Discussion

Caution is necessary in interpreting these results for clinical purposes. Although the proliferation of skin in the cultures described may be compared to that of skin over burns involving epidermis only, the effect of substances on tissue culture probably gives an overestimate of their toxicity *in vivo*. Any antibiotic applied to the surface of a wound is continuously diluted by the tissue fluids which are exuded, and is also removed from the site of application into the blood stream. Nevertheless, the relative toxicity of different antibiotics to the skin can probably be assessed by the method described. It is possible, however, that the toxic effects of aureomycin are somewhat underestimated in comparison with those of other agents, because of its instability at the pH and temperature of incubation used in the tests.

As penicillin has been used in this unit for several years as a routine for local application to burns, it is interesting to consider its toxicity to skin as shown by tissue culture. *In vitro*, 1,000 units (0.6 mg.)/ml. did not harm skin, while 10,000 units (6 mg.)/ml. caused severe inhibition or death of cells. When applied to burns, 1,000 units of penicillin per ml. has been found to have no harmful effects. For a short period a cream containing 10,000 units of penicillin per g. was applied to burns colonized by *Str. pyogenes* (Jackson *et al.*, 1951) and no ill effects were observed in individual cases. The tissue-culture tests would appear, in this instance, to overestimate the toxicity of penicillin G to epithelium. It is possible, however, that the higher concentration of penicillin might cause a minor degree of interference with healing, which could be detected only by comparing the healing times of a large number of treated cases with those of a comparable control series.

Another factor which must be considered in interpreting the results of these experiments for clinical purposes is the solubility of the antibiotic in tissue fluids. There is greater risk in using a high concentration of an antibiotic when it is very soluble than when it is relatively insoluble. For example, a saturated solution of aureomycin at an approximately neutral reaction does not cause any severe inhibition as judged by the present tests. On the other hand, polymyxin will easily dissolve in a concentration of 10 mg./ml., and at this level it is decidedly toxic to skin *in vitro*. Similarly, penicillin G will form solutions considerably stronger than that which will prevent the growth of epithelium in culture.

Lépine *et al.* (1950) tested the effect of aureomycin and of chloramphenicol on explants of chick embryo lung, and found that proliferating epithelial cells and fibroblasts were retarded in growth by 0.01 mg./ml. and completely inhibited by 1 mg./ml. of these substances. It is probable that the difference between these findings and those reported above can be attributed to the nature of the test materials. Adult human tissue which was used in the present experiment might reasonably be expected to show effects more comparable to those which occur in healing human burns.

Reports are available concerning the effects of penicillin and streptomycin on cells in culture. Both of these antibiotics are regarded for tissue-culture purposes as being non-toxic to normal cells at concentrations of 100 units/ml. (Cameron, 1950). It will be noted that in the present experiments the maximum non-toxic level is set higher at 1,000 units/ml. It must be understood, however, that the object of these experiments is to determine the maximum non-toxic level, with particular relation to clinical treatment, and that where there is a safe margin between toxicity and bactericidal properties it is clearly desirable for tissue-culture purposes not to exceed the bactericidal concentration more than is absolutely necessary.

Summary

The effects of varying concentrations of a range of antibiotics upon human skin cultivated *in vitro* are described.

By this method the highest concentrations of these substances free from toxic effects are assessed as follows: aureomycin hydrochloride, 0.2 mg./ml.; terramycin hydrochloride, 0.02 mg./ml.; chloramphenicol, 0.01 mg./ml.; polymyxin E, 2 mg./ml.; polymyxin B sulphate, 0.2 mg./ml.; penicillin G, 0.6 mg./ml. (1,000 units/ml.); dihydrostreptomycin sulphate, 1 mg./ml. (1,000 units/ml.); neomycin sulphate, 1 mg./ml.; "A18" hydrochloride, 0.02 mg./ml.

The relationship of these results to the clinical effects of local applications of antibiotics is discussed.

We wish to acknowledge the technical assistance of Mr. J. R. Cooper and Miss M. Hulse, and to thank Glaxo Laboratories Ltd., Burroughs Wellcome and Co., and the M.R.C. Antibiotics Clinical Trials (Non-Tuberculous Conditions) Committee for providing antibiotics.

