

tions and strict laboratory control are essential. Dosage requirements are usually less in these patients.

SUMMARY AND CONCLUSIONS

A case of cerebral thrombosis following the administration of a mercurial diuretic is reported. While this may have been coincidental, it is pertinent that recent studies indicate thrombotic phenomena are more prone to occur in congestive failure following initiation of diuresis. Hæmoconcentration and prothrombin increase predispose to these complications. Where time permits a gradual rather than intensive plan of treatment, while less dramatic, may be a safer method of management. There is good evidence that anticoagulant therapy is effective in reducing thromboembolic complications with their attendant mortality during the early treatment of congestive heart failure.

A brief summary is also given of other reported untoward effects of mercurials.

In conclusion it is again emphasized that mercurials are valuable and often indispensable for our treatment of heart failure, but undesirable effects may occur and we should be alert to recognize their occurrence.

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THE PROBLEM OF PENICILLIN RESISTANT STAPHYLOCOCCAL INFECTION*

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AN INCREASING NUMBER of reports from all parts of the world concerning the prevalence of penicillin resistant staphylococci are appearing in the medical literature. Spink and co-workers¹ in 1944 reported 12% of 68 strains to be penicillin resistant. Gallardo,² Plow,³ Bondi and Dietz⁴ in 1945 all reported a similarly low incidence of penicillin resistant strains. Barber⁵ in 1948 reported that the incidence of penicillin resistant strains in her studies was 14% in 1946; 38% in 1947 and 58% in 1948. From these reports and others it is apparent that this ubiquitous organism has a peculiar faculty for adaptation to the influence of noxious agents in the environment. Further it appears from the work of Barber *et al.*⁶ (1948 and 1949) and others that an increasing number of the penicillin resistant strains are being isolated from institutional infections. These workers have also shown that staphylococci isolated from widely separated hospitals in

England belong mainly to two particular phage groups. It is suggested from their work that a particular strain, having a high resistance to penicillin is propagated in hospitals by cross infection.

The nasal carrier rate for pathogenic staphylococci is known to vary considerably and amongst the general population a carrier rate of 30 to 50% can usually be expected, McFarlane,⁷ 1939, Cunliffe,⁸ 1949. Various authors including Barber,⁶ 1949, Voureka and Hughes,⁹ 1949, Rowntree and Thompson,¹⁰ 1949 have shown that these organisms are predominantly penicillin sensitive. Forbes¹¹ has shown that these "wild staphylococci", isolated from clinical infections outside the hospital are usually more sensitive to penicillin than those isolated from hospital patients.

It has been suggested that intimate contact with a hospital environment may affect the carrier rate in hospital workers. Recently this has been the subject of study by Rowntree and Barbour¹² in Australia. They reported that student nurses, within a period of 5 weeks from beginning ward duty, showed an increased staphylococcal nasal carrier rate from 52.6 to 71.4%. The number carrying penicillin resistant strains rose during the same period from 4.3 to 32.1%. Those nurses whose cultures were in-

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initially negative were more prone to become carriers of the penicillin resistant ward strains of staphylococci.

Having been confronted with the clinical problem of increasing penicillin resistance in staphylococcal infections, we have sought to establish the trend of the development of penicillin resistant strains in hospital workers and to compare their carrier rate with the carrier rate in the general population of our community. It was hoped that this would provide knowledge that would assist us in controlling staphylococcal skin and wound infections in our hospital and also draw attention to this phenomenon so that efforts might be made to either prevent or delay the occurrence of resistance to other antibiotics.

Recent experience in the Vancouver General Hospital indicates that there has been a sharp increase in the number of penicillin resistant staphylococcal cultures isolated from hospital patients, *e.g.*, 46% in 1947 to 74% in 1951. (See Table II below). Nasal carrier rates among hospital personnel were studied in 1949 when there was an increase in skin infections in the newborn, and again in 1950 when wound infections in surgical wards were prevalent. The results of these tests during these two periods indicated that there was a high incidence of penicillin resistant staphylococci in the nasal cultures from the maternity nursing staff and the operating room personnel (see Table I below).

MATERIAL AND METHODS

In order to estimate the significance of these findings and to compare them with a control group a study was made of the incidence of pathogenic staphylococci in the hospital workers and in three groups outside the General Hospital, namely, (1) a group of children attending the out patient department, (2) girls residing in two city dormitories, and (3) the medical staff of the City Health Department.

