10 µg.) in the standard solution, and r_1 and r_2 the volume in ml. of the extract before and after the preliminary washing with isobutanol, then the aneurin content of the urine is

$$\frac{xv}{10} \times \frac{r_2}{r_1} \times \frac{1}{U} \text{ µg. per ml.}$$

$$\left(= \frac{4v}{10} \times \frac{r_2}{r_1}, \text{ when, as in usual circumstances, } x=4 \text{ and } U=1 \right).$$

5. *Interpretation of Results.*—Past work has shown that a normal adult male* subject receiving not less than the reputed requirement of vitamin B₁ (300 I.U.=900 µg. of aneurin daily) excretes at least 90 µg. of aneurin daily (Wang and Harris, 1939). The excretion rises with each increase in the intake, rapidly adjusting itself to such changes. On a diet deficient in the vitamin the excretion quickly falls to a steady value of about 60 to 90 µg., where it is maintained for some time (Wang and Yudkin, 1940).

On the basis of observations such as the foregoing, nutritional status may be assessed by measurement of the "resting level of excretion" plus the response to daily test doses. A "resting" excretion of below 90 µg. combined with one or more days' delay before attainment of the plateau of excretion after the daily standard test doses (350 I.U.) can be assumed to indicate an insufficient intake. For further discussion of standards for excretion tests earlier papers from this laboratory may be consulted (e.g., Wang and Harris, 1939; Wang and Yudkin, 1940).

It is perhaps worthy of note that the differentiation between normal and deficient subjects by means of their urinary response is less steeply graded for vitamin B₁ than, for example, for vitamin C, and this means that saturation tests are somewhat easier for the latter than for the former. Thus, special emphasis has to be laid on the fact that the excretion of aneurin is relatively "labile," adjusting itself fairly rapidly to each change in the intake, as mentioned above. As a result, the "resting level" of excretion may sometimes do little more than reflect the intake during the few days immediately preceding the collection of the urine. With test doses the deficient subject satisfactorily answers to the test by giving less response than the normal subject on at least the first day, or first and second days, of test dosing; yet after a further day or so both deficient and normal will have reached an equal degree of excretion. (With extreme deficiency of long standing the response to test doses may be delayed a little further.) But for vitamin C, in contrast, the deficient subject may give little or no response at all to test doses for a period of some days, and full saturation will not be finally reached (in developed scurvy) until 7 to 10 days: thus the difference between normal and deficient is made more dramatically apparent than for vitamin B₁.

6. *Collection of Urine.*—If the urine is not to be tested within an hour or two of its being passed it can be preserved by the addition of a few ml. of glacial acetic acid (or HCl) and toluene.

7. *Avoidance of Certain Drugs.*—It is important that the patient should not take aspirin, quinine, or related drugs for some hours before or during the time of the test, since these may cause the excretion of highly fluorescent substances in the urine and so make an accurate determination of thiochrome impossible.

Summary

Working directions are given for the method of estimating vitamin B₁ in urine in the test for nutritional status, various improvements in technique being incorporated.

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* The minimal level of excretion by females may possibly be slightly lower (cf. Toverud, 1940; Robinson *et al.*, 1940). Precise figures for children, and the more detailed standards for varying intermediate degrees of deficiency, such as have now been worked out for vitamin C (Harris, 1943), still remain to be filled in.

LOCAL ORAL MEDICATION WITH SULPHANILAMIDE IN LOZENGE FORM*

BY

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The local application of sulphonamides has been the subject of much interest lately, and this method of treating oral lesions is attracting attention, though a report on the use of sulph-anilamide following dental extractions was noted several years back in the *Journal of the Canadian Dental Association*. That the oral cavity may be a valuable site for absorption of drugs, and particularly in the case of oral lesions, should not cause much surprise. The rich vascular bed of the buccal mucosa is readily available, as witness the immediate relief of substernal pain in angina pectoris after the use of a tablet of nitro-glycerin sublingually. Intranasal application of drugs also has its advocates. Cattell (1943) points out "that no outstanding new discoveries in the field of sulphonamide therapy have occurred during the past year, but that, on the other hand, the period has been one of continual progress in the application of the sulphonamides."