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EXFOLIATIVE CYTOLOGICAL CONTROL IN OCCUPATIONAL CANCER OF THE BLADDER

BY

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[WITH SPECIAL PLATE]

The relative ease with which exfoliation of cells occurs from bladder tumours into the urine has been noted by Papanicolaou (1947, 1948) in the day-to-day cases of unknown aetiology, and by Goldblatt (1947) in cases of known aetiology in the dyestuffs industry. The utilization of this fact in the early diagnosis of bladder tumours in workers is the subject of this paper.

Whereas American authors have repeatedly emphasized (Papanicolaou, 1947; Fremont-Smith *et al.*, 1948) that exfoliative cytological diagnosis must be regarded as an adjunct to the more usual procedures (cystoscopy, biopsy, x-ray examination), the situation is somewhat different in the consideration of occupational bladder tumours in this country. Routine cystoscopy is stated to be practised in America, Switzerland, and Italy (Müller, 1951; di Maio, 1937, 1949; Barsotti and Vigliani, 1949) in factories where occupational bladder tumours have arisen among workers in certain departments that manufacture or use dyestuffs intermediates. Such a routine, at intervals of say six or twelve months, is the best if not an infallible way to detect tumours at a stage early enough to ensure hopeful or successful treatment.

In Britain, routine cystoscopy has never commended itself (Goldblatt, 1947) to workers. Only when, by the repeated and increasing appearance of red blood corpuscles in the urine, the presence of a tumour is rendered probable are workers amenable to persuasion and agree to undergo cystoscopy before and periodically after appropriate operation or treatment. This is quite understandable, inasmuch as the workman experiences

no symptoms in the early stages, and may, in spite of previous instruction in the nature of the occupational hazard, be unable to visualize a process which is asymptomatic. The term "tumeurs silencieuses" (Billiard-Duchesne, 1947) graphically evokes this fact. Such persuasion is often necessary even before the occurrence of visible haematuria, when repeated detection of even a few red blood cells microscopically in the urine lends probability to the presence of a tumour.

The disadvantage of reliance on the detection of haematuria as a criterion of tumour of the bladder is that it is often too late a sign to render surgical measures hopeful. In some cases of occupational bladder tumour even microscopy fails to reveal haematuria before infiltration of a malignant process into the vesical muscle has occurred.

The inverse situation of microscopic or even visible haematuria without an attendant tumour is not uncommon among workers who have accidentally absorbed (through the skin or by inhalation) certain aromatic amines and derivatives of them (Goldblatt, 1947, 1949b). In such cases of haemorrhagic cystitis exfoliated and apparently normal bladder cells are detected in the urine.

It will be apparent that the need is for some examination which permits recognition of a tumour at the earliest possible stage in the medical supervision of workers who, as a result of repeated exposure to certain aromatic amines years ago, when working conditions were bad, may at any time manifest a neoplastic process in the bladder, or who may develop a recurrent tumour process after previous treatment.

In day-to-day hospital practice it is inevitable that the cases should come to the notice of the urologist only when the neoplastic process (innocent or malignant) has obtruded itself upon the patient or on the attention of his medical attendant. By this time the tumour is established and may already be at an advanced stage of development.

To make detection possible at an early stage it would be necessary to examine all urine samples taken in hospital by a cytological technique of a kind similar to that so successfully applied by Papanicolaou and Traut (1943) in the field of cervical and other tumours. The application of these ideas to factory workers, among whom it is certain that some bladder tumours will be found and from whom routine urine samples can be obtained regularly, commends itself at once, especially if, as is the case in this country at least, routine cystoscopy of workers is not feasible. The detection of exfoliated cells indicative of or raising the suspicion of neoplastic or pre-neoplastic origin even in the absence of all other signs or symptoms would logically lead to cystoscopic investigation.

Whereas, as pointed out by Schmidlapp and Marshall (1948), "false positive reports are especially undesirable," such results among dyestuffs workers are much less undesirable than false negatives. False positives arise from the misinterpretation of appearances. But, as will be seen, "false" positives can sometimes be more reliable than the cystoscopist, and may, after repeated efforts, be vindicated by the discovery of a small and secluded tumour.

If a neoplasm is present it is very probable that cytological examination of a number of specimens of urine over a relatively short period will yield positive

results. The difficulties encountered are considered below. It is thus apparent that the number of initial cystoscopic examinations will be diminished, since they will, in general, follow only when the cytological report indicates their necessity. Experience has already shown that the number of such examinations has been diminished by half, and that positive cases have been detected in the absence of microscopic haematuria.