Nasal swabs from the subjects were plated directly to mannite salt agar, and mannite positive colonies were subcultured and tested for coagulase production by the slide test. Mannite fermenting coagulase positive strains of staphylococci have been regarded as pathogenic. Antibiotic sensitivity tests were determined by the disc method using penicillin, 15 units per ml. and aureomycin 100 micrograms per ml.

RESULTS

Table I illustrates the carrier rates among five groups studied.

TABLE I.

Group	Number studied	Carrier rates of Staph. pyogenes	% of strains resistant to penicillin
A.....	110	65%	11%
B.....	65	35%	26%
C.....	40	27%	18%
D.....	68	48%	70%
E.....	65	51%	79%

A—Children C.H.C.
B—Girls Y.W.C.A.
C—Personnel City Health Department.
D—Hospital Staff Maternity.
E—Hospital Staff Operating Room.

Group A was a group of children, aged 6 to 16 years who were attending the Children's Out-patient Department for various reasons other than respiratory infection. The carrier rate in this group was 65%, the highest rate of any group studied. It is noteworthy, however, that few of these children (11%) carried penicillin resistant strains. In Group B and Group C, the carrier rates were low, 35 and 27% respectively, and again the incidence of penicillin resistant strains was low, 26% in the girls boarding home and 18% in the city health workers. In Group D and Group E, the two groups of hospital workers, the carrier rates were higher, 48 and 51% and in both these groups the majority of these strains, 70 and 79%, were penicillin resistant.

TABLE II.

STAPHYLOCOCCI ISOLATED AT V.G.H.		
Year	Number of strains tested	Penicillin resistant
1947.....	59	46%
1948.....	83	64%
1949.....	164	76%
1950.....	533	74%
1951.....	450	73%

Table II shows the percentages of penicillin resistant strains isolated from routine cultures coming to the Bacteriological Laboratory. Over 98% of these strains are from hospital patients.

DISCUSSION

If we assume that the *in vivo* response parallels the *in vitro* sensitivity these results at first sight suggest that penicillin is no longer the antibiotic of choice in the treatment of staphylococcal infection. However, our material represents a selected group of strains as many of the organisms were isolated from patients that had responded poorly to penicillin and some of the strains were from infections likely acquired in hospital. In view of the results reported here and

since, in our experience, the organisms isolated from outpatients are rarely penicillin resistant, we feel that the problem is mainly one of cross infection in hospital. As these resistant infections are thus created by the hospital environment, they can therefore fairly be classified as "iatrogenic infections".

That there is some danger of repeating this situation with other antibiotics is indicated from our early experience with aureomycin. During 1949 and early 1950, the penicillin resistant strains were invariably sensitive to aureomycin but over the past year an increasing number of aureomycin resistant strains have been encountered and now almost 20% of the strains are relatively resistant to aureomycin. So far, "aureomycin resistant, penicillin sensitive" strains are rare in our experience.

The present study reveals that there exists amongst hospital workers a significantly higher carrier rate for penicillin resistant staphylococci than among a control group of dormitory resident girls, outpatient children and outside medical workers. These figures are in accord with the previous studies on this subject by Barber^{5, 6} and others.^{10, 11} The evidence presented from the experience of the Vancouver General Hospital regarding penicillin resistance in staphylococci isolated from infections during the past four years emphasizes the trend towards the increasing numbers of resistant strains of this organism that have been isolated from a hospital population. Most physicians in hospital practice have experienced therapeutic failures which could be attributed to penicillin resistant infection.¹³ This tendency towards resistance, coupled with or because of, the high carrier rate in hospital workers may provide an explanation for recent hospital outbreaks of staphylococcal infection. With the widespread use of penicillin in hospitals sensitive strains may be greatly reduced while resistant strains are permitted to thrive. Cross infection would appear to be a major factor in this process.

The character of the nasal flora in the newborn in relation to the occurrence of staphylococcal skin pustules may be relevant to this problem. For example, recently in one nursery, there was a minor outbreak of pustules, four cases over a four week period. At the end of this time eleven of the twenty babies in the nursery were nasal carriers of pathogenic staphylococci and ten of the eleven nasal strains isolated were resistant to penicillin. In a similar nursery on

the floor above, where no cases had occurred, there were no nasal carriers of pathogenic staphylococci in the fourteen occupants.

PREVENTION OF ANTIBIOTIC RESISTANCE

It would be helpful in this problem if practical suggestions were available to physicians regarding the use of new antibiotics in a manner that would avoid the production of resistant strains. Unfortunately there is as yet insufficient knowledge on which to base valid suggestions in this regard.