It was a search for a suitable means of local oral application and absorption of the drug that prompted me, with the advent of sulphanilamide in 1937, to use it in a vehicle that would permit its slow release in the oral cavity and by direct contact promote local healing and defence against such organisms as are inhibited or destroyed by it. Then, as now, the mode of action of the drug cannot be regarded as fully settled, but justification for its application need not await complete elucidation of a *modus operandi*. The present report is based on the results of the direct application of sulphanilamide in a lozenge specifically for the purpose of testing its efficacy in cases of acute follicular tonsillitis, the aetiological agent being *Str. haemolyticus*, common at Fort Francis E. Warren, and the subject of much concern to all.

The manner of sulphanilamide administration as practised to-day calls for large doses of the drug—some 7 to 9 g. daily—for therapeutic effect upon a small area on the tonsils or adjacent pharyngeal wall. Other tissues resent playing host to the drug by producing an added lesion at times more deadly than the original condition. Stated in other words, an attempt was made to reverse the order of mass saturation preceding local therapeutics by a maximal local effect with a minimal blood concentration of the drug.

The vehicles used at the time were chicle (chewing gum) and lozenge. The lozenge proved the more satisfactory means. It could be held in the mouth for a period up to 45 minutes, was palatable, and liberation of the drug was slow and uniform. Several lozenges could be used daily, and no disturbing chewing manipulations were required. It was satisfactory both for children and for adults. A lozenge weighing 2 g. and containing 0.065 g. of sulphanilamide proved best suited for the treatment. Observations made at the time on mucosal staining, using prontosil and methylene blue in chicle and chocolate, agree with those of Arnett (1943).

The present study is a resumption of the above, though on a much larger scale and under better-controlled conditions. It is intended as a preliminary report, for it would have been more satisfactory had the work been carried through the entire winter season. The incidence of upper respiratory infection is as high during March as in any of the preceding months, and it is felt that enough clinical data have been obtained to warrant further investigation at a future date.

The increase in upper respiratory infections is an accompaniment of the expanding army. For the time being, fortunately, the diseases are mild, though at times of epidemic proportions. Nevertheless, they incapacitate fairly large numbers of new arrivals during their basic training period. This is inevitable owing to the close contact of the men, hence the rapid passage of infection from one individual to another. The problem

* This study was made possible through the assistance and co-operation of Col. D. W. McEnery, post surgeon, Fort Francis E. Warren, Wyoming.

is keenly recognized as an acute one, and attempts at control were in formation (*Army Medical Bulletin*, 1942) even preceding mobilization.

Therapeutics

Patients sent to the main hospital received lozenges, those to the Station Hospital Annexe had routine therapy consisting of aspirin, codeine, fluids, and gargles. Ward records of both institutions were compared. At the main hospital, for purposes of this study, any non-follicular red throat was regarded as influenza. It is impossible consistently to separate influenza from non-follicular tonsillitis. Acute tonsillitis, as defined by Cecil (1941), "is an acute inflammation of the palatine or faucial tonsils, but in nearly all cases the other lymphatic tissues in this region are involved. The tonsils are increased in size and hyperaemic. Many cheesy spots project from the crypts. A false membranous exudate may be present in other cases and a similar picture present in adjacent lymphoid tissue." This is the type of tonsillitis that is so common in this region. Throat culture of 24 cases on admission showed 22 to be positive for *Str. haemolyticus*.

Each patient was given eight lozenges to take—one each hour between 8 and 11 a.m., one at 4 p.m., two after the evening meal, and the last just before bedtime. The last dose is considered important, as the residual sulphanilamide during sleep is less subject to removal than at any other time. Fluids and food were forbidden between meals, as they would wash out the sulphanilamide present in the saliva and adherent to the tonsils and pharyngeal mucosa. The patient was encouraged to take fluids at meal-times. When the morning temperature reached normal, even though the previous evening temperature was 99°, and if the patient felt well, he was sent to quarters with a two-day supply of lozenges—six daily—and was given light duty for two days. The reason for the early discharge was based on the theory that if the drug was effective in the hospital it would respond in the same manner in quarters. Fluids were restricted, and further exposures, as entailed in getting out of bed for gargles or fluids several times a day, were avoided. Blood sulphanilamide estimations on several cases recorded infinitesimal quantities.