Material

The factories in which these studies of urine sediment cytology were carried out were for the most part those from which the cases collected and analysed by Goldblatt (1949a) were obtained. The description of the operations performed in these factories by him applies, except that the amelioration of working conditions and improvement of chemical processes have advanced even further.

The material was placed at my disposal by Dr. Michael H. C. Williams, his colleague, Dr. Charles Cresdee, and Dr. T. S. Scott, and they, as well as workers and plant managers, helped to establish the complicated arrangements necessary to obtain specimens of urine from the workers and to be certain of their identification. During the past year the urines from about 1,000 dyestuffs workers have been examined by the Papanicolaou technique (1942). The co-operation of Mr. Poole Wilson and his staff at the Urological Department of the Salford Royal Hospital was essential to the progress of the work and was freely given.

Technique

Urine is collected in a numbered vessel and an equal volume of 95% ethanol or industrial alcohol is added. About 40 ml. of this mixture is centrifuged for 15 minutes at 2,000 r.p.m. After the supernatant liquid has been poured off, smears are either made at once or the deposit can be kept for some days in a refrigerator, a little absolute ethanol having been first added. Smears are made by spreading a small amount of the urine deposit with another cleansed slide on numbered slides which have been washed in ethanol, polished, and smeared with albumin in glycerol. When the smear begins to cloud slightly round the edges or in its thinner parts the slide is placed in fixative (95% alcohol and ether, equal volumes). The smear must not be allowed to dry at any time.

The Staining Process.—Fixative→80% (15–30 seconds)→70%→50% EtOH→distilled water→haematoxylin 2 minutes→distilled water→distilled water→50% EtOH→3% NH₄OH in 70% EtOH→70%→80%→95% EtOH→orange G 1½ minutes→95%→95% EtOH→Papanicolaou EA 65 polychrome stain, 1½ minutes→95%→95%→100% EtOH→equal parts EtOH+xylol→xylol (three changes)→mount in Canada balsam→apply cover slips and allow to dry for at least one hour.

Using a binocular microscope with a mechanical stage, objectives ×10, 16 mm., ×40, 4 mm., and wide-field eyepieces ×10 and ×15, the smear is examined under the low power by starting from a marked end of the slide and moving on from each transverse sweep until the whole slide has been traversed. Any doubtful or unusual cells are scrutinized under high power. Areas containing suspicious cells or clusters of cells are located by an appropriate marking for detailed study.

The recognition of significant cells in the smear requires a thorough familiarity with the variability of normal cells and of all non-tumour cells that may be present. This must be combined with an experienced eye for the criteria of malignancy laid down by Papanicolaou (Papanicolaou and Traut, 1943), which may be summarized as follows.

The Criteria of Malignancy

There is no one single criterion of malignancy. These criteria must be used in combination, a sufficient number of them being accepted by the experienced eye as indicative

of neoplastic change. A diagnosis of malignancy is never made on the presence of one cell or cluster of cells only.

In the words of Papanicolaou (1947): "A conclusive positive diagnosis should be based as much as possible on clusters of malignant cells or small fragments of cancerous tissue and not on single exfoliated cells. The criteria are not exclusively cytologic (structural abnormalities of the nucleus and of the cytoplasm), but also histologic (anisocytosis, and anisonucleosis, crowding of cells, irregular pattern, etc.)." This dictum of Papanicolaou's is reminiscent of that of Dudgeon and Wrigley (1935) in reference to their diagnosis of pulmonary tumours by the application of the wet-film method to particles of tissue in the sputum. They stated that "we never made a diagnosis of new growth unless plaques or clusters of malignant cells were seen."

In spite of these dicta, however, it is possible to make a positive diagnosis of a smear which shows only individual cells, each of which possesses a sufficient number of the criteria given below. This has certainly been the case in our experience of smears from urine. In the present series of cases most of the confirmed smear diagnoses showed only individual malignant cells, and in one or two cases only about 10 malignant cells were visible in each smear.