In the past, the following recommendations for the use of antibiotics have been widely accepted, namely: (1) The early use of massive dosage. (2) The use of *in vitro* sensitivity tests for the selection of the appropriate antibiotic. (3) The use of known synergistic combinations for certain infections (*e.g.*, penicillin and streptomycin). (4) The avoidance of multiple antibiotic therapy without laboratory control (shotgun treatment). (5) The avoidance of indiscriminate antibiotic prophylaxis or their frequent use for trivial infections.

While these rules have seemed rational and have been useful guides in antibiotic therapy there is little scientific support for the idea that strict adherence to them would prevent the development of bacterial resistance with the use of some new antibiotic.

It is possible that in the future we may have more knowledge upon which to base advice for the choice of antibiotic combinations. The experimental work of Jawetz and co-workers^{14, 15, 16} suggests that the antibiotics may be divided into two groups, namely: (a) Those whose chief action is bactericidal, *e.g.*, penicillin, streptomycin and possibly bacitracin, and; (b) Those which are mainly bacteriostatic, *e.g.*, chloromycetin, aureomycin, terramycin.

The results of their experiments suggest that a combination from within group (a) is synergistic whereas a combination from (a) and (b) is antagonistic. If these findings prove valid on clinical application they may provide a rational basis for choice of antibiotic combinations and thus contribute materially to the prevention of antibiotic resistance.

SUMMARY

Carrier rates among hospital and non-hospital workers have been compared and found to be considerably higher in hospital personnel,² the

incidence of penicillin resistant strains isolated from routine cultures steadily increased to a fairly high level (74%). The importance of the rôle of pathogenic penicillin resistant staphylococcal carriers amongst hospital workers in the spread of institutional infections is described.⁴ The problem of the prevention of antibiotic resistance is discussed.

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EFFECT OF ACTH, CORTISONE, AND DESOXYCORTICOSTERONE ON BURN SHOCK*

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ALTHOUGH SOME of the phenomena which occur after severe burns have been shown to involve the pituitary-adrenal system, opinion differs as to the efficacy of certain endocrine materials in decreasing the mortality from shock after burning. Recently You and Sellers¹ reported that giving desoxycorticosterone acetate (DCA) to rats for a period *prior* to burning increased the incidence of survival. However, there was no evidence of an increased number of survivals when DCA was given after burning.

The present report describes experiments to determine the effect of ACTH and cortisone on the prevention of shock, and on the survival of rats following burns. The criterion was taken to be survival for longer than three days after the burn. Death within three days was assumed to be the result of "shock" rather than the later, less well defined causes of death such as "toxæmia", infection, etc.

MATERIALS AND METHODS

Albino rats of the Wistar strain were kept in group cages and were fed Fox Breeder Cubes (Master Feeds) and water *ad libitum*. Burning was carried out by immersing the backs of the rats (under ether anaesthesia) in water (containing a wetting agent) at 90° C. for a period of 40 seconds. Animals dying within 15 minutes after burning were excluded from the series, for death in these cases was not attributable to secondary shock.

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The effects of ACTH,* cortisone,* and DCA* on the survival under these conditions were compared to the effect of saline.

RESULTS

The results, and details of treatments are presented in tabular form (Table I). It will be seen that treatment with saline produced an increased rate of survival. Pre-treatment with DCA also increased survivals. There is some suggestion that pre-treatment with cortisone may have had a slight beneficial effect, but given after burning no increase was observed.

The results with ACTH, in the dosage used, did not differ significantly from the control values.

DISCUSSION

The experiments were carried out in series by testing one or more treated groups against a control group. Considerable variation was observed in the different experiments, but this cannot be demonstrated adequately in a single table. Thus, a higher rate of survival in a treated group in an experiment in which the control survival rate was also high, does not suggest that the particular treatment (or regimen) was more effective. The suggestion that pre-treatment with cortisone had a beneficial effect seems less likely when experiments are examined individually.

Administration of large doses of physiological saline was more effective than any other treatment. The well known action of DCA on mineral metabolism, and the absence of an appreciable effect with ACTH or cortisone strengthen the suggestion previously made (You and Sellers, 1950) that pre-treatment with DCA may decrease mortality from burn shock by affecting the electrolyte relationship in body fluids.

*Two brands of ACTH were used, one supplied by Armour Laboratories, Chicago, and the other by the Connaught Medical Research Laboratories, University of Toronto, (equivalent to LA-1A standard). Cortisone acetate, supplied by Merck and Company Limited, Montreal, Quebec, was diluted for use with normal saline. "Percorten" in oil, supplied through the courtesy of Ciba Company Limited, Montreal, Quebec.