Eighty-six cases of tonsillitis thus treated spent on an average 2.6 days in hospital; 69 treated influenza cases averaged 2.4 days in hospital. Ten cases receiving a full systemic dosage of sulphonamides during this period were not considered in formulating the statistics. Only 7% of admissions received the drug in full doses. At the Station Hospital Annexe during the month of March 41 tonsillitis cases averaged 5.1 days in hospital. The average in 71 influenza cases was 5.7 days.

TABLE I

Days	Hospital						Annexe					
	Tonsillitis (March)		Influenza (March)		Tonsillitis (February)		Tonsillitis		Influenza			
	Cases	H.D.*	Cases	H.D.	Cases	H.D.	Cases	H.D.	Cases	H.D.	Cases	H.D.
1	13	13	18	18	0	0	0	0	0	0	0	0
2	25	50	25	50	0	0	0	0	2	4	4	4
3	38	114	15	45	16	48	4	12	3	9	9	9
4	8	32	6	24	19	76	7	28	7	28	7	28
5			4	20	27	135	15	75	23	115	23	115
6			1	6	24	144	10	60	18	108	18	108
7	1	7			5	35	3	21	10	70	10	70
8	1	8			6	48	2	16	3	24	3	24
9					Routine		Routine		2	18	2	18
10	Lozenges		Lozenges		3	30			2	20	2	20
11					1	11			1	11	1	11
Totals	86	224	69	163	101	527	41	212	71	407	71	407
	Aver. hosp. days, 2.6		Aver. hosp. days, 2.4		Aver. hosp. days, 5.2		Aver. hosp. days, 5.1		Aver. hosp. days, 5.7			

* H.D. = Hospital days.

Many cases at the Station Hospital Annexe had a normal temperature for one and two days before discharge. No criticism of such routine therapy is intended. However, the comparison revealed itself as the work proceeded. If it is possible to reduce the average stay in hospital to 2.6 days by local oral therapy, a considerable saving of beds is made. The results obtained at the three dispensaries are in accord with those at the hospital. The opinions of the dispensary medical officers are uniform, and may be summarized as follows:

1. 50% of the usual hospital cases are now referred direct to quarters.

2. There is a fall of temperature to near normal in 24 to 48 hours.

3. Many cases that show the spotted throat and a normal temperature are aborted by use of the lozenge—i.e., no subsequent rise of temperature occurs.

4. There is rapid alleviation of pain and soreness of throat.

5. The dispensary medical officers feel that the lozenge therapy avoids the frequent necessity for walking to and from wash-rooms that gargles and fluids entail at the barracks, and that these interruptions of bed-rest are done away with entirely.

One immediate effect noticed at hospital and dispensary was the relief of throat pain, which may occur within two hours. This relief was so striking that lozenges containing 3 gr. were supplied to the dental clinics for use in cases of multiple extraction and badly healing wounds. Thus far, not enough material has been gathered to express an opinion with regard to their usefulness for the last-mentioned purpose.

As shown in Table I, 44% of tonsillitis patients and 62% of influenza patients were discharged with normal temperatures within 48 hours. At the Station Hospital Annexe only 2% of all patients were discharged during the same period; in terms of hospital days, 131 to 4—a saving of 127 hospital days. No tonsillitis patients in February were discharged within 48 hours. Only 7% of the total hospital patients for March received sulphanilamide in the usual massive systemic dosage, against 30% at the annexe. It is understood that patients admitted to the hospital were at least moderately ill, with temperature as a rule above 100°.

