brom. gr. 30, tinct. opii m. 20; 11 p.m., catheterized, morphine gr. 1/4.
 Feb. 28: 2 p.m., enema, pot. brom. and chloral gr. 30 aa.

Second Stage.—At 5.30 p.m. on Feb. 28 the patient began to "bear down," and the head appeared at the vulva. She was transferred to the labour ward, having poor pains at 15-minute intervals. The head did not appear again until 6.30 p.m., and showed no advance by 7.30 p.m. The general condition was good; the pulse rate was still 130 and of good volume. The foetal heart rate was 132. It was decided to terminate with forceps. She was anaesthetized with gas-and-oxygen and ether. The head was found well down, arrested in the transverse diameter. There was a small caput. The head was rotated; during this manoeuvre a loose band of oedematous tissue was felt between the head and the sacrum. On further investigation this proved to be the prolapsed anterior cervical lip; the cervix having sloughed round the anterior two-thirds of its circumference, the head was presenting through the "rent." There were multiple loops of cord round the child's neck, which were pulsating slowly. As the "vital" part of the cervix had already separated, only the posterior third being left attached, it was considered that the danger of haemorrhage from the uterine arteries, and tearing into the vaginal vaults, was now over. Forceps were therefore applied to the head, through the rent, above the ring of detached cervix. The 8-lb. baby was easily delivered, but unfortunately it was stillborn. The cervix was delivered in front of the head, the posterior third evidently tearing off when traction was applied to the head.

Third Stage.—The placenta was expressed in 10 minutes. At no time during labour or delivery was there any abnormal or excessive bleeding. A careful examination was made both by hand and with the speculum, and a small tear in the left vaginal vault was sutured with No. 3 catgut. After delivery the patient was suffering from shock; her pulse was thready—rate 140—but the blood pressure was 110/80. She responded well to ordinary restorative measures.