Papanicolaou's criteria are: (1) Enlargement and prominence of the nucleus. Alteration of the nuclear-cytoplasm ratio. (2) Alteration of the chromatin pattern. (3) Increase in the chromatin and hyperchromasia. (4) Abnormal shape of the nucleus. (5) Anisonucleosis (variation in nuclear size in a group of cells). (6) Enlargement and increase in the number of nucleoli and karyosomes. (7) Increase in size of cells. (8) Bizarre cell shapes. (9) Mitotic figures are very rarely seen in exfoliated cells, but are significant when seen.

Classification of Cells Seen in the Smear

Since cells at all stages of development from normality to malignancy may be seen in a smear, Papanicolaou introduced a system of grading which permits both a finer classification of cells and a safety margin where doubt is experienced (Table I).

TABLE I.—Papanicolaou's Grading

Class	Diagnosis	Characters of Cells in Smear	Tumour Possibly Present in Bladder
I	Negative	Normal cells only	None
II	"	Atypical but not malignant	Papilloma (?)
III	Suspicious	Abnormal but not conclusively malignant	Papilloma, papillary carcinoma?
IV	Positive	Cells and clusters highly suggestive of malignancy	Carcinoma
V	"	Cells and clusters without doubt malignant	"

The discovery of the presence of Class IV and V cells must be followed by cytосcopy. The presence of Class III cells calls for repeated re-examination at short intervals. The presence of Class II calls for re-examination at more frequent intervals than heretofore.

Since Dean (1948) has stated that "the detection of benign papillomata by the method as at present applied therefore is of little value," it is important to note that Schmidlapp and Marshall (1950) emphasize that "by far the greater number of papillomata are reported in Class II." Dean's figures seem discouraging for benign papillomata. He found that in a group of 36 patients with histologically proved benign bladder tumours the smear reports were:

Classes I and II	..	27; no malignant cells
Class III	..	8; suspicious cells
Classes IV and V	..	1; malignant cells

It is not clear whether the urines (male and female) were repeatedly examined. Probably they were not. If, as would be the case were all these patients under factory control, urine samples were repeatedly obtained, it is highly probable that the number of false negatives would become

negligible in a short time, or, put otherwise, that the number of tumours which would escape cytосcopy would be practically zero.

Cells Seen in Smears from Normal Urine

In smears from normal men's urine it is unusual to find more than three or four transitional cells, but occasionally a large number of *normal cells* of all types are seen.

1. *Squamous Epithelial Cells (in Voided Urine)* (Special Plate, Fig. 1).—These may derive from the fossa navicularis, and are present in large numbers if the prepuce is long. They are also numerous if the patient is having oestrogen therapy for carcinoma of the prostate. In female urine they are, of course, very numerous.

2. *Transitional Epithelial Cells* (Fig. 1).—These show a great variation in size, in shape, and in many other ways, which may be due to the fact that in section the normal transitional epithelium shows cells having a variety of shapes and sizes, some of which are multinucleated. Also the cells are soaking in urine before, during, and after exfoliation, which may cause them to swell and become vacuolated. These cells form the lining of very muscular organs and are being continually distorted and stretched. The normal cellular variations seen are: variation in size of the cells; vacuolation of cytoplasm; bi- and multi-nucleation; variation in size of the nucleus; and clusters of vacuolated cells. In these cells, however, the nucleus shows no hyperchromasia and has a fine, evenly distributed chromatin network, often palely staining, and the nuclear cytoplasmic ratio is always within normal limits. The cytoplasm often shows a well-defined ectoplasm and endoplasm, and sometimes there may be 20 nuclei or more in a single cell.

3. *Renal Cells from the Collecting Tubules*.—These are small round cells, about twice the size of a polymorph, with deeply staining cytoplasm and a small round dark nucleus; they are sometimes seen in clusters of a cast-like formation.

4. *Leucocytes* (Fig. 2).—Polymorphs and lymphocytes. *Histiocytes*:—These are usually smallish cells, though they can vary considerably in size. They have a deeply staining frothy cytoplasm and often contain ingested particles, among which can sometimes be seen one or two phagocytosed red blood cells. The nucleus is usually small, dark, spherical or oval in shape, and eccentrically placed, and may be multiple.

5. *Red Blood Cells* (Fig. 2).—These are seen occasionally.