Prophylaxis

The companies used for prophylactic treatment were composed of new men beginning their basic training. Lozenges were taken at 9 a.m., 10.30 a.m., 1.30 p.m., and at bedtime. Fluids were restricted. In order to avoid carrying over cases in process of development the first three days of administration were not included in the statistics. The lozenges were continued for another fourteen days, each company being examined every morning, with the following results:

Co. K, 240 men, examined by Lieut. J. A. Moore; 100 receiving lozenges developed one case of tonsillitis, or 1% incidence; 140 controls showed 14 cases, or 10%.

Co. F, 167 men, all receiving lozenges, showed 3 cases, or 1.8%.

Co. D, 110 men, 55 receiving lozenges, showed 2 cases, or 3.6%; 55 controls showed 10 cases, or 18%.

Co. G, 257 men, all controls, produced 21 cases, or 8%.

Of 24 throat cultures in Co. F, six were positive for *Str. haemolyticus*, while of 24 throat cultures in Co. G 9 were positive for *Str. haemolyticus*. Blood determinations of the drug on all specimens analysed were recorded as too low for reading.

TABLE II.—Results of Prophylaxis

		Tonsillitis		Influenza	
		Cases	%	Cases	%
Co. K ..	Treated, 100	1	1	14	14
	Controls, 140	14	10	28	20
Co. F ..	Treated, 167	3	1.8	13	7.7
	Controls, 55	2	3.6	8	14
Co. D ..	Treated, 55	10	18	10	18
	Controls, 55	21	8	27	10
Co. G ..	Controls, 257				

Owing to a temporary failure in production the supply of lozenges was reduced in the case of Co. F for two days of the experimental period, and none was administered to all companies on the tenth day of the fourteen-day period.

Discussion

Many pertinent questions can be raised regarding this mode of therapy. The saliva drug content was not estimated, as it would not prove the case one way or the other. Arnett (1943) reports that the salivary sulphadiazine level ranged from 33 to 96 mg. per 100 c.cm. of saliva from chewing 0.3 g. of that drug in paraffin for a period of two hours. As noted previously, blood sulphanilamide levels with lozenges being too low to read, one must infer that a local oral effect is responsible for the results. The amount of the drug—0.065 g.—present in the lozenge, spaced at intervals of an hour, can conceivably produce a bacteriostatic action, particularly in persons of good health. No attempt is made to free the oral cavity of *Str. haemolyticus*. Several questions thus arise. After the initial

two weeks of prophylactic therapy, what is the subsequent course? This remains to be answered, though the companies treated are to be followed up while at Fort Warren. Should a longer period than two weeks be tried? Is there a danger of creating a mass-sulphanilamide-fast organism? Such a possibility, particularly with the pneumococcus, *in vitro* and *in vivo*, has been indicated in a recent report of Schmidt, Sesler, and Deltwiler of Cincinnati, working with mice. Are there intraseasonal variations that may alter the figures offered in this report?

Summary

The incorporation of sulphanilamide in a lozenge offers a means of prolonged medication for such lesions of the mouth and pharynx as are amenable to treatment with the drug.

The results obtained in several hundred cases treated therapeutically and prophylactically indicate that this mode of sulphonamide medication shows promise.

I am indebted to Capt. Paul Schneider, Lieut. Leo Weyerich, Lieut. Walter Schwebel, and Lieut. James Moore for valuable assistance in formulating the statistical data and in observation of the patients treated therapeutically in the dispensaries. Capt. A. Walter Ecklund of the hospital laboratory kindly performed the laboratory work involved in this study.

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HYPOCHROMIC ANAEMIA IN ADOLESCENT MALES

BY

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Nine cases of hypochromic anaemia in adolescent males have been referred to me by military medical boards in Manchester during the past two years. Their ages range from 17 to 19, and they present a striking similarity in their clinical and haematological features. A tenth case, that of a man aged 45, belongs to the same group and indicates the later course of the condition in the absence of efficient treatment. Detailed observation was hampered by the men's unwillingness to lose work by attending for investigation and review. It has been

adolescent males receives little emphasis in current textbooks and the routine examination of recruits throughout the country must have revealed a considerable number of similar cases, the following brief clinical report is presented with a view to drawing attention to the condition, which may be more common than is realized.