Atypical but Non-malignant Cells in Smears

A number of conditions such as infection and renal or vesical calculi can give rise to metaplasia and produce atypical cells which can easily be confused with malignant cells by the inexperienced technician. Erythrocytes, leucocytes, mucus, and crystals, if present in quantity, can all interfere with the staining reaction and confuse the cytological picture.

Cellular Picture in Cases of Neoplasm

"Benign" *Papillomata*.—The cells from these tumours are columnar, and appear singly or in clusters which show palisading. They are fairly small, with round or oval palely staining nuclei situated at one pole of the cell, and show none of the criteria of malignancy (Fig. 3).

Carcinomata.—The cells from these tumours show the criteria of malignancy given above (Figs. 4 and 5).

Advantages of the Smear Method of Detection

1. It often permits recognition of the presence of a tumour in the very early stages. Growths, when extensive and relatively far advanced, often do not give such good results with the smear technique because they are likely to have undergone degeneration, ulceration, and sloughing.

2. Positive results may be found in the absence of all other signs—for example, haematuria.

3. When applied to urine it offers no physical disturbance to the workers, and can be repeated as often as may be necessary.

4. Stained and mounted smears can be kept indefinitely for future comparison, and, further, these can be compared and correlated with any pathological sections of biopsy material obtained at operation, as illustrated in Fig. 6.

Disadvantages of the Smear Method

1. Since for the satisfactory screening of large numbers of dyestuffs workers, three or four times a year at least, many hundreds of slides must be very carefully scrutinized, it is apparent that several technicians must be methodically trained, relatively expensively equipped, and given suitable laboratory space.

2. The alternative methods of collecting and fixing specimens in the factory and sending them to a competent cytologist in hospital or sending the worker to the hospital periodically will be found, in general, unsatisfactory. Inconvenient as it may be, it is essential that the work should be done in the factory. Urine examinations are properly a part of the life of a dyestuffs factory. Only those who are in daily contact with the workers can develop the required personal interest in the vital business of screening the urines.

3. Negative findings on a single occasion do not exclude a tumour. It may be necessary to examine many urine smears at different times before the presence of a tumour, especially a "benign" tumour, is reported.

4. If the method in its application to workers is time-consuming, this is not incommensurate with the very important results that are attainable.

Results

In Table II an analysis is given of the results of the examination of the urines of 1,000 men. Table III presents the results of various diagnostic procedures on cases of vesical tumour.

TABLE II

No. of men whose urines were studied	1,000
No. of these men whose urines were examined for red blood cells as a routine at the factory medical departments	998
26 were reported by smear technique as suspicious or positive	
15 new cases	11 cases previously operated on for bladder tumour
13 confirmed by cystoscopy (86.7%)	2 unconfirmed by cystoscopy (13.3%)
4 with no R.B.C. in urine	1 case of vesical varix
4 with occasional R.B.C. in urine	1 case of stone in renal calix
* 1 diagnosed on smear only	
4 with haematuria	
6 confirmed by cystoscopy (54.6%)	3 cases which on cystoscopy showed only red, rough, or mossy areas in bladder (27.3%)
* 1 diagnosed on smear only	2 not confirmed on cystoscopy (false positives) (18.1%)

* These two cases had never been included in the routine urine examinations for red cells which had been established years before.

It will be seen in Table II that 5 out of the 13 cases confirmed by cystoscopy and 1 out of the 6 "recurrence" cases confirmed by cystoscopy were diagnosed on the smear technique alone. It is on these six cases that we wish to place great stress, for it is on the discovery of such cases that the recommended use of the smear technique rests. The reference numbers of these cases as seen in Table III are H5, H8, H6, C28, A2, and BRes. There is no doubt that but for the cytological diagnosis these cases would not have come to operation until a much later date. The exact amount of time gained is at the moment unpredictable.

TABLE III

No.	Red-cell Test	Smear Test and Class	Cystoscopy Report	Histological Report on Section of Tumour
<i>New Cases</i>				
B33	None	Malignant IV	Early carcinoma	Papilloma and anaplastic carcinoma
B25	"	" V	Multiple papillomata	—
B91	"	" V	Small papilloma	Malignant papilloma
C29	"	" IV	Carcinoma	Squamous-cell carcinoma
H5	Occasional	" IV	Carcinoma of apex	Transitional cell carcinoma
H8	"	" V	Small papilloma	—
H6	"	" V	Carcinoma	—
C28	"	" V	Multiple papilloma	Malignant papilloma
H19	"	" V	Small varicosity	—
C38	Present	Suspicious III-IV	N.A.D. Stone in ureter	—
H9	Increasing	Malignant IV	Malignant papilloma	Malignant papilloma
H1	"	" V	Papilloma	—
A1	Haematuria	Papilloma IV	"	—
C48	"	" IV	"	Transitional papilloma
A2	Not done	Malignant V	Malignant papilloma	" "
<i>Men who have had Tumours in the Past</i>				
BRes	Not done	Malignant IV	Papilloma	Pyuria
BEng	Haematuria	Papilloma IV	"	"
B37	Present	Malignant V	Rough red area	"
H92	"	" V	Inoperable carcinoma	"
H4	"	" V	Mossy-looking area	"
C19	"	Malignant papilloma V	Papilloma	"
H28	"	Malignant IV	Mossy area	"
H7	"	" V	Carcinoma	"
H89	"	" V	N.A.D. (diverticulum)	"
H2	"	" IV	Carcinoma	"
H3	"	" V	N.A.D.	"

It will be noted in Table III that in seven cases the cystoscopic diagnosis was papilloma or multiple papilloma, whereas the smear report was malignant, and that in two cases (B91 and C28) the histological report on the tumours was malignant papilloma.

Difficulty arises quite frequently in obtaining the full histological report on the tumour tissue because the urologist may, having seen a papilloma, often proceed to fulgurate it at once rather than try to get a biopsy specimen. The presence of cryptic malignancy may thus be missed.

It is of interest to note that in case H19 the smear report was "malignant," whereas the cystoscope showed only a small varicosity. In spite of this negative cystoscopic result, repeated examinations of urine smears have shown the persistent presence of malignant cells. Only the future can show what the final judgment may be.

Attention must also be drawn to cases B37, H4, and H28, in all the urines of which malignant cells were seen and the cystoscopic reports of which were "rough red area," "mossy-looking area," and "mossy area." These three cases, all having had bladder tumours at some time, were found in the factory routine examination to have persistent microscopic haematuria. The finding of malignant cells on the smears on three consecutive occasions seemed to clinch the diagnosis, but, as stated, cystoscopy did not show tumours but merely somewhat abnormal areas. Time alone can decide whether on these dubious areas tumours will later be manifest.

In respect of the two "false" positives (H89 and H3), similar remarks apply, cystoscopy up to date being negative in spite of positive reports on smears obtained on three consecutive occasions and repeated microscopic haematuria. The false positive case C38 arose through a manifest misinterpretation of appearances. So far one false negative result has been recorded. This occurred in a man who had previously had a tumour. Two smears of his urine

were examined over a period of three months. They contained no atypical or abnormal cells, but on review cystoscopy a small papilloma was discovered in his bladder.

Ideally, in order to reduce the risk of false negatives to a minimum, the urine should be collected on rising, should be fresh when examined, and at least four smears should be studied from each deposit.

Since the Papanicolaou staining method does not always show red blood cells clearly even when these are present in considerable numbers, it is desirable to devise new fixing and staining methods whereby both tumour cells and blood cells can be well seen in the same preparation.

Summary and Conclusions

The Papanicolaou smear technique for the detection of tumour cells has been applied to the urines of 1,000 workers in three dyestuffs factories where there was a hazard due to carcinogens.

Twenty-six cases were reported as suspicious or positive. Of these, 19 (73.1%) were confirmed by cystoscopy, 3 (11.5%) were suspicious on cystoscopy, and 4 (15.4%) were false positives. There has up to date been one false negative result.

Six of these cases were diagnosed and confirmed by cystoscopy in the absence of haematuria or other signs of bladder disease. These cases lend great weight to the method.

Experience has shown that the presence of a tumour can be diagnosed on the appearance in a smear of a number of single cells, not necessarily arranged in clusters.

The diagnosis of a tumour cell rests upon a combination of cytological criteria and requires much training and experience.

It is thought that the smear method should be applied extensively in factories where there is reason to believe that the workers have been exposed to bladder carcinogens.

It is not recommended that the search for microscopical haematuria should be abandoned. The two tests should run in parallel.

By applying the smear technique to cases in which possible recurrence must be sought for years, it may be possible to reduce the number of periodic review cystoscopies. It has already been possible to reduce the number of first cystoscopies by about half in the factories referred to.