In each case the anaemia was first noticed in early or middle childhood. Apart from Case 4, the mildest of the series, there is no history of serious illness. None gave a history of haemorrhage, bleeding piles, or jaundice. No family history of anaemia or jaundice was elicited. All the patients had lived a normal life, enjoying the usual boyhood activities, and were following occupations normal to their age without difficulty. Their pallor had been accepted as their natural complexion, and in most cases had not prompted them to seek medical advice. Patient No. 9 (aged 45) did not seek advice on account of his anaemia, which he regarded as trivial and incurable. He had lived an active life as an engineer and was in good general health. His history indicates the benign course of the untreated condition. This man showed good general development, but some of the youths looked small and immature for their age. The majority had not started to shave. None of them were aware of any symptoms of ill-health apart from slight breathlessness in the most severe cases. All professed to having received an adequate pre-war diet, including plenty of meat, vegetables, and fruit. Their post-war diet appeared to be that of the population at large.

On physical examination all the youths had a smooth pale skin with no evidence of jaundice. In four cases the tongue was noted to be smooth; in the remainder its appearance was normal. In nearly all the cases an apical systolic murmur of haemic origin was present. The spleen was just palpable in four cases, and in one, the most severe, was enlarged two fingerbreadths below the costal margin. Four cases showed spoon nails. In one of these the nails were normal and healthy after eleven months' treatment with iron. All but one (Case 10) showed evidence of deficient gastric acidity—complete achlorhydria in 5 cases and marked hypochlorhydria in 4. Table I gives the ages of the patients and the blood counts. Before treatment typical microcytes and ring cells were present and there was considerable anisocytosis with some poikilocytes. Case 5 was the most severe, and showed an unusual number of macrocytes—possibly a response by the marrow to the marked lack of iron. There was no direct evidence of haemolysis, since no case before treatment showed any reticu-

TABLE I

Case	Age (Years)	Treatment (Daily)	Period of Treatment	Haemoglobin (% Haldane Scale)		Mean Diameter of Red Blood Cells (microns)		Red Blood Cells (millions per c.mm.)		Leucocytes (per c.mm.)
				Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	
1	19	3 "iron" tablets None	12 months 4 "	56 —	— 110	6.8 —	— 7.2	4.96 —	— 6.6	8,000 —
2	19	6 fersolate tablets 3 fersolate tablets None	15 weeks 8 months 6 "	48 — —	102 116 114	6.8 — —	7.6 7.4 —	3.97 — —	— 6.42 —	5,800 — —
3	18½	3 "iron" tablets	3 "	48	102	6.8	7.4	4.01	5.46	8,000
4	17½	"Iron" tablets, dosage unknown	5 "	72	114	6.8	7.0	4.89	6.47	6,000
5	18½	1½ oz. Parrish's food 6 fersolate tablets 3 fersolate tablets	3 " 5 weeks 6 "	36 — —	46 102 112	7.9 — —	7.6 — —	2.55 — —	3.32 5.28 —	4,300 — —
6	19	—	—	50	—	6.9	—	4.49	—	3,800
7	19	—	—	58	—	6.9	—	5.20	—	5,000
8	19	—	—	48	—	6.7	—	4.34	—	6,800
9	45	6 fersolate tablets	10 weeks	58	108	6.9	7.0	5.61	6.41	8,000
10	17	6 fersolate tablets	5 "	46	100	6.9	7.2	4.71	6.30	5,400

possible, however, to note the effect of treatment in seven of the ten cases. These seven cases all responded fully to adequate treatment with iron. No obvious cause was elicited, and to term the condition "idiopathic" is merely to admit ignorance of their origin. Since this type of anaemia in

leucocyte increase or excess of urobilin in the urine. The serum bilirubin was at the lower limit of normality. The red cell fragility to saline was normal.

Where treatment could be observed all seven cases responded to iron by mouth (Table I). When we were able to undertake