It is a pleasure to express my thanks to Mrs. Dorothy Moran and to Miss Lucy North for their help in many of the technical operations, to Mr. K. D. Cooper for taking the photomicrographs for me, and to Dr. Alexander Munn for helpful co-operation. I wish to thank Dr. M. W. Goldblatt, head of the Industrial Hygiene Research Laboratories, at whose instance this work was carried out, and who has assisted in the preparation of this paper.

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MILIARY TUBERCULOSIS IN A CASE OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS TREATED WITH A.C.T.H.

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[WITH SPECIAL PLATE]

Knowledge of the therapeutic response to A.C.T.H. and cortisone has outstripped understanding of those diseases benefited by their action. It is significant that the introduction of these steroids comes at a time when a new concept of medicine—namely, the body's reaction to disease rather than to individual diseases—is taking the place of the older aetiological notions. Klemperer, Pollack, and Baehr (1941), in making a pathological analysis of 20 consecutive cases of acute lupus erythematosus, showed that the common denominator of the multiform lesions was degeneration of the collagen connective tissue. They pointed out that the same common denominator was present in lesions of rheumatic fever, scleroderma, and periarteritis nodosa. The establishment of a group of diseases on the grounds of a common morphology prepared the way for a mode of treatment unhampered by aetiological considerations. The reports of the physiological effects of A.C.T.H. and cortisone on tissue and tissue changes, and the subsequent release of these steroids for clinical trial, provided the means and opportunity.

It was not surprising that some of the first patients to whom these steroids were administered were sufferers from acute lupus erythematosus. In the beginning it seemed as if the treatment of this hitherto fatal condition would be revolutionized. But in the past two years reports in this country and from America suggested that, despite the prompt and striking remissions in clinical manifestations, the disease process continued. Soffer, Levitt, and Baehr (1950), in a series of 14 patients with three deaths, reported that renal abnormalities and anaemia persisted in all cases, leucopenia in 10, and the "lupus erythematosus cell" in 13. Similar conclusions were reached by Brunsting, Slocumb, and Dicot (1950), in a series of seven patients with three deaths. The initial fall in the E.S.R. was not sustained. The low serum proteins in some cases after clinical remission returned to normal, but the raised alpha₂-globulin remained unchanged (Reiner, 1950).

Short remissions of three to four months were reported, but it was agreed generally that most patients required a maintenance dose. Attempts to discontinue treatment in the hope of a natural remission induced a severe exacerbation of the disease.

Shortly after the first enthusiastic accounts of the therapeutic trials with A.C.T.H. and cortisone came reports from Hart and Rees (1950) and Michael *et al.* (1950) that cortisone enhanced the evolution of tuberculosis even in those animals who possessed a high natural resistance to the disease. McNee (1950), commenting on the physiological responses to these steroids, stated that wounds showed no signs of healing and abscesses no signs of granulation-tissue formation in animals or patients to whom they were being adminis-

J. G. S. CRABBE: EXFOLIATIVE CYTOLOGICAL CONTROL IN OCCUPATIONAL CANCER OF BLADDER

FIG. 1.—Urine deposit smear, showing normal transitional and squamous epithelial cells. ($\times 375$.)

FIG. 2.—Urine deposit smear, showing red and white blood cells, histiocytes. ($\times 375$.)

FIG. 3.—Urine deposit smear, showing a group of "benign" papilloma cells with definite palisading. ($\times 775$.)

FIG. 4.—Urine deposit smear, showing malignant cells and cell clusters. ($\times 375$.)

FIG. 5.—Urine deposit smear, showing separate malignant cells in bizarre forms. ($\times 775$.)

FIG. 6.—Section from the same tumour as Figs. 4 and 5. ($\times 375$.)

BETTY WALKER: MILIARY TUBERCULOSIS IN A
CASE OF ACUTE DISSEMINATED LUPUS
ERYTHEMATOSUS

FIG. 1.—Radiograph of chest before treatment with A.C.T.H.

FIG. 2.—Radiograph of chest in January, 1951: numerous miliary deposits with early confluence of lesions.

FIG. 3.—Radiograph of chest in November, 1951: miliary deposits undergoing calcification.

FIG. 1

FIG. 2

FIG